The Magnitude and Profile, Distribution Patterns and Associated Factors of AIDS-related Opportunistic Diseases in Adults on Antiretroviral Therapy in Malawi

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ABSTRACT

Background: Over one million people in Malawi are HIV infected and many suffer from AIDS-related opportunistic diseases (ODs). However, little is known about the clinical profiles of these ODs and their associated risk factors. We describe the burden and spectrum of ODs in HIV-infected adults on combined antiretroviral therapy (cART) since the countrywide scale-up of free HIV treatment.

Methods: A retrospective chart review was conducted across all three regions in Malawi. Clinical data on prevalent and incident AIDS-related ODs in patients commenced cART from 2004-2015 were abstracted from case notes between March and May 2016.

Results: A total of 9,953 patients were included in the analysis. 60.84% were females and relatively younger than males with mean age difference of 4.75 ± 2.9 years. Overall mean age was 40.72 ± 12.19 years. 86.85% were young and middle-aged adults of productive age-group (15-54 years). 65.08% were urban residents and 59.55% were from Southern region. 12,814 AIDS-related opportunistic events were extracted: 56.54% were prevalent AIDS-defining clinical conditions and the rest were incident AIDS-recurrent cases. 7.65% of patients had no OD manifestation. Commonly occurring aetiological agents were mycobacterial (36.31%), bacterial (20.77%), fungal (15.77%) and viral (15.11%) pathogens. Overall, the most prevalent ODs were mycobacterium tuberculosis (34.39%), bacterial pneumonia (11.21%), nontyphoid Salmonella bacteraemia (9.57%), HIV-wasting syndrome (8.93%), candidiasis (6.81%), isosporiasis (5.24%), pneumocystis pneumonia (4.02%) and cryptococcal meningitis (3.72%). In the multivariable logistic regression, healthcare facility types, gender, age-group, geographical location, CD4 cell count, viral load levels, treatment initiation eligibility criteria and low socio-economic status were statistically significantly associated with manifestation of AIDS-related opportunistic diseases.

Conclusion: ODs were highly pervasive among HIV-infected adults in Malawi including treatment-experienced patients which affect largely the productive population. Strategies for effective prevention, early detection and proactive management of AIDS-related opportunistic diseases need to be established and strengthened across all patient groups, in all regions and across all ART health facilities regardless of their levels.

Keywords: Human Immunodeficiency Virus, Acquired Immunodeficiency syndrome, Antiretroviral therapy, AIDS-related opportunistic diseases, Magnitude, Spectrum.

BACKGROUND

The human immunodeficiency virus (HIV) epidemic remains one of the greatest global health challenges faced by humanity in the 21st century (UNAIDS, 2016). It is the longest epidemic/pandemic ever faced by humanity. 74.9 (58.3–98.1) million people have been infected with HIV since the epidemic started and 37.9 (32.7–44.0) million are currently living with HIV of which, 36.2 million are adults (UNAIDS, 2019a). Furthermore, 32.0 (23.6–43.8) million people have died of AIDS-related illnesses and 770,000 (570,000–1.1 million) of deaths occurred in 2018 (UNAIDS, 2019a). HIV causes progressive depletion of CD4 T lymphocyte cells leading to debilitating, life-threatening ODs (Chaisson & Moore, 1997; FMOH, 2008; Hogg *et al.*, 1999; Miller *et al.*, 1999; Mitiku *et al.*, 2015; Siberry *et al.*, 2013). Earlier epidemiological studies established that over 90% of ODs are responsible for AIDS-related mortalities (Lifson *et al.*, 1988). Due to its pathophysiology, HIV progression is directly linked to ODs which may constitute the initial manifestation of HIV infection indicating significant immunodeficiency (Lifson *et al.*, 1988). Different factors including exposure to potential pathogens and their virulence, degree of host immunity and antimicrobial prophylaxis usage, are (known to be) responsible for the development of ODs among people living with HIV (PLHIV) (Chaisson & Moore, 1997).

AIDS-related opportunistic diseases are directly linked to many negative personal effects. These include reducing patient's quality of life, speed-up HIV progression rate, affect patient's response to ART specifically in HIV/TB co-infection, increase stigma, limit patient's ability to personal development and social functions, and are associated with high medical costs (Chaisson & Moore, 1997; Staine, 2007). Opportunistic conditions therefore are a precursor to poverty at both family and national level and remain a major cause of morbidity/mortality among PLHIV even after initiating treatment (Simmons *et al.*, 2013; Weldegebreab *et al.*,

2018). Following ART initiation, some patients fail to reach the required ART threshold or a sustained response to antiretroviral agents leading to death (Benson *et al.*, 2004; FMOH, 2008). Factors such as late HIV diagnosis, initial acquisition of drug-resistant HIV strain, suboptimal ART use and/or poor adherence, drug toxicities and interactions, poverty, poor nutrition and high exposure to infections have been attributed to mortality post-ART initiation (Bonnet *et al.*, 2005; Brooks *et al.*, 2009; Corey *et al.*, 2007; Manosuthi *et al.*, 2007; Moges & Kassa, 2014; Paton *et al.*, 2006; Sun *et al.*, 2006).

Although the natural pathophysiological pattern of HIV tends to be similar in most patients, the patterns of ODs that largely define the symptomatic and clinical manifestation of HIV infection tend to differ across different global regions (Colebunders & Latif, 1991; Holmes *et al.*, 2003; Selik *et al.*, 1987). There is therefore existing disparity in magnitude and profile of AIDS-related opportunistic conditions between high-income and low-income countries and within the low-middle income countries (Iroezindu, 2016; UNAIDS, 2017a; WHO, 2007). Thus; while HIV patients in developed nations rarely suffer from serious ODs, these remain major morbidity and mortality causes within resource-limited nations (Benson *et al.*, 2004; Corey *et al.*, 2007; Croxford *et al.*, 2017; Ghys *et al.*, 2007; Hogg *et al.*, 1999; Reniers *et al.*, 2014). As such, the need for HIV programmes to determine the magnitudes and profile of ODs affecting PLHIV in any nation is crucially imperative. This will assist to deliver impactful interventions and effectively manage resources.

Since the national scale-up of free antiretroviral drugs (ARVs) to eligible HIV-infected persons in 2004, Malawi has accomplished much in terms of HIV service expansion. Antiretroviral therapy (ART) clinics grew from 9 (in 2003) to 23, 60, 130 and 716 by December 2004, 2005, 2006 and 2015 respectively) (Jahn *et al.*, 2016; NAC, 2003; WHO, 2005). However, despite

the WHO estimates of Malawi's antiretroviral therapy need of approximately 130,000 and 169,000 HIV-infected eligible patients in 2003 to 2005; only 4,000, 13,000 and 28,110 HIV-positive patients received ART in 2003, 2004 & 2005 respectively (Jahn *et al.*, 2016; NAC, 2003; WHO, 2005). By December 2015, 68% of approximately 1.1 million Malawi's HIV population was receiving ART (Malawi-MoH, 2017; MOH, 2017; WHO & UNAIDS, 2016). Moreover, the 2016/2017 indicators progressively shown Malawi being on course with the WHO's 90-90-90 targets (Chirwa *et al.*, 2018; Malawi-MoH, 2017; UNAIDS, 2017b). Furthermore, evidence indicates that HIV prevalence among the 15-49-year-olds has been declining steadily from 16.4% in 1999 to 11.8% in 2004 and 10.8% in 2010 and presently; 9.2% in 2018 (UNAIDS, 2019b; UNAIDS & MOH, 2015). The country's rapid and successful ARV scale-up from 2004-2015 has markedly changed HIV epidemic trajectory and reduced its incidence, mortality, and morbidity. By December 2015, 1 in 20 HIV-infected adults were on antiretroviral treatment, thereby averting approximately 275,000 deaths and gaining 1.4 million life-years of mostly young adults in their peak productive life (UNAIDS & MOH, 2015). By Dec 2018, 90% of PLHIV knew their status, of which 87% were on treatment and 89% were virally suppressed (AVERT, 2019; UNAIDS, 2019b).

However, despite tremendous gains, the incidence and prevalence of AIDS-related opportunistic diseases in Malawi remains arguably high in both ART-exposed and ART-naïve patients (Geubbels & Bowie, 2006; Kalua *et al.*, 2018). However, nationwide evidence of their magnitudes and profiles, and distribution patterns and aetiological factors, are lacking. Few studies have concentrated on data from individual ART centres with relatively small sample sizes, and mainly targeting specific clinical conditions, thereby, limiting their generalisability (Caruz *et al.*, 1998; Geubbels & Bowie, 2006; Jahn *et al.*, 2016; Kanyerere *et al.*, 2016; Kumwenda *et al.*, 2001; MDHS, 2010; Pilcher *et al.*, 2004; van Oosterhout *et al.*, 2005). This

study intends to address this deficit and provide national representative data on AIDS-defining and recurrent opportunistic conditions (ADROC) among HIV-infected adults on combined antiretroviral therapy (cART) in Malawi. Besides, the study aims to compare ADROC trends during early and late ART periods.

MATERIALS AND METHODS

Study settings

This study was conducted in 8 ART facilities randomly selected across all three regions of Malawi. These are specialised clinics dedicated to HIV care, majority of which are within existing health facility establishments. Data collection centres included one primary level (health centre) facility, 4 secondary level (district hospitals) and 3 tertiary level (central hospitals) facilities. Despite differences in facility's levels, in general, routine activities at each facility included assessment of patients prior to admission into care. HIV-infected persons are referred from either satellite HIV testing centres or screened from the facility's general out-patient department, accident and emergency or in-patient wards and from antenatal clinics under Option B+/PMTCT criteria. At the ART centre, patients are re-tested of HIV (confirmatory testing) before admitted into HIV care. Those with a positive confirmatory HIV test are screened for existence of comorbid conditions (ODs) and ART eligibility. Traditionary, screening involved classifying patients into WHO clinical stages I-IV of HIV, but later included baseline CD4 cell count (and viral load levels, where required) measurements. WHO stage III & IV and low CD4 count below recommended thresholds have traditionary been treatment-initiation criteria and such patients were commenced on standardised antiretroviral therapy. If patient's condition does not satisfy ART-initiation (based on guidelines in use), they were closely monitored with 3-month scheduled clinical reviews or whenever the person feels

unwell, except mothers under Option B+/PMTCT criteria since July 2011. Since 2016, the guidelines treatment-eligibility have however changed test-and-treat whereby, every HIV-positive person is expected to commence treatment regardless of stage, CD4 count or pregnancy/breastfeeding. This study recruited only patients who were eligible for and commenced on standard ART regimen, regardless of present outcome. HIV patients' medical records called ART Master cards were used as sampling frames.

Study Design and Study Participants

A retrospective chart review (RCR) study was conducted between March and May 2016. Subjects were HIV-infected adults aged 15+ years who commenced antiretroviral therapy under the standardised treatment protocols between Jan 2004 and Dec 2015. Participants were randomly selected from the 8 participating health facilities. All [AIDS-defining](#) and [recurrent opportunistic conditions \(diseases\)](#) were considered as study outcomes.

Study time was structured into two time-periods corresponding to major milestones in HIV management in relation to treatment initiation clinical eligibility criteria. The first period was designated "early-ART 2004-2011". This refers to period between 2004-2011 when cART was initiated to only severely ill patients with either clinical stage III or IV of HIV disease or, CD4 cell count <200 cells/ μ L. This was based on 2003 & 2006 WHO recommended guidelines for ART initiation (Jahn *et al.*, 2016; MOH, 2011; WHO, 2006; WHO, 2010b; WHO, 2010c; WHO, 2013). The second period was designated "late-ART (2011-2015)" and refers to period between 2011-2015 when ART access was expanded to include patients with CD4 count $\leq$ 350 cells/ μ L regardless of WHO clinical stage (MOH, 2011; WHO, 2010b; WHO, 2010c; WHO, 2013).

Sample Size and Sampling Procedure

The sample size was determined using the following simple formula and assumptions recommended and endorsed for prevalence studies (Charan & Biswas, 2013; Daniel, 1999; Daniel & Cross, 2013; Gorstein *et al.*, 2007; Hajian-Tilaki, 2011; Naing *et al.*, 2006):

$$n = Z \frac{\alpha^2}{2} \left(\frac{P(1-P)}{d^2} \right) \times D$$

Where: n = is the sample size; P = expected prevalence of ODs in Malawi @ 10.6% based on 2010 MDHS; d = margin of error between sample and population sizes (n vs N) (0.006); $Z \frac{\alpha^2}{2}$ = statistical critical value at 95% confidence interval (1.96); D = design effect for a cluster sampling of sampling frames (DHOs, health facilities & ART Master cards) estimated @ 2.0.

The estimated sample size; ($n=8,654$), was adjusted by 15% allowance to compensate for poor medical records documentation observed during the pilot study, resulting in final sample size of ($n=9,953$). A three-stage systematic sampling method was used to select the required health facilities and medical records. To select health facilities, the 2015 Ministry of Health HIV Unit report was used (Jahn *et al.*, 2016; NAC/MOH & UNAIDS, 2015). The report stated that a total of 716 ART facilities were operational in Malawi (*ibid.*). It was further established that 4 of these ART centres were in central hospitals, 44 in district and CHAM hospitals, 35 in rural hospitals and 328 in health centres while the rest ($N=305$) were dispensaries and private hospitals. For this study, only static, public sector, and not-for-profit health facilities ($N=411$), across all administrative District Health Offices (DHOs) were considered as potential data collection centres. I determined to sample from 8 ART centres from 5 DHOs and proportionally divide the sample size according to per-facility patient load. Participating DHOs and ART facilities were randomly selected using probability sampling techniques; stratified random

sampling and the systematic random sampling from the formula.... $K=N/n$ (Trochim, 2000; Trochim, 2007)

.....where

- N is the number of cases (DHOs or ART Centres) in the sampling frame.

- n is the number of cases (DHOs or ART Centres) in the sample.

The procedure involved stratifying participating sites and subjects into DHOs, ART facilities and patients' medical records (the Master cards). The randomly selected DHOs were Mzimba, Lilongwe, Blantyre, Thyolo and Chiradzulu, which together contributed a total of 238 static ART centres. Furthermore, independently, 3 central hospital-based, 4 district hospital-based and 1 health centre-based ART facilities were randomly selected as data collection centres.

At each ART centre, exclusion criteria were applied to the main data frame [N_1], to form a stratum of eligible patients [N_2], the final data frame. Likewise, the sampling procedure was replicated to randomly select medical records from N_2 . Then, anonymised patients' serial numbers [from (N_2)] were randomly listed from which... $n_1, n_2, n_3, n_4, n_5, \dots, n_x$ serial numbers were randomly picked.

Data Collection Tools and Procedures

Data were collected using an electronic ADROC research tool developed *a priori*. The data collection tool reflected information on the ART master card – a patient medical record used from point of entry to ART services. The tool was specifically designed to capture data on both prevalent and incident AIDS-associated clinical conditions and their associated factors. The tool was piloted at 2 centres; a central hospital and district hospital based centres following which, minor amendments were made. At every centre I recruited and trained a sizable research

team with unrestricted access to the local data. The teams were trained on the contents of the tool and how to use it to collect relevant data.

Data Management and Quality Assurance

Strict adherence to data collection standards was encouraged and closely monitored at each centre by close supervision of data extraction exercise. Data were checked for completeness and consistency and randomly double-entered to ensure high data quality from point of entry.

Data Analysis

Descriptive statistics were used to analyse socio-demographic and clinical parameters. For continuous variables, mean with standard deviation ($\pm$ SD) and median with interquartile range (IQR) were reported. Findings between patient with and patients without manifestation of aetiological factors or the opportunistic disease were compared. The two-sample *t*-test (and the one-way analysis of variance, where appropriate) were used to determine and compare statistically significant differences between means of independent variables. For categorical variables, frequency or proportion values were expressed as absolute numbers or percentages and differences compared between the two patient groups for statistical significance using Chi-square test. Bivariable logistic regression was used to determine crude associations between independent variables and OD manifestations. Odds ratios with 95% confidence intervals (OR 95% CI) were used as a measure of association. Multivariable analysis was used to determine independent effects of selected variables on OD manifestation while controlling for the effects of other variables in a complete case analysis. Independent factors with a $p \leq 0.25$ from the crude analysis were entered into final model with associations reported as adjusted odds ratio (aOR, 95% CI). Significance level was set by a two-tailed alpha (α) of 0.05. The multicollinearity

tolerance test, Hosmer-Lemeshow test and the linktest regression diagnostic tests were used to judge goodness-of-fit of final model. Data analysis was conducted using Stata software special edition for windows v15.1.

RESULTS

Socio-Demographic Characteristics of Study Participants

The socio-demographic characteristics of participants are presented in Table 1. A total of 9,953 medical records of HIV-infected adults were recruited. These patients were once initiated on ART between Jan 2004 and Dec 2015 following standardised national treatment protocols. Medical records retrieval rate was 100% of the planned records. The overall mean ($\pm$ SD) age was 40.72 ± 12.19 years. Most subjects were females (60.84%), which were also relatively younger than males; mean age: 38.86 vs 43.61 years respectively, and significant mean age difference of 4.75 years ($p < 0.0001$). 83.25%, were young, middle-aged adults of productive group aged 20-54 years old. Majority of patients (65.08%) were urban residents and from Southern region (59.55%) while Northern and Central regions accounted for 15.92% and 24.53% respectively. 78.76% were married and 13.87% were either divorced or widowed while only 7.36% were ever-single. The preponderance (67.68%) were recruited from tertiary-level health facilities. The proportions of patients with primary and secondary education attainment were indifferent; 33.65% and 32.75% respectively, while 7.16% had no formal education. More than half (55.32%), were permanently employed while the rest were self-employed and 33.62% were engaged in office-based work.

Table 1: Socio-Demographic Characteristics of HIV-infected Adults on Combined Antiretroviral Therapy in Malawi, 2004- 2015

Characteristic	Number (%)	Characteristic	Number (%)
Care type		Marital status	
Primary care	735 (7.38)	Previously married	1,380 (13.87)
Secondary care	2,482 (24.94)	Married (partnership)	7,837 (78.74)
Tertiary care	6,736 (67.68)	Single (never married)	733 (7.36)
Total	9953 (100.00)	Total	9953 (100.00)
Gender		Education levels	
Female	6,055 (60.84)	No education	713 (7.16)
Male	3,898 (39.16)	Primary	3,349 (33.65)
Total	9953 (100.00)	Secondary	3,260 (32.75)
Age-range (years)		Higher	2,631 (26.43)
15-19 (Adolescents)	358 (3.60)	Total	9953 (100.00)
20-39 (Young adults)	4,501 (45.22)	Employment status	
40-54 (Mid-Aged Adults)	3,785 (38.03)	Employed	5,506 (55.32)
55+ (Older Adults)	1,306 (13.12)	Self-employed	4,447 (44.68)
Total	9953 (100.00)	Total	9953 (100.00)
Residential area		Occupation classification	
Rural	2,047 (20.57)	Manual jobs	1,658 (16.66)
semi-urban	1,427 (14.34)	Others job types	4,949 (49.72)
Urban	6,477 (65.08)	White collar jobs	3,346 (33.62)
Total	9953 (100.00)	Total	9953 (100.00)
Regional area		ART-initiation criteria	
Central Region	2,441 (24.53)	CD4+ count	2,475 (24.87)
Northern Region	1,585 (15.92)	PMTCT	261 (2.62)
Southern Region	5,927 (59.55)	WHO III	4,781 (48.04)
Total	9953 (100.00)	WHO IV	2,436 (24.48)
Guardian escort		Total	9953 (100.00)
None (no guardian)	1,471 (14.78)		
Yes (with guardian)	8,481 (85.21)		
Total	9953 (100.00)		

Baseline Clinical Characteristics of Study Participants

The clinical characteristics of the study participants are presented in Table 2. All enrolled patients were once initiated on ART following the national standardised treatment protocols. 72.52% commenced treatment with advanced HIV disease: WHO clinical stage III (48.04%) and stage IV (24.48%). Moreover, 27.49% were asymptomatic when commenced treatment. Thus, these had either low CD4 cell count below recommended threshold (24.87%) or were under the Option-B+/PMTCT criteria (breastfeeding or pregnant) (2.62%).

Overall, the mean $\pm$ SD clinical latency was 527.11 $\pm$ 324.93 days and was somewhat shorter in females; mean difference: 28.49 days but lacked statistical significance ($p=0.0926$).

The mean HIV duration was 2,331.41 $\pm$ 1,387.99 days while mean ART duration was 1,805.15 $\pm$ 1,135.99 days. Although all patients commenced treatment following standardised regimes protocols; 67.10% were commenced with Efavirenz-based regimen, 28.53% with Nevirapine-based regimens while a small proportion (4.37%), were started on treatment using non-standard ART regimens. Of all participants, 95.41% were continued on first-line ART regimens while 3.29% (N=327) had been switched onto second-line regimen; the boosted-Ritonavir formulations. This means that these patients had first-line antiretroviral treatment failure. Only 1.31% (N=130) were receiving NS formulations as maintenance regimens.

Data on clinical surrogate makers; CD4 count and viral load test results, were extracted at two time-points: as initial (baseline) and as subsequent results (the latter was the most recent available test result). Overall, the mean ($\pm$ SD) initial CD4 count was 145.08 $\pm$ 95.05 cells/ μ L. Most patients; 68.69%, were severely immunosuppressed with initial CD4 count <250 cells/ μ L. Following ART treatment, test results in most patients improved considerably to normal healthy adult levels. Such that, the overall mean ($\pm$ SD) subsequent CD4 count was 648 $\pm$ 328.66 cells/ μ L, and 68.59% of patients had subsequent CD4 count >500 cells/ μ L. Correspondingly, most patients had severe virologic failure when they commenced treatment. Thus, with overall mean ($\pm$ SD) initial VL levels of 992,768 $\pm$ 949,436 copies/mL, 78.79% of patients had >100,000 copies/mL initial VL results. Likewise, the overall mean ($\pm$ SD) subsequent VL was relatively lower following cART; 117,083.7 $\pm$ 381,017 copies/mL and up to 70.73% were virally suppressed (VL<1000 copies/mL) of which, (N=3,992) had undetectable viral load results of <40 copies/mL.

Table 2: Clinical Characteristics of HIV-infected Adults on ART in Malawi, 2004-2015

Characteristic	Number (%)	Characteristic	Number (%)
ART-initiation criteria		Current ART regimen type	
CD4+ count	2,475 (24.87)	Nevirapine-based	2,416 (24.27)
PMTCT	261 (2.62)	Efavirenz-based	7,080 (71.13)
WHO III	4,781 (48.04)	Boosted-Ritonavir	327 (3.29)
WHO IV	2,436 (24.48)	Non-std.	130 (1.31)
CD4 initial results		Contraception: Barrier type	
0-250 cells/ μ L	6,956 (69.89)	Yes	7,087 (71.20)
$\geq$ 251 cells/ μ L	2,988 (30.02)	No	2,866 (28.80)
CD4 recent results		HIV duration	
100-500 cells/ μ L	3,125 (31.40)	1-2 yrs.	1,342 (13.48)
501-1,000 cells/ μ L	5,201 (52.26)	3-5 yrs.	2,610 (26.22)
$\geq$ 1001+ cells/ μ L	1,625 (16.33)	6-10 yrs.	4,440 (44.61)
		>10 yrs.	1,561 (15.68)
Initial VL test results		ART duration	
<10,000 copies/mL	798 (8.02)	1-2 yrs.	2,154 (21.64)
10,000-100,000 copies/mL	1,305 (13.11)	3-5 yrs.	3,243 (32.58)
>100,000 copies/mL	7,842 (78.79)	6-10 yrs.	3,933 (39.52)
		>10 yrs.	623 (6.26)
Recent VL tests results		Clinical latency range	
<40 copies/mL	3,992 (40.11)	1-2 years	6,964 (69.97)
40-1,000 copies/mL	3,048 (30.62)	3-5 years	2,259 (22.70)
1,001-10,000 copies/mL	1,041 (10.46)	$\geq$ 6 years	730 (7.33)
10,001-100,000 copies/mL	757 (7.61)		
>100,000 copies/mL	1,115 (11.20)		
Initial ART regimen type		Patient-outcome	
Nevirapine-based	2,840 (28.53)	Treatment adherent	6,758 (67.90)
Efavirenz-based	6,678 (67.10)	Defaulters & LTFU	2,018 (20.28)
Non-std.	435 (4.37)	Died	1,177 (11.83)

Treatment Outcomes Status of Study Participants

Figure 1 illustrates last treatment outcome status recorded during most recent patient follow-up visits. 67.90% of patients were alive and continuing with treatment, 20.28% were either defaulters, lost to follow-up or stopped treatment whereas 11.83% had died.

Figure 1: Treatment Outcomes of cART-exposed adults in Malawi; 2004-2015

The Magnitude and Profile of AIDS-Associated Opportunistic Conditions

From Jan 2004 to Dec 2015, a total of 12,814 episodes of opportunistic disease (AIDS events) were recorded from enrolled patients (N=9,953). 59.01% (N=7,559) cases were prevalent AIDS-defining clinical conditions (ADCCs) that manifested in treatment-naïve patients whereas 40.99% (N=5,255) were incident AIDS-recurrent conditions which manifested in treatment-experienced patients. The overall period prevalence of prevalent OD events among treatment-naïve patients during this period was an estimated 72.55%. In contrast, the overall period prevalence of incident OD events among treatment-experienced patients within the same period was an estimated 55.76% with repeated occurrences in some conditions. Six aetiological agents were responsible for the abstracted opportunistic events and mycobacterial agents were most prevalent (36.31%) while neoplastic conditions were the least manifested with only 3.44% regardless of study's treatment period (Fig. 2). In 7.65% (N=761) of patients, no AIDS event had occurred, hence, remained asymptomatic.

Figure 2: Distribution of AIDS Conditions Aetiological Factors; Total and by ART Periods in Malawi; 2004-2015

The risk of opportunistic diseases occurring ranged from 1–4 times per patient. Most patients (60.25%) had only a single AIDS event episode, 29.17% had dual-AIDS event episodes whereas 2.01% and 0.92% had triple and quadruple opportunistic disease event episodes respectively (Fig. 3).

Figure 3: Frequency of AIDS opportunistic events per patient

Most AIDS event episodes (67.68%), were diagnosed in tertiary health facilities while secondary and primary facilities accounted for 24.94% and 7.38% respectively. Figure 4 illustrates frequencies of new HIV-seropositive cases and frequency of opportunistic diseases stratified by year of enrolment (admission) into HIV care. 16.44% (N=1,636) of HIV cases were diagnosed before 2004 (outside the study period). Within the study period, high new HIV cases were registered into care between Jan 2005 and Dec 2007 with rates of 11.27%, 12.76% and 12.56% respectively. Likewise, OD events rates were higher in 2006 (12.96%) followed by 2005 rates but were least in 2015 (1.62%).

Figure 4: Frequency of HIV diagnosis cases and ODs by enrolment year; 2004-2015

The Prevalence of Opportunistic Diseases

The frequency of opportunistic diseases among enrolled patients is given in Table 3. Overall, tuberculosis (TB) was most prevalent OD (35.39%). Based on clinical classification of TB, pulmonary tuberculosis (PTB) was more prevalent (20.44%) than extrapulmonary type (EPTB, 13.95%). Other most occurring ODs included bacterial pneumonia (11.53%), non-typhoid

311 salmonella bacteraemia (9.85%), HIV wasting syndrome (9.02%), candidiasis (7.01%),
 312 isosporiasis (5.17%), pneumocystis pneumonia (4.02%) and cryptococcal meningitis (3.72%).
 313

314 **Table 3: Frequency of ADI Events Stratified for ART-Initiation Period and Health Facility Type**

	Overall	Early-ART (2004-2011)	Late-ART (2011-2015)	Tertiary healthcare facilities	Secondary healthcare facilities	Primary healthcare facilities	OR (95% CI): primary & secondary rates Vs tertiary h/facilities
AIDS condition	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)	
M. Tuberculosis	4392 (34.39)	3482 (34.20)	910 (35.14)	3027 (25.75)	1019 (24.53)	346 (27.20)	1.11 (1.02, 1.21)**
Pulmonary tuberculosis	2611 (20.44)	2067 (20.30)	544 (21.00)	1853 (21.23)	553 (17.63)	205 (22.14)	1.23 (1.12, 1.36)**
Extrapulmonary tuberculosis	1781 (13.95)	1415 (13.89)	366 (11.13)	1174 (13.45)	466 (14.86)	141 (15.23)	0.91 (0.81, 0.98)**
Bacterial pneumonia	1431 (11.53)	1156 (11.35)	275 (10.62)	937 (7.97)	406 (9.77)	88 (6.92)	0.89 (0.79, 0.98)**
Nontyphoid Salmonella bacteraemia	1222 (9.85)	985 (9.67)	237 (9.15)	793 (6.75)	352 (8.47)	77 (6.05)	0.87 (0.76, 0.98)**
HIV-wasting syndrome	1140 (9.02)	914 (8.98)	226 (8.73)	738 (6.28)	314 (7.56)	88 (6.92)	0.86 (0.76, 0.98)**
Candidiasis	870 (7.01)	694 (6.82)	176 (6.80)	588 (5.00)	214 (5.15)	68 (5.35)	0.99 (0.85, 1.15)
Isosporiasis	669 (5.17)	527 (5.18)	142 (5.48)	460 (3.91)	167 (4.02)	42 (3.30)	1.05 (0.89, 1.24)
Pneumocystis pneumonia	513 (4.02)	407 (4.00)	106 (4.09)	364 (3.10)	117 (2.82)	32 (2.52)	1.18 (1.09, 1.43)**
Cryptococcal meningitis	475 (3.72)	385 (3.78)	90 (3.47)	332 (2.82)	114 (2.74)	29 (2.28)	1.11 (1.09, 1.36)**
Cryptosporidiosis	376 (2.94)	293 (2.88)	83 (3.20)	266 (2.26)	81 (1.95)	29 (2.28)	1.61 (0.93, 1.45)
Herpes Simplex virus	300 (2.35)	247 (2.43)	53 (2.05)	198 (1.68)	81 (1.95)	21 (1.65)	0.92 (0.73, 1.18)
Kaposi's Sarcoma (KS)	298 (2.33)	242 (2.38)	56 (2.16)	199 (1.69)	72 (1.73)	27 (2.12)	0.96 (0.75, 1.22)
Nontuberculous mycobacteria (NTM)	245 (1.92)	199 (1.95)	46 (1.78)	169 (1.44)	56 (1.35)	20 (1.57)	1.06 (0.81, 1.40)
Cytomegalovirus infection	160 (1.25)	114 (1.12)	46 (1.78)	146 (1.24)	10 (0.24)	21 (1.65)	5.07 (2.98, 8.79)**
Mycosis	156 (1.22)	116 (1.14)	40 (1.54)	138 (1.17)	12 (0.29)	6 (0.47)	3.72 (2.27, 6.09)**
HIV-encephalopathy	137 (1.07)	108 (1.06)	29 (1.12)	100 (0.85)	34 (0.82)	3 (0.24)	1.30 (1.18, 1.89)**
Invasive Cervical Cancer	108 (0.85)	82 (0.81)	26 (1.00)	81 (0.69)	20 (0.48)	7 (0.55)	1.43 (1.39, 2.23)**
HIV-cardiomyopathy	82 (0.64)	67 (0.66)	15 (0.58)	52 (0.44)	28 (0.67)	2 (0.16)	0.83 (0.53, 1.30)
HIV-nephropathy	69 (0.54)	54 (0.53)	15 (0.58)	49 (0.42)	15 (0.36)	5 (0.39)	1.17 (0.70, 1.97)
Toxoplasmosis	53 (0.42)	45 (0.44)	8 (0.31)	40 (0.34)	6 (0.14)	7 (0.55)	1.47 (1.38, 2.76)**
Progressive multifocal leukoencephalopathy	42 (0.33)	36 (0.35)	6 (0.23)	29 (0.25)	7 (0.17)	6 (0.47)	1.07 (0.55, 2.05)
Non-Hodgkin's lymphoma	33 (0.26)	28 (0.28)	5 (0.19)	21 (0.18)	10 (0.24)	2 (0.16)	0.83 (0.41, 1.70)
Totals	12,814 (100%)	10,181 (100%)	2,590 (100%)	8,727 (100%)	3,135 (100%)	926 (100%)	--

** statistically significant odds ratio of primary & secondary health facilities' rates Vs tertiary health facilities

Most AIDS conditions tended to be diagnosed in tertiary health facilities compared to primary and secondary facilities combined. Thus, mycobacterial tuberculosis [OR=1.11, 95% CI: (1.02, 1.21)], cytomegalovirus infection: [OR=5.07, 95% CI: (2.98, 8.79)], mycosis [OR=3.72, 95% CI: (2.27, 6.09)], toxoplasmosis [OR=1.47, 95% CI: (1.38, 2.76)], HIV encephalopathy [OR=1.30, 95% CI: (1.18, 1.89)] and invasive cervical cancer [OR=1.43, 95% CI: (1.39, 2.23). In a general viewpoint, the estimated OD prevalence during early-ART (2004-2011) and late-ART (2011-2015) periods mostly proportionally indifferent. For example, TB prevalence during early-ART was 34.2% compared to 35.14% during late-ART while candidiasis was 6.82% versus 6.8% for early-ART and late-ART periods, respectively.

PREDICTORS AND RISK FACTORS OF AIDS OPPORTUNISTIC DISEASE EVENTS BASED ON AETIOLOGICAL FACTORS.

Factors Associated with AIDS-related Bacterial Opportunistic Diseases

The crude and adjusted associations of AIDS-related bacterial disease manifestation are given in [Table 4](#). AIDS-associated bacterial diseases include bacterial pneumonia and nontyphoid *Salmonella* bacteraemia. In the multivariable regression analysis, health facility level, residential and regional areas, marital and employment status, treatment initiation criteria, CD4 cell count and viral load levels, remained statistically significantly associated with manifestations of bacterial opportunistic conditions. Such that, patients from secondary level health facilities were 34% more likely to have had bacterial ODs compared to those from primary level facilities [aOR 1.34, 95% CI: (1.08, 1.66)]. Urban residents were 15% more likely to manifest bacterial conditions compared to rural residents [aOR 1.15, 95% CI: (1.01, 1.30)]. Compared with patients from central region, those from southern region were 9% more likely: [aOR 1.09, 95% CI: (1.07, 1.23)], whereas those from northern region were 21% less

likely [aOR 0.79, 95% CI: (0.67, 0.94)] to manifest bacterial conditions. Ever-single patients had 51% higher probability of bacterial conditions than previously married ones, [aOR 1.51, 95% CI: (1.20, 1.90)] and self-employed patients were 12% less likely to manifest bacterial conditions [aOR 0.88, 95% CI: (0.79, 0.97)].

Compared to patients who commenced treatment due to low CD4 count, those advanced disease: clinical stage III of HIV were >2 times more likely, [aOR 2.22, 95% CI: (1.93, 2.55)] and those with clinical stage IV were nearly 2 times more likely, [aOR 1.98, 95% CI: (1.71, 2.31)] to have had bacterial OD manifestation. Consequently, increased recent subsequent CD4 count of >1000 cells/ μ L was associated with 10% reduction in the manifestation of bacterial ODs compared to having CD4 count <500 cells/ μ L, [aOR 0.90, 95% CI: (0.76, 0.96)]. Likewise, patients with high initial (baseline) viral failure of >1000 copies/mL were 92% more likely to have bacterial condition compared to those with VL<1000 copies/mL. Treatment defaulters were 24% more likely to have had bacterial conditions than patients continuing with treatment (aOR 1.24 , 95% CI: (1.02, 1.49)).

Factors Associated with AIDS-related Fungal Opportunistic Diseases

Fungal opportunistic conditions accounted for 15.68% of all AIDS-conditions and include candidiasis, pneumocystis pneumonia, cryptococcal meningitis and mycosis. The crude and adjusted associations of AIDS-related fungal disease manifestations are given in [Table 4](#). In the multivariable analysis, patients from secondary and tertiary healthcare facilities were 33%, [aOR 1.33, 95% CI: (1.26, 4.91), nearly 4½ times more likely to manifest fungal AIDS-condition, aOR, 4.42, 95% CI: (1.38, 14.07)], compared to patients in primary facilities. Compared with patients from rural areas, the risk of fungal conditions was increased by 15% and 52% among patients from urban and semi-urban areas, [aOR 1.15, 95% CI: (1.09, 1.93)]

and aOR=1.52, 95% CI: (1.48, 2.76)] respectively. Patients with advanced HIV disease: clinical stage III and stage IV at commencement of antiretroviral treatment were 18% and 85% more likely to have had a fungal OD, [aOR 1.18, 95% CI: (1.03, 1.36)], and [aOR 1.85, 95% CI: (1.59, 2.16)] respectively, compared to patients who commenced treatment due to low CD4 count. Patients with initial CD4 count >250 cells/ μ L were 49% less likely to have had fungal disease compared to those with <250 cells/ μ L, [aOR 0.59, 95% CI: (0.52, 0.66)]. Similarly, patients with recent subsequent CD4 count between 500-1000 cells/ μ L and >1000 cells/ μ L, were both less likely to have had fungal opportunistic diseases, [aOR 0.61, 95% CI: (0.38, 0.98) and aOR 0.68, 95% CI: (0.38, 0.73)] respectively, compared to those with <500 cells/ μ L recent CD4 count. Consequently, the likelihood of fungal OD manifestation was increased by 70% among patients with >1000 copies/mL baseline (initial) viral load compared to those with <1000 copies/mL, [aOR 1.70, 95% CI: (1.23, 2.35)]. Other factors with increased risk of fungal conditions were 20-39 years age-group (7%) compared to 15-19 years old and being married (9%) compared to previously married. However, having primary or secondary education attainment were both associated with reduced risk of fungal diseases by 3% and 7%, respectively, compared to patients with no education attainment. Compared to treatment compliant, noncompliant patients: defaulters or lost-to-follow-up (LTFU) was 78% more likely to have had fungal condition [aOR 1.78, 95% CI: (1.64, 1.97)].

Factors Associated with AIDS-related Viral Opportunistic Diseases

Viral diseases accounted for 14.4% of all AIDS-events in this study. In the multivariable analysis outlines in [Table 5](#), patients attending secondary and tertiary health facilities were respectively, approximately 4 times and 5 times more likely to have had viral ODs, [aOR 3.72, 95% CI: (1.88, 15.79) and 4.72, 95% CI: (1.15, 19.32)], compared to those attending primary

level health facilities. Equally, compared to rural residents, patients from semi-urban and urban areas were 23% and 13% more likely to have had viral disease, [aOR 1.23, 95% CI: (1.02, 1.48) and aOR 1.13, 95% CI: (1.08, 2.48)]. Similarly, patients from southern region were 14% more likely to manifest viral diseases compared to those from central region, [aOR 1.14, 95% CI: (1.01, 1.30)] and married patients were 95% more likely to have had viral OD than previously married patients, [aOR 1.95, 95% CI: (1.81, 3.51)]. Compared to patients initiated cART for low CD4 count, those with advanced HIV disease; clinical stage III and stage IV, were respectively 43% and 75% more likely to have had a viral OD: [aOR 1.43, 95% CI: (1.23, 1.65), and [aOR 1.75, 95% CI: (1.49, 2.06)].

Patients with initial severe viraemia: baseline VL >1000 copies/mL were 92% more likely to have had viral condition compared to those with <1000 copies/mL, [aOR 1.92, 95% CI: (1.67, 2.28)]. Likewise, patients with recent subsequent suppressed viraemia: VL between 40-1000 copies/mL, were 37% more likely to have had viral OD, [aOR 1.37, 95% CI: (1.29, 2.04) whilst those with severe viraemia: VL >1000 copies/mL, over 2 times more likely [aOR=2.23, 95% CI: (1.82, 2.55)], compared to those with undetectable. Similarly, the probability of viral OD manifestation was increased by 79% and 83% with HIV duration of 6-10 years and >10 years, respectively compared to patients with shorter HIV duration of <2 years, [aOR 1.79, 95% CI: (1.43, 2.46)] and [aOR 1.83, 95% CI: (1.41, 3.68)].

The odds of manifesting viral ODs were reduced by 27% and 26% among patients aged 20-39 years and 40-54 years compared to those aged 15-19 years and by 31% in individuals with higher education level compared to those with no education, [aOR 0.39, 95% CI: (0.35, 0.97)]. Patients initiated treatment under the universal Option B+/PMTCT criteria were 35% less likely to manifest viral ODs compared to those commenced treatment because of having low

CD4 count, [aOR 0.65, 95% CI: (0.42, 0.91)], and by 11% among patients with recent subsequent CD4 count >1000 cells/ μ L than those with 100-500 cells/ μ L.

Factors Associated with AIDS-related Mycobacterial Opportunistic Diseases

Mycobacterial opportunistic diseases accounted for 37.24% of all AIDS-conditions in the study and they include both types of *mycobacterium tuberculosis* (TB) and non-tuberculous mycobacteria (NTM). In the multivariable logistic regression analysis outlined in [Table 5](#), mycobacterial conditions were statistically significantly increased by 8% among patient from northern region compared to those from central region, [aOR 1.08, 95% CI: (1.04, 1.23)]. The prevalence was likewise increased by 16%, 18% & 23% among individuals with primary, secondary, and higher levels of education compared to those without education ($p<0.05$). Likewise, mycobacterial OD occurrence was increased by 3-fold and 73% in patients with clinical stage III and stage IV at treatment initiation, [aOR 3.13, 95% CI: (2.80, 3.49)], and [aOR 1.73, 95% CI: (1.1.53, 1.96)] compared to those with low CD4 count. Correspondingly, the likelihood of mycobacterial condition manifestation was increased by 21% in patients with initial baseline VL >1000 copies/mL compared to those with <1000 copies/mL and by 51% in those receiving non-standard ART regimen as maintenance treatment than those maintained on Nevirapine-based regimens, [aOR 1.51, 95% CI: (1.03, 2.19)]. Compared to patients with 1-2 years HIV duration, those with 3-5 years, 6-10 years and >10 years of living with HIV were 10%, 12% and 19% more likely to have had AIDS-related mycobacterial opportunistic conditions.

In contrast, the probability of mycobacterial opportunistic disease occurrence was reduced by 25% among patients with initial CD4 count >250 cells/ μ L compared to those with <250

cells/ μ L, [aOR 0.75, 95% CI: (0.55, 0.96)]. The probability was equally reduced by 23% and 15% in secondary and tertiary hospital health facilities compared to patients in primary level health facilities, [aOR 0.77, 95% CI: (0.64, 0.92) and aOR 0.85, 95% CI: (0.72, 0.91)] and by 55% among patients initiated treatment due to Option B+/PMTCT than those initiated due to low CD4 count, [aOR 0.45, 95% CI: (0.32, 0.64)].

Factors Associated with AIDS-related Protozoal (Parasitic) Opportunistic Diseases

The crude and adjusted regression analysis results of protozoal diseases are summarized in [Table 6](#). AIDS-defining protozoal conditions include cryptosporidiosis, isosporiasis and toxoplasmosis and accounted for 8.2% of all AIDS events in this study. In the multivariable analysis, male patients were 5% more likely to have had protozoal conditions compared to females, [aOR 1.05, 95% CI: (1.02, 1.25)]. Similarly, office-based workers were 26% more likely to have had protozoal conditions than manual workers; [aOR 1.26, 95% CI: (1.05, 1.58)]. Patients with stage III and stage IV of HIV disease at ART initiation were 36% and 26% respectively, more likely to manifest protozoal OD compared to those initiated treatment due to low CD4 count, [aOR 1.36, 95% CI: (1.1.13, 1.64)] and [aOR 1.26, 95% CI: (1.02, 1.56)]. Patients with high initial viral failure: VL>1000 copies/mL were 15% more likely to have had protozoal condition than those with VL<1000 copies/mL, [aOR 1.15, 95% CI: (1.07, 1.79)].

Furthermore, patients on non-standard ART maintenance regimens were 78% more probable to have had protozoal infections compared to those maintained on nevirapine-based regimens, [aOR 1.78, 95% CI: (1.08, 2.93)]. Above the expectation, patients with >10 years treatment duration were 71% more probable to have had a protozoal disease compared to those with <2 years on treatment, [aOR 1.71, 95% CI: (1.05, 3.08)].

In contrast, the probability of protozoal OD manifestation significantly reduced by 35%, 32% and 44% among patients aged 20-39 years, 40-54 years, and 55+ years old compared to those aged 15-19 years. Likewise, the probability was reduced by 19% and 23% among patients with recent subsequent CD4 count between 500-1000 cells/ μ L and >1000 cells/ μ L compared with those with <500 cells/ μ L. Equally, patients commenced treatment with Efavirenz-based regimens had 17% less likelihood of manifesting protozoal conditions compared to those commenced on Nevirapine-based regimens, [aOR 0.83, 95% CI: (0.71, 0.97)].

Factors Associated with AIDS-related Neoplastic Opportunistic Diseases

AIDS-related opportunistic neoplastic diseases accounted for only 3.1% of all AIDS events in the study. They include invasive cervical cancer, Kaposi' sarcoma and non-Hodgkin lymphoma (WHO, 2007). The crude and adjusted associations of AIDS-related bacterial disease manifestation are given in [Table 6](#).

In the multivariable analysis, patients from secondary and tertiary health facilities were 86% and 94% more likely to have had opportunistic neoplasm compared to those attending primary health facilities, [aOR 1.86, 95% CI: (1.55, 2.35) and aOR 1.94, 95% CI: (1.63, 2.42)]. Small-scale unskilled workers were 48% more likely to have had neoplasm compared to those doing manual work, [aOR 1.48, 95% CI: (1.05, 2.08)]. Equally, compared to patients initiated treatment for low CD4 count, those who had advanced HIV disease – WHO clinical stage IV were over 3 times more likely to have had opportunistic neoplasm, [aOR 3.24, 95% CI: (2.46, 4.27)]. Patients with initial baseline VL >1000 copies/mL were 74% more likely to have had HIV-related cancer than those with <1000 copies/mL, [aOR 1.74, 95% CI: (1.39, 2.40)].

In contrast, the probability of opportunistic neoplasms were significantly reduced by 27% in males compared to females, [aOR 0.73, 95% CI: (0.56, 0.95)]; by 42% among ever-single patients compared to previously married. Patients who commenced treatment because of universal Option B+/PMTCT criteria had 77% reduced probability of manifesting neoplasm [aOR 0.23, 95% CI: (0.06, 0.96)]. Similarly, those commenced under clinical stage III of HIV had 31% reduced probability [aOR 0.69, 95% CI: (0.49, 0.97)] compared to those started treatment due to low CD4 count.

DISCUSSION

This retrospective chart review study has elucidated common types and magnitude of opportunistic diseases prevailing among adult PLHIV in Malawi on combined antiretroviral therapy. The study has also outlined factors associated with the manifestation of AIDS-related opportunistic diseases aetiological agents.

Participants were once commenced on regular ART under the national standardised treatment protocol between 2004-2015. We extracted all AIDS-related conditions that are traditionally AIDS-defining (both incident and prevalent cases) that occurred among the enrolled patients during the 11 year data generation period. Opportunistic events frequency ranged from 1- 4 times per patient such that 60.25%, 29.17%, 2.01% and 0.92% of patients had single, dual, triple, and quadruple opportunistic events.

The overall cumulative period prevalence of ODs in the present study was remarkably high (128.31%) due to repeated occurrences. This finding compares with 120.97% overall prevalence from Taiwan University Hospital study which reported a total of 1,263 OD events

from (n=1,044) patients (Sun *et al.*, 2006). However, our finding is much lower than 268.06% overall prevalence estimated from TASO HIV facilities in Uganda which reported a total of 291,168 OD episodes from (n=108,619) HIV patients from 2001 to 2013 (Rubaihayo *et al.*, 2016).

Of all AIDS-opportunistic events identified in this study (N=12,814), 59.01% were prevalent cases whereas 40.99% were incident cases. Therefore, the prevalence of incident ODs affecting adult PLHIV on ART in Malawi between 2004 and 2015 was an estimated 55.76% with repeated occurrences. This finding is comparable to 48.0% prevalence reported in Hiwot Fana Hospital (Mitiku *et al.*, 2015); 42.8% prevalence reported in Debre Markos Hospital (Moges & Kassa, 2014) both from Ethiopia. The finding is likewise comparable to 47.6% prevalence reported from both Taiwan University Hospital (Sun *et al.*, 2006) and from Tshepang Clinic South Africa (Mzileni *et al.*, 2008). However, this finding is relatively higher than 19.7% prevalence reported in Gondar Hospital (Damtie *et al.*, 2013), 22.4% prevalence reported in South East Nigeria (Iroezindu, 2013) and 30% prevalence reported in Bamrasnaradura institute Thailand (Knauer *et al.*, 2005). The observed difference between the current study and studies that reported lower prevalence could be due to methodological differences in subject selection, study period, diagnostic capacity, or degree of host immunity. For example, Gondar Hospital study period was short (February-April, 2012) and involved both treatment naïve and exposed patients, the study from Nigeria was conducted for median duration of 3 years while the Thailand study had a 15 month follow-up period.

The present study summarised clinical data representing 1.0% of people living with HIV in Malawi and 1.03% of HIV infected adults accessing antiretroviral therapy. Majority were urban residents (65.08%) within the productive group of 15-49 years (78.22%) and women (60.84%).

Moreover, 82.21% relied guardian escort to health facility which may signify poor physical condition during initial presentation. Most patients were married (78.74%), had low education (40.81%), and were of low socio-economic status (49.72%) engaged in unskilled jobs although the majority were permanently employed (55.32%). The nature of patients in the current study is comparable to other studies elsewhere within the sub-Saharan Africa region ART programmes such as Uganda, Ethiopia and South Africa (Iroezindu, 2013; Mageda *et al.*, 2012; Mitiku *et al.*, 2015; Moges & Kassa, 2014; Rubaihayo *et al.*, 2016; Theuring *et al.*, 2015; Weldegebreal *et al.*, 2018). In a cross-sectional serial review of observational data of adult PLHIV in Uganda, 64% were found to be women, 77% were of low education and 76% had low socio-economic status (Rubaihayo *et al.*, 2016). Likewise, a study in Nigeria which analysed both pre-HAART and post-HAART data found that 65.8% of subjects were women and half (50.4%) were of low socio-economic status (Iroezindu, 2013). Furthermore, a health facility-based cross-sectional study in Ethiopia found that 61.8% were women, 96.2% were within productive group, 50.8% were married and 68.6% had low education ((Weldegebreal *et al.*, 2018). The fact that the proportion of women was consistently higher in these studies, including the present one, may imply that men probably remain under-represented in most ART programmes in the SSA with consequently less favourable national programme outcomes. Additionally, this also signify that women remain disproportionately affected by HIV/AIDS.

Overall, of all opportunistic events in the current study, opportunistic infections accounted for 96.9% compared to 3.1% of opportunistic neoplastic conditions (cancers); Kaposi' sarcoma, invasive cervical cancer and Non-Hodgkin lymphoma. This finding is consistent with that from Uganda (Rubaihayo *et al.*, 2015). This evidence signifies that opportunistic infections; other than opportunistic neoplasms, are the principal causes of morbidity and mortality among adult PLHIV within the SSA (Staine, 2007). Tuberculosis prevalence in the current study was

comparatively high (35.39%) compared to findings from other studies elsewhere (Iroezindu, 2013; Mageda *et al.*, 2012; Mitiku *et al.*, 2015; Moges & Kassa, 2014; Rubaihayo *et al.*, 2016; Theuring *et al.*, 2015; Weldegebreel *et al.*, 2018). This observed difference was due to high rates of TB in Malawi. With the advent of HIV, Malawi has progressively experienced higher rates of respiratory infections particularly TB (Harries *et al.*, 1998; Kanyerere *et al.*, 2016; Kanyerere *et al.*, 2014; Kwanjana *et al.*, 2001; Warndorff *et al.*, 2000; Zachariah *et al.*, 2003). TB remains to be most common in Malawi with PTB affecting approximately 11,000 people per year (Kalua *et al.*, 2018). Besides, a substantial proportion of TB suspects are AAFB ‘smear negative’ and hence clinically diagnosed, although some, approximately 17%, may be later culture confirmed (Hargreaves *et al.*, 2001).

One opportunistic disease; the atypical disseminated leishmaniasis, was not seen in the present study. This suggests either its absence in Malawi or lack of diagnostic capability; however, the former seems likely. Epidemiological evidence shows that there have only been 2 cases of leishmaniasis reported (WHO, 2010a). Both were diagnosed at post-mortem, the first case reported in 1979 and both patients had travelled to Tanzania.

Accordingly, no opportunistic events were extracted in the current study prior to 2004; before public sector rollout of ART programmes. As expected, the burden of opportunistic conditions during early-ART period (2004-2011), was indeed high; accounting for 79.83% compared to 20.17% in late-ART (2011-2015). During both periods, mycobacterial agents were common aetiological agents of ODs followed by bacterial, fungal, and viral agents (Fig 3). The most prevalent conditions during early-ART era were tuberculosis (34.2%), recurrent, severe bacterial pneumonia (11.35%), nontyphoid Salmonella (NTS) bacteraemia (9.67%), HIV wasting syndrome (8.98%), candidiasis (6.82%) and chronic isosporiasis (5.18%). This pattern of

results was equally similar with that of late-ART period. This might be because these ODs are highly endemic in Malawi and relatively easy to diagnose. Similar conditions were also observed in previous studies across Africa, particularly the Sub-Saharan region (Damtie *et al.*, 2013; Iroezindu, 2013; Mitiku *et al.*, 2015; Moges & Kassa, 2014).

Study Limitations & Strengths

To my knowledge, this national representative study was the first to establish and aggregate nationwide information relating to opportunistic diseases among adult PLHIV receiving combined antiretroviral therapy in Malawi. The study has used sufficient sample size with wider geographical coverage (all three regions) and involved all existing health facility types to ensure generalisability. The study has shown the estimated national prevalence level of opportunistic diseases in HIV adult patients, revealed their types, magnitude and factors associated with their occurrences. This was done in a helpful way to inform public health and clinical practice and the procurement and distribution of drugs (for treating ODs) other than ARVs at all healthcare facility levels. Besides, the study has attempted to reflect a true picture of all common ODs prevalent among adult PLHIV in Malawi in that it has included ART-naïve patients qualifying for and commenced on cART with or without OD prophylaxis treatments. These patients were then followed-up for different time periods for as long as they remained in care and their current treatment outcomes documented, – finally giving a picture of ODs in both ART-naïve and ART-experienced patients.

However, the fact that the study was conducted using pre-existing medical records retrospectively, it is subjected to limitations. These may emanate from incomplete recording of vital clinical information and diagnostic capability of some collaborating health facilities. Thus,

the study used data collected primarily not for medical research, hence, some variables which would have been vital and helpful in the interpretation of the results like ART adherence, opportunistic disease prophylaxis received, functional status and the clinical surrogate markers were either completely absent or missing for some patients. It is therefore imperative that future (prospective) cohort studies should target those data. Besides, most research collaborating centres had no capability and competence to readily perform cultures or confirmatory diagnosis of ODs. As such, some conditions were diagnosed clinically which would have potentially imparted diagnosis accuracy. Thirdly, the study did not assess pre-ART burden of ODs prior to the 2004 nationwide rollout declaration of cART. As such, the national rate of decline in the burden of ODs due to cART could not be ascertained. Fourthly, some ODs were not captured in some research centres probably due to inadequate diagnostic capability. Besides, a small proportion of all TB cases (N=109, 2.48%) were clinically unclassified when retrieved but treated as PTB for consistency. Next, due to limited resources, some potential OD cases seen in lower health facilities; primary (health centres) or secondary (district/faith-based hospitals), were referred to tertiary health facilities. These could have been underestimated or missed as not all referred cases were reaching the referral centres.

CONCLUSION

This study has demonstrated that opportunistic diseases were pervasive among adult PLHIV in Malawi. This imply that ODs remain recognisably clinical and public health challenges. The results, however, show that the frequency and profile of ODs have changed since free cART was rolled-out nationally to all clinically eligible patients. However, the changes are varied by factors such as type of ODs, time period, age-group, gender, and geographical areas. Multiple

aetiological pathogens, in particular mycobacterial causes, continue to dominate as primary causes of serious ODs in Malawi. Precisely, tuberculosis, bacterial pneumonia, nontyphoid *Salmonella* bacteraemia, HIV-wasting syndrome, candidiasis, isosporiasis and *Pneumocystis* pneumonia were among most common AIDS-related opportunistic diseases encountered by adult PLHIV. These diseases therefore warrant particular attention and consideration Malawi's HIV/AIDS care programmes. However, this must not be at the expense of other aetiological factors and serious ODs that had relatively low prevalence like KS and ICC. Healthcare facility types, gender, age, geographical location, CD4 cell count and high viraemia, and ART initiation clinical eligibility were commonly occurring independent predictors strongly associated with manifestation of serious ODs. These factors require special consideration when managing HIV patients especially screening for disease progression. Hence, screening and prevention strategies of HIV and ODs need to be redesigned, monitored, and prioritised. The need to strengthen strategies and care models that highlight early identification of new HIV-positive cases and the need for nationwide accelerated implementation of test-and-treat approach cannot be overemphasised. Prophylaxis treatment must be widely implemented and closely monitored in the routine management of people with HIV irrespective of ART use. Additionally, AIDS-related opportunistic diseases diagnostic capabilities need to be strengthened in all centres initiating and monitoring ART.

Authors' contributions

HS conceived the study, participated in the study design, data collection, analysis, and manuscript writing.

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Competing interests

The author declares that he has no competing interests.

Availability of data and materials

All relevant data generated or analysed during this study are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

The study obtained ethical approval from the University of Warwick Research Ethics Committee, the Biomedical and Scientific *Research Ethics Committee* (BSREC)); BSREC approval number: REGO-2015-1576, and from Malawi Research Ethics Committee, the

National Health Sciences Research Committee (NHSRC) under the Ministry of Health; NHSRC approval number: NHSRC # 16/3/1555. Approval from NHSRC was granted after obtaining “Letters of No Objection” from each of the 8 data collection centres. The need for consent to participate was waived off due to the nature of and source of study’s data.

Abbreviations

ADROC	AIDS-defining & recurrent opportunistic conditions
HAART	highly active antiretroviral therapy
cART	Combined antiretroviral therapy
HIV	human immunodeficiency virus
IQR	interquartile range
AIDS	acquired immunodeficiency syndrome
OD	opportunistic disease/s
OC	Opportunistic condition/s
TASO	The AIDS Support Organisation
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organisation
MDHS	Malawi demographic and health survey

Competing interest

The author/s declare that they have no competing interest

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Table 4: Factors Associated with Manifestation of Bacterial and Fungal Opportunistic Diseases in HIV-infected adults in Malawi; 2004-2015

Characteristics	Bacterial Factors				Fungal Factors			
	Univariable findings		Multivariable findings		Univariable findings		Multivariable findings	
	OR (95% CI)	p-value	aOR (95% CI)	p-value	OR (95% CI)	p-value	aOR (95% CI)	p-value
Care type (<i>n</i> =9953)								
Primary care	1.00 (ref)							
Secondary care	1.38 (1.13, 1.69)	0.002	1.34 (1.08, 1.66)	0.008	1.09 (1.30, 3.91)	0.007	1.33 (1.26, 4.91)	0.016
Tertiary care	1.11 (0.92, 1.35)	0.262	1.08 (0.88, 1.31)	0.468	4.43 (1.41, 13.97)	0.008	4.42 (1.38, 14.07)	0.004
Gender (<i>n</i> =9953)								
Female	1.00 (ref)							
Male	1.00 (0.91, 1.10)	1.00	1.05 (0.93, 1.18)	0.4	0.98 (0.89, 1.09)	0.727	0.97 (0.85, 1.10)	0.596
Age-group (<i>n</i> =9950)								
15-19 years	1.00 (ref)							
20-39 years	1.17 (0.89, 1.52)	0.255	1.26 (0.94, 1.70)	0.121	1.16 (1.07, 1.55)	0.031	1.07 (1.03, 1.47)	0.017
40-54 years	1.13 (0.86, 1.48)	0.375	1.19 (0.88, 1.62)	0.25	1.08 (1.01, 1.44)	0.051	1.02 (1.01, 1.42)	0.008
55+ years	1.13 (0.85, 1.51)	0.408	1.14 (0.83, 1.58)	0.422	1.13 (0.83, 1.54)	0.348	1.06 (0.75, 1.50)	0.738
Residential area (<i>n</i> =9953)								
Rural	1.00 (ref)							
Semi-urban	1.05 (0.90, 1.24)	0.524	1.16 (0.97, 1.38)	0.096	1.45 (1.38, 4.33)	0.006	1.52 (1.48, 2.76)	0.019
Urban	1.03 (0.91, 1.16)	0.675	1.15 (1.01, 1.30)	0.032	1.38 (1.24, 2.28)	0.009	1.15 (1.09, 1.93)	0.006
Regional area (<i>n</i> =9953)								
Central region	1.00 (ref)							
Northern Region	0.72 (0.62, 0.85)	0.0001	0.79 (0.67, 0.94)	0.006	0.89 (0.75, 1.05)	0.153	0.89 (0.75, 1.06)	0.182
Southern Region	1.12 (1.00, 1.25)	0.05	1.09 (1.07, 1.23)	0.033	1.00 (0.89, 1.13)	0.991	1.00 (0.89, 1.14)	0.947
Marital status (<i>n</i> =9949)								
Previously married	1.00 (ref)							
Married (partnership)	1.01 (0.88, 1.16)	0.888	1.00 (0.87, 1.16)	0.98	1.10 (1.05, 1.28)	0.023	1.09 (1.03, 1.28)	0.025
Single (never married)	1.27 (1.03, 1.57)	0.023	1.51 (1.20, 1.90)	0.001	1.00 (0.79, 1.27)	0.971	1.04 (0.80, 1.36)	0.751
Education level (<i>n</i> =9953)								
No education	1.00 (ref)							
Primary	0.89 (0.74, 1.08)	0.242	0.93 (0.76, 1.14)	0.506	0.91 (0.74, 0.97)	0.035	0.97 (0.79, 0.99)	0.007
Secondary	0.88 (0.72, 1.06)	0.176	0.91 (0.74, 1.12)	0.354	0.86 (0.70, 0.91)	0.013	0.93 (0.75, 0.96)	0.053
Higher	0.96 (0.79, 1.17)	0.682	1.01 (0.82, 1.25)	0.923	0.95 (0.78, 0.97)	0.006	1.04 (1.02, 1.30)	0.037
Employment status (<i>n</i> =9953)								
Employed	1.00 (ref)							
Self-employed	0.89 (0.81, 0.98)	0.02	0.88 (0.79, 0.97)	0.011	0.91 (0.82, 1.01)	0.067	0.93 (0.84, 0.94)	0.022
Occupation type (<i>n</i> =9953)								
Manual jobs	1.00 (ref)							
Other job types	0.98 (0.86, 1.12)	0.73	0.94 (0.81, 1.09)	0.394	1.10 (0.95, 1.27)	0.206	1.06 (0.91, 1.24)	0.466
White collar	0.97 (0.85, 1.12)	0.723	0.93 (0.79, 1.08)	0.331	1.06 (0.91, 1.23)	0.461	0.99 (0.84, 1.18)	0.934
ART initiation criteria (<i>n</i> =9953)								
CD4 count	1.00 (ref)							

PMTCT	0.99 (0.68, 1.42)	0.942	1.03 (0.71, 1.49)	0.87	1.11 (0.78, 1.57)	0.574	1.11 (0.78, 1.58)	0.567
WHO III	2.13 (1.87, 2.42)	0.0001	2.22 (1.93, 2.55)	0.0001	1.25 (1.10, 1.43)	0.001	1.18 (1.03, 1.36)	0.02
WHO IV	1.97 (1.70, 2.28)	0.0001	1.98 (1.70, 2.31)	0.0001	1.89 (1.63, 2.18)	0.0001	1.85 (1.59, 2.16)	0.0001
CD4-initial results (<i>n</i> =9944)								
0-250 cells/μL	1.00 (ref)							
>250 cells/μL	1.00 (0.91, 1.11)	0.94	1.02 (0.91, 1.13)	0.768	0.61 (0.54, 0.69)	0.0001	0.59 (0.52, 0.66)	0.0001
CD4-recent results (<i>n</i> =9951)								
100-500 cells/μL	1.00 (ref)							
501-1000 cells/μL	1.00 (0.90, 1.11)	0.968	1.04 (0.90, 1.20)	0.612	0.65 (0.45, 0.95)	0.033	0.61 (0.38, 0.98)	0.025
>1000 cells/μL	0.88 (0.76, 0.92)	0.051	0.90 (0.76, 0.98)	0.027	0.75 (0.45, 1.24)	0.082	0.68 (0.38, 0.73)	0.009
VL-initial results (<i>n</i> =9945)								
<1000 copies/mL	1.00 (ref)							
>1000 copies/mL	1.66 (1.24, 2.22)	0.001	1.92 (1.68, 2.27)	0.023	1.70 (1.23, 2.35)	0.001	1.25 (0.89, 1.76)	0.196
VL-recent results (<i>n</i> =9953)								
0-40 copies/mL								
41-1000 copies/mL	0.97 (0.86, 1.08)	0.543	0.97 (0.85, 1.10)	0.59	1.15 (1.02, 1.30)	0.025	1.14 (1.00, 1.31)	0.052
>1000- copies/mL	0.96 (0.86, 1.08)	0.489	0.87 (0.74, 1.01)	0.073	1.12 (0.99, 1.26)	0.076	1.22 (1.04, 1.44)	0.016
Current ART regimen (<i>n</i> =9953)								
Nevirapine-based	1.00 (ref)							
Efavirenz-based	1.10 (0.98, 1.23)	0.091	1.08 (0.96, 1.21)	0.206	1.08 (0.96, 1.22)	0.202	1.08 (0.96, 1.22)	0.215
Boosted-Ritonavir	1.41 (1.09, 1.83)	0.01	1.39 (1.06, 1.81)	0.016	0.80 (0.58, 1.10)	0.174	0.78 (0.57, 1.09)	0.142
Non-std.	1.21 (0.81, 1.83)	0.354	1.26 (0.83, 1.91)	0.277	0.68 (0.41, 1.15)	0.151	0.69 (0.41, 1.17)	0.167
HIV duration (<i>n</i> =9953)								
1-2 years	1.00 (ref)							
3-5 years	1.15 (0.99, 1.35)	0.075	1.14 (0.90, 1.44)	0.267	0.90 (0.76, 1.06)	0.194	0.91 (0.71, 1.17)	0.469
6-10 years	1.01 (0.87, 1.17)	0.918	1.02 (0.76, 1.38)	0.88	0.90 (0.78, 1.05)	0.196	0.95 (0.68, 1.32)	0.751
>10 years	1.05 (0.88, 1.26)	0.553	1.09 (0.72, 1.66)	0.676	0.80 (0.66, 0.96)	0.018	0.89 (0.56, 0.94)	0.017
ART duration (<i>n</i> =9953)								
1-2 years	1.00 (ref)							
3-5 years	1.04 (0.91, 1.18)	0.571	1.02 (0.83, 1.24)	0.881	0.94 (0.82, 1.07)	0.347	0.99 (0.79, 1.24)	0.932
6-10 years	0.90 (0.80, 1.02)	0.106	0.97 (0.74, 1.27)	0.819	0.92 (0.81, 1.05)	0.238	0.98 (0.73, 1.32)	0.899
>10 years	0.88 (0.71, 1.09)	0.242	0.91 (0.62, 1.35)	0.649	0.78 (0.61, 0.98)	0.037	0.89 (0.58, 0.93)	0.011
Clinical latency (<i>n</i> =9953)								
1-2 years	1.00 (ref)							
3-5 years	1.10 (0.99, 1.23)	0.084	1.05 (0.90, 1.22)	0.532	0.97 (0.85, 1.09)	0.579	1.01 (0.86, 1.19)	0.91
> 5 years	1.09 (0.91, 1.31)	0.328	1.00 (0.75, 1.32)	0.991	0.91 (0.75, 1.11)	0.355	1.00 (0.73, 1.36)	0.995
Treatment outcomes (<i>n</i> =9953)								
Treatment adherent	1.00 (ref)							
Defaulters & LTFU	1.12 (1.00, 1.26)	0.051	1.10 (1.07, 1.24)	0.053	1.02 (0.90, 1.16)	0.109	1.19 (1.14, 1.90)	0.017
Died	1.29 (1.12, 1.48)	0.001	1.24 (1.02, 1.49)	0.031	0.91 (0.77, 1.07)	0.258	1.78 (1.64, 1.97)	0.022

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Table 5: Factors Associated with Manifestation of Viral and Mycobacterial Opportunistic Diseases in HIV-infected adults in Malawi; 2004-2015

Characteristics	Viral Factors				Mycobacterial Factors			
	Univariable findings		Multivariable findings		Univariable findings		Multivariable findings	
	OR(95% CI)	p-value	aOR (95% CI)	p-value	OR(95% CI)	p-value	aOR(95% CI)	p-value
Care type (<i>n</i> =9953)								
Primary care	1.00 (ref)							
Secondary care	4.04 (1.96, 17.02)	0.023	3.72 (1.88, 15.79)	0.041	0.77 (0.65, 0.90)	0.002	0.77 (0.64, 0.92)	0.003
Tertiary care	4.64 (1.14, 18.88)	0.029	4.72 (1.15, 19.32)	0.042	0.90 (0.77, 1.04)	0.16	0.85 (0.72, 0.91)	0.046
Gender (<i>n</i> =9953)								
Female	1.00 (ref)							
Male	0.93 (0.84, 1.04)	0.22	0.94 (0.82, 1.07)	0.333	1.10 (1.01, 1.19)	0.026	1.02 (0.93, 1.13)	0.646
Age-group (<i>n</i> =9950)								
15-19 years	1.00 (ref)							
20-39 years	0.83 (0.63, 1.09)	0.19	0.73 (0.54, 0.99)	0.041	0.93 (0.75, 1.15)	0.514	0.94 (0.73, 1.20)	0.623
40-54 years	0.84 (0.64, 1.11)	0.22	0.74 (0.54, 0.91)	0.051	0.95 (0.76, 1.18)	0.631	0.92 (0.72, 1.19)	0.541
55+ years	0.87 (0.65, 1.17)	0.35	0.77 (0.55, 1.07)	0.124	1.04 (0.83, 1.32)	0.717	0.95 (0.72, 1.25)	0.709
Residential area (<i>n</i> =9953)								
Rural	1.00 (ref)							
Semi-urban	1.20 (1.00, 1.43)	0.05	1.23 (1.02, 1.48)	0.031	1.02 (0.89, 1.17)	0.801	0.95 (0.82, 1.10)	0.523
Urban	1.43 (1.39, 2.30)	0.007	1.13 (1.08, 2.84)	0.004	0.97 (0.88, 1.07)	0.571	0.94 (0.84, 1.04)	0.246
Regional area (<i>n</i> =9953)								
Central region	1.00 (ref)							
Northern Region	0.91 (0.77, 1.09)	0.31	0.97 (0.81, 1.16)	0.709	1.02 (0.90, 1.15)	0.203	1.08 (1.04, 1.23)	0.029
Southern Region	1.15 (1.01, 1.30)	0.03	1.14 (1.00, 1.30)	0.046	0.94 (0.86, 1.04)	0.24	0.97 (0.87, 1.07)	0.503
Marital status (<i>n</i> =9949)								
Previously married	1.00 (ref)							
Married (partnership)	2.04 (1.10, 3.78)	0.03	1.95 (1.81, 3.51)	0.046	0.99 (0.88, 1.11)	0.879	0.96 (0.85, 1.08)	0.464
Single (never married)	0.90 (0.71, 1.14)	0.4	0.86 (0.66, 1.13)	0.277	1.04 (0.87, 1.24)	0.685	1.09 (0.89, 1.34)	0.414
Education level (<i>n</i> =9953)								
Primary	1.00 (ref)							
Primary	0.89 (0.72, 1.09)	0.26	0.89 (0.71, 1.11)	0.306	1.18 (1.00, 1.39)	0.051	1.16 (1.07, 1.38)	0.017
Secondary	0.98 (0.80, 1.21)	0.86	1.01 (0.80, 1.26)	0.957	1.19 (1.01, 1.40)	0.039	1.18 (1.10, 1.41)	0.009
Higher	0.87 (0.71, 0.98)	0.022	0.69 (0.35, 0.97)	0.017	1.21 (1.02, 1.43)	0.027	1.23 (1.02, 1.49)	0.031
Employment status (<i>n</i> =9953)								
Employed	1.00 (ref)							
Self-employed	0.97 (0.88, 1.08)	0.6	1.00 (0.89, 1.11)	0.941	1.10 (1.01, 1.19)	0.024	1.08 (0.99, 1.18)	0.088
Occupation type (<i>n</i> =9953)								
Manual jobs	1.00 (ref)							
Other job types	1.01 (0.87, 1.17)	0.89	1.04 (0.89, 1.22)	0.619	0.97 (0.87, 1.08)	0.583	0.98 (0.87, 1.11)	0.758
White collar	0.90 (0.77, 1.05)	0.19	0.92 (0.77, 1.09)	0.329	0.98 (0.87, 1.10)	0.736	0.92 (0.81, 1.06)	0.247
ART initiation criteria (<i>n</i> =9953)								
CD4 count	1.00 (ref)							
PMTCT	0.65 (0.42, 0.91)	0.041	0.65 (0.42, 0.91)	0.053	0.45 (0.32, 0.63)	0.0001	0.45 (0.32, 0.64)	0.0001

WHO III	1.39 (1.21, 1.60)	0.0001	1.43 (1.23, 1.65)	0.0001	2.93 (2.65, 3.25)	0.0001	3.13 (2.80, 3.49)	0.0001
WHO IV	1.74 (1.50, 2.03)	0.0001	1.75 (1.49, 2.06)	0.0001	1.63 (1.45, 1.84)	0.0001	1.73 (1.53, 1.96)	0.0001
CD4-initial results (<i>n</i> =9944)								
0-250 cells/ μ L	1.00 (ref)							
>250 cells/ μ L	1.08 (0.97, 1.21)	0.18	1.07 (0.96, 1.20)	0.217	1.05 (0.96, 1.15)	0.255	1.15 (1.05, 1.26)	0.003
CD4-recent results (<i>n</i> =9951)								
100-500 cells/ μ L	1.00 (ref)							
501-1000 cells/ μ L	1.05 (0.93, 1.18)	0.46	1.10 (0.94, 1.29)	0.217	1.01 (0.93, 1.11)	0.785	0.93 (0.82, 1.05)	0.247
>1000 cells/ μ L	0.95 (0.81, 0.98)	0.015	0.89 (0.82, 0.97)	0.028	1.08 (0.96, 1.22)	0.194	0.98 (0.84, 1.14)	0.764
VL-initial results (<i>n</i> =9945)								
<1000 copies/mL	1.00 (ref)							
>1000 copies/mL	1.32 (1.17, 1.79)	0.008	1.92 (1.67, 2.28)	0.016	1.66 (1.33, 2.08)	0.0001	1.79 (1.62, 1.91)	0.052
VL-recent results (<i>n</i> =9953)								
0-40 copies/mL	1.00 (ref)							
41-1000 copies/mL	1.37 (1.92 – 2.03)	0.016	1.37 (1.29 – 2.04)	0.027	0.96 (0.88, 1.06)	0.45	0.96 (0.86, 1.07)	0.49
>1000 copies/mL	2.26 (1.84 – 2.89)	0.007	2.23 (1.82 – 2.55)	0.042	0.95 (0.86, 1.04)	0.26	0.94 (0.83, 1.08)	0.38
Current ART regimen (<i>n</i> =9953)								
Nevirapine-based	1.00 (ref)							
Efavirenz-based	0.88 (0.78, 0.99)	0.04	0.87 (0.77, 0.98)	0.021	0.94 (0.86, 1.03)	0.212	0.96 (0.87, 1.06)	0.411
Boosted-Ritonavir	0.93 (0.69, 1.26)	0.66	0.92 (0.68, 1.25)	0.606	1.04 (0.83, 1.31)	0.719	1.00 (0.78, 1.27)	0.979
Non-std.	0.70 (0.42, 1.16)	0.16	0.71 (0.42, 1.18)	0.184	1.46 (1.03, 2.09)	0.035	1.51 (1.04, 2.19)	0.029
HIV duration (<i>n</i> =9953)								
1-2 years	1.00 (ref)							
3-5 years	0.99 (0.83, 1.18)	0.943	0.96 (0.74, 1.25)	0.743	1.09 (1.06, 1.13)	0.052	1.10 (1.08, 1.20)	0.081
6-10 years	1.91 (1.64, 2.31)	0.005	1.79 (1.43, 2.46)	0.014	1.12 (1.09, 1.15)	0.027	1.12 (1.07, 1.27)	0.015
>10 years	1.15 (1.76, 2.74)	0.034	1.83 (1.41, 3.68)	0.041	1.19 (1.03, 1.38)	0.018	1.19 (1.03, 1.71)	0.036
ART duration (<i>n</i> =9953)								
1-2 years	1.00 (ref)							
3-5 years	0.99 (0.85, 1.14)	0.858	1.04 (0.83, 1.31)	0.726	0.98 (0.88, 1.10)	0.739	1.01 (0.84, 1.20)	0.955
6-10 years	1.05 (0.91, 1.21)	0.5	1.16 (0.85, 1.57)	0.345	1.04 (0.94, 1.16)	0.42	1.10 (0.87, 1.40)	0.419
>10 years	1.02 (0.80, 1.29)	0.884	1.27 (0.82, 1.96)	0.285	1.23 (1.03, 1.47)	0.026	1.15 (0.82, 1.61)	0.413
Clinical latency (<i>n</i> =9953)								
1-2 years	1.00 (ref)							
3-5 years	1.01 (0.89, 1.14)	0.917	1.01 (0.86, 1.20)	0.873	1.10 (1.00, 1.21)	0.054	1.08 (0.95, 1.23)	0.244
>5 years	0.91 (0.74, 1.12)	0.354	0.97 (0.71, 1.32)	0.846	1.09 (0.93, 1.26)	0.294	1.00 (0.78, 1.27)	0.993
Treatment outcomes (<i>n</i> =9953)								
Treatment adherent	1.00 (ref)							
Defaulters & LTFU	1.08 (0.95, 1.23)	0.243	1.07 (0.93, 1.23)	0.323	0.93 (0.84, 1.02)	0.128	0.99 (0.89, 1.10)	0.812
Died	1.04 (0.88, 1.22)	0.632	1.07 (0.86, 1.32)	0.556	0.98 (0.86, 1.11)	0.702	0.92 (0.78, 1.09)	0.354

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Table 6: Factors Associated with Manifestation of Protozoal (Parasitic) and Neoplastic Opportunistic Diseases among HIV-infected adults in Malawi; 2004-2015

Characteristics	Protozoal Factors				Neoplasm Factors			
	Univariable findings		Multivariable findings		Univariable findings		Multivariable findings	
	OR (95% CI)	p-value	aOR (95% CI)	p-value	OR (95% CI)	p-value	aOR (95% CI)	p-value
Care type (<i>n</i> =9953)								
Primary care	1.00 (ref)							
Secondary care	0.91 (0.68, 1.22)	0.537	0.97 (0.72, 1.32)	0.871	1.92 (1.60, 2.40)	0.048	1.86 (1.55, 2.35)	0.014
Tertiary care	1.05 (0.80, 1.36)	0.741	1.09 (0.83, 1.43)	0.531	1.97 (1.65, 2.43)	0.008	1.94 (1.63, 2.42)	0.007
Gender (<i>n</i> =9953)								
Female	1.00 (ref)							
Male	1.07 (1.03, 1.23)	0.043	1.05 (1.02, 1.25)	0.046	0.72 (0.58, 0.90)	0.003	0.73 (0.56, 0.95)	0.021
Age-group (<i>n</i> =9950)								
15-19 years	1.00 (ref)							
20-39 years	0.69 (0.50, 0.96)	0.026	0.65 (0.45, 0.94)	0.024	1.77 (0.86, 3.63)	0.118	1.20 (0.55, 2.62)	0.641
40-54 years	0.71 (0.51, 0.99)	0.041	0.68 (0.46, 0.99)	0.046	1.73 (0.84, 3.55)	0.137	1.20 (0.55, 2.64)	0.644
55+ years	0.58 (0.40, 0.85)	0.005	0.56 (0.36, 0.85)	0.007	1.71 (0.80, 3.63)	0.167	1.35 (0.59, 3.08)	0.476
Residential area (<i>n</i> =9953)								
Rural	1.00 (ref)							
Semi-urban	0.99 (0.78, 1.25)	0.905	0.92 (0.71, 1.18)	0.496	0.99 (0.70, 1.42)	0.973	1.05 (0.72, 1.53)	0.818
Urban	1.06 (0.89, 1.27)	0.483	1.02 (0.85, 1.22)	0.844	0.99 (0.76, 1.28)	0.935	1.00 (0.76, 1.31)	0.984
Regional area (<i>n</i> =9953)								
Central region	1.00 (ref)							
Northern Region	1.14 (0.92, 1.42)	0.239	1.08 (0.86, 1.35)	0.517	0.96 (0.69, 1.35)	0.828	1.01 (0.70, 1.45)	0.949
Southern Region	1.04 (0.88, 1.23)	0.636	1.06 (0.89, 1.26)	0.498	1.03 (0.81, 1.32)	0.796	1.00 (0.77, 1.29)	0.976
Marital status (<i>n</i> =9949)								
Previously married	1.00 (ref)							
Married (partnership)	1.13 (0.92, 1.39)	0.25	1.11 (0.90, 1.37)	0.338	0.96 (0.72, 1.28)	0.77	1.01 (0.74, 1.37)	0.962
Single (never married)	1.20 (0.88, 1.64)	0.246	1.05 (0.74, 1.49)	0.785	0.49 (0.28, 0.88)	0.017	0.58 (0.31, 0.89)	0.054
Education level (<i>n</i> =9953)								
Primary	1.00 (ref)							
Primary	0.85 (0.64, 1.13)	0.26	0.90 (0.67, 1.21)	0.48	0.99 (0.64, 1.53)	0.965	1.14 (0.72, 1.82)	0.571
Secondary	0.99 (0.75, 1.30)	0.921	1.08 (0.80, 1.45)	0.62	1.03 (0.67, 1.58)	0.903	1.25 (0.78, 2.01)	0.349
Higher	1.00 (0.75, 1.32)	0.977	0.99 (0.73, 1.36)	0.973	1.12 (0.72, 1.73)	0.611	1.42 (0.87, 2.32)	0.158
Employment status (<i>n</i> =9953)								
Employed	1.00 (ref)							
Self-employed	0.92 (0.80, 1.06)	0.244	0.90 (0.78, 1.04)	0.165	0.96 (0.78, 1.18)	0.673	1.03 (0.82, 1.29)	0.783
Occupation type (<i>n</i> =9953)								
Manual jobs	1.00 (ref)							
Other job types	1.15 (0.94, 1.41)	0.182	1.16 (0.93, 1.44)	0.187	1.31 (0.96, 1.79)	0.094	1.48 (1.05, 2.08)	0.025
White collar	1.23 (1.02, 1.52)	0.054	1.26 (1.05, 1.58)	0.052	1.25 (0.90, 1.74)	0.18	1.28 (0.89, 1.84)	0.179

ART initiation criteria (<i>n</i> =9953)									
CD4 count	1.00 (ref)								
PMTCT	1.18 (0.75, 1.85)	0.484	1.24 (0.78, 1.96)	0.358	0.27 (0.06, 1.09)	0.065	0.23 (0.06, 0.96)	0.043	
WHO III	1.32 (1.11, 1.58)	0.002	1.36 (1.13, 1.64)	0.001	0.69 (0.50, 0.94)	0.02	0.69 (0.49, 0.97)	0.03	
WHO IV	1.21 (0.99, 1.49)	0.062	1.26 (1.02, 1.56)	0.034	3.24 (2.46, 4.27)	0.0001	3.43 (2.53, 4.65)	0.0001	
CD4-initial results (<i>n</i> =9944)									
0-250 cells/μL	1.00 (ref)								
>250 cells/μL	0.98 (0.84, 1.14)	0.793	0.99 (0.85, 1.16)	0.944	1.05 (0.84, 1.32)	0.645	0.93 (0.74, 0.97)	0.054	
CD4-recent results (<i>n</i> =9951)									
100-500 cells/μL	1.00 (ref)								
501-1000 cells/μL	0.90 (0.77, 1.04)	0.154	0.81 (0.66, 0.99)	0.042	1.10 (0.87, 1.39)	0.434	0.98 (0.71, 1.34)	0.888	
>1000 cells/μL	0.89 (0.72, 1.10)	0.283	0.77 (0.60, 1.00)	0.047	1.03 (0.75, 1.42)	0.85	0.85 (0.57, 1.26)	0.416	
VL-initial results (<i>n</i> =9945)									
<1000 copies/mL	1.00 (ref)								
>1000 copies/mL	1.39 (1.19, 2.11)	0.012	1.15 (1.07, 1.79)	0.042	1.11 (1.06, 1.90)	0.023	1.74 (1.39, 2.40)	0.036	
VL-recent results (<i>n</i> =9953)									
0-40 copies/mL									
41-1000 copies/mL	1.06 (0.90, 1.25)	0.481	0.97 (0.80, 1.16)	0.719	1.02 (0.80, 1.30)	0.869	0.98 (0.75, 1.28)	0.863	
>1000 copies/mL	1.06 (0.90, 1.25)	0.502	0.99 (0.79, 1.24)	0.924	0.82 (0.63, 1.06)	0.129	0.76 (0.53, 1.10)	0.142	
Current ART regimen (<i>n</i> =9953)									
Nevirapine-based	1.00 (ref)								
Efavirenz-based	0.98 (0.83, 1.15)	0.791	1.01 (0.86, 1.19)	0.891	1.05 (0.82, 1.35)	0.68	1.05 (0.81, 1.35)	0.718	
Boosted-Ritonavir	0.82 (0.53, 1.26)	0.373	0.84 (0.55, 1.30)	0.434	1.20 (0.67, 2.13)	0.54	1.24 (0.69, 2.24)	0.474	
Non-std.	1.81 (1.10, 2.97)	0.02	1.78 (1.08, 2.93)	0.024	1.52 (0.69, 3.36)	0.297	1.59 (0.70, 3.57)	0.265	
HIV duration (<i>n</i> =9953)									
1-2 years	1.00 (ref)								
3-5 years	1.00 (0.80, 1.26)	0.974	0.85 (0.59, 1.22)	0.387	1.09 (0.78, 1.54)	0.608	0.93 (0.55, 1.57)	0.784	
6-10 years	0.98 (0.79, 1.21)	0.836	0.72 (0.45, 1.14)	0.16	0.96 (0.69, 1.33)	0.803	0.79 (0.40, 1.57)	0.508	
>10 years	0.91 (0.71, 1.18)	0.496	0.56 (0.30, 1.05)	0.071	1.05 (0.72, 1.54)	0.799	1.00 (0.40, 2.52)	0.996	
ART duration (<i>n</i> =9953)									
1-2 years	1.00 (ref)								
3-5 years	1.07 (0.89, 1.30)	0.473	1.23 (0.89, 1.69)	0.203	1.06 (0.80, 1.41)	0.682	1.12 (0.71, 1.77)	0.616	
6-10 years	1.08 (0.90, 1.30)	0.422	1.42 (0.93, 2.16)	0.103	1.02 (0.77, 1.35)	0.89	1.23 (0.66, 2.29)	0.511	
>10 years	1.07 (0.79, 1.46)	0.662	1.71 (0.95, 3.08)	0.076	1.05 (0.66, 1.68)	0.83	1.14 (0.48, 2.71)	0.772	
Clinical latency (<i>n</i> =9953)									
1-2 years	1.00 (ref)								
3-5 years	0.85 (0.72, 1.01)	0.07	1.00 (0.79, 1.25)	0.974	1.07 (0.84, 1.36)	0.588	1.02 (0.73, 1.42)	0.911	
>5 years	0.96 (0.74, 1.25)	0.776	1.37 (0.91, 2.06)	0.131	0.79 (0.51, 1.23)	0.31	0.73 (0.38, 1.39)	0.334	
Treatment outcomes (<i>n</i> =9953)									
Treatment adherent	1.00 (ref)								
Defaulters & LTFU	0.94 (0.79, 1.12)	0.476	0.95 (0.79, 1.15)	0.613	0.92 (0.71, 1.20)	0.544	0.77 (0.58, 1.02)	0.069	
Died	0.87 (0.69, 1.08)	0.212	0.78 (0.59, 1.04)	0.089	0.94 (0.68, 1.31)	0.731	1.15 (0.74, 1.79)	0.523	

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Figures

Figure 1

Treatment Outcomes of cART-exposed adults in Malawi; 2004-2015

Figure 2

Distribution of AIDS Conditions Aetiological Factors; Total and by ART Periods in Malawi; 2004-2015

Figure 3

Frequency of AIDS opportunistic events per patient

Figure 4

Frequency of HIV diagnosis cases and ODs by enrolment year; 2004-2015