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TITLE

High Cancer Burden Among Antiretroviral Therapy Users in Malawi: a Record Linkage Study of Observational HIV Cohorts and Cancer Registry Data

AUTHORS

Marie-Josèphe Horner[1,2], PhD, MSPH; Steady Chasimpha, MPH[3], Msc; Adrian Spoerri[4], PhD, MPH; Jessie Edwards[1], PhD; Julia Bohlius[4], MD, MScPH; Hannock Tweya[5], PhD, MPH; Petros Tembo[5], BSc; Franklin Nkhambule[6], BSc; Eddie Moffo Phiri[6], BSc; William C. Miller[7], MD, PhD; Kennedy Malisita[6], MBBS, MPH; Sam Phiri[5,8,9], PhD, MSc; Charles Dzamalala[3,10], MBBS, MMed; Andrew F. Olshan[1, 11], PhD; Satish Gopal[1,2,10,11,12,13], MD, MPH

AFFILIATIONS

[1] Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, United States
[2] UNC Project-Malawi, Lilongwe, Malawi
[3] Malawi Cancer Registry, Blantyre, Malawi
[4] Institute of Social and Preventive Medicine, University of Bern, Switzerland
[5] The Lighthouse Trust, Kamuzu Central Hospital, Lilongwe, Malawi
[6] Queen Elizabeth Central Hospital HIV Clinic, Blantyre, Malawi
[7] Epidemiology, College of Public Health, Ohio State University, Columbus, Ohio, United States
[8] Department of Public Medicine, University of Malawi, Blantyre, Malawi
[9] Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, United States
[10] University of Malawi College of Medicine, Blantyre, Malawi
[11] Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, United States
[12] UNC Institute for Global Health & Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, United States
[13] Malawi Cancer Consortium & Regional Center of Research Excellence for Non-Communicable Diseases, Lilongwe, Malawi

CONTACT INFORMATION

Marie-Josèphe Horner
mjhorner@live.unc.edu
135 Dauer Drive
2101 McGavran-Greenberg Hall, CB #7435
Chapel Hill, NC 27599-7435

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Cancer among ART users in Malawi

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In sub-Saharan Africa, limited epidemiological data describe cancer burden among ART users. Integrated cancer screening and management in HIV clinics, especially for KS and cervical cancer, remain important priorities in the current Malawi context.

ABSTRACT

Background

With antiretroviral therapy (ART), AIDS-defining cancer incidence has declined and non-AIDS defining cancers are now more frequent among HIV-infected populations in high-income countries. In sub-Saharan Africa, limited epidemiological data describe cancer burden among ART users.

Methods

We used probabilistic algorithms to link cases from the population-based cancer registry with electronic medical records supporting ART delivery in the Malawi's two largest HIV cohorts, Lighthouse Trust (LT; 2007-2010) and Queen Elizabeth Central Hospital (QECH; 2000-2010). Age-adjusted cancer incidence rates (IR) and 95% confidence intervals were estimated by cancer site, early versus late incidence periods (4 -24 and >24 months after ART start), and WHO stage among naïve ART initiators enrolled for at least 90 days.

Results

We identified 4,346 cancers among 28,576 persons. Most people initiated ART at advanced WHO stage (LT stage 3/4: 55%; QECH stage 3/4: 66%); 12% of patients had prevalent malignancies at ART initiation, which were predominantly AIDS-defining eligibility criteria for initiating ART. Kaposi sarcoma (KS) had the highest IR (634.7 per 100,000 person-years), followed by cervical cancer (36.6). KS incidence was highest during the early period 4-24 months after ART initiation. Non-AIDS defining cancers (NADC) accounted for 6% of new cancers.

Conclusions

Under historical ART guidelines, NADC were observed at low rates, and were eclipsed by high KS and cervical cancer burden. Cancer burden among Malawian ART users does not yet mirror high-income countries. Integrated cancer screening and management in HIV clinics, especially for KS and cervical cancer, remain important priorities in the current Malawi context.

SUMMARY

Kaposi sarcoma and cervical cancer dominate the cancer burden among antiretroviral therapy users in Malawi under historical treatment guidelines. A broad spectrum of non-AIDS defining malignancies may be an emerging concern among aging HIV populations in Africa.

INTRODUCTION

Three AIDS-defining malignancies, Kaposi sarcoma (KS), cervical cancer, and non-Hodgkin lymphoma (NHL) are among the top 10 cancers in sub-Saharan Africa (SSA), where 70% of global HIV burden is concentrated [1, 2]. Rapid scale-up of antiretroviral therapy (ART) availability over the past decade [1] is likely to affect regional cancer burden. In high-income countries, cancer risk among HIV populations is evolving, with notable declines in risk of KS, NHL, and some non-AIDS defining cancers (NADC) over the course of ART expansion since 1996 [3]. The burden of certain NADC is now projected to increase and surpass that of AIDS-defining cancers (ADC) due to growth and aging of the population living with HIV [4]. But extrapolations from high-income countries may not apply to SSA, where delays in accessing HIV care are substantial, advanced immunosuppression at ART initiation is common [5], and prevalence of oncogenic viral infections is high [6]. Epidemiological evidence is therefore needed to understand cancer trends specifically in SSA.

In the Malawi HIV-Cancer Match Study, we aim to characterize cancer incidence among ART initiators. In Malawi, HIV prevalence is 9% and ART coverage has reached 67%, using a threshold for ART eligibility of 500 CD4 cells/µL or WHO clinical stages 3 and 4 [7]. Our work differs from previous studies in the region [8-10], in that we used two of the largest, actively traced cohorts of ART users in the country over a period spanning national ART scale-up from 2000 through 2010. We also conducted cross-sectional linkage of cancers using the population-based national cancer registry.

METHODS

Populations

Study subjects were HIV-infected people receiving ART at Lighthouse Trust (LT) and the Queen Elizabeth Central Hospital (QECH) HIV clinics. In the central region, LT in the capital, Lilongwe, is Malawi's largest public ART provider. In the south, the QECH HIV clinic is situated in Blantyre, Malawi's second largest city. Clinics use electronic monitoring systems to routinely collect demographic information, WHO stage at clinic enrollment, ADC clinical diagnoses (KS and cervical cancer only), drug regimens, and patient outcomes [11, 12]. Active tracing is used for patient follow-up and ascertainment of vital status. In Malawi, CD4 count measurement was historically restricted to stage 1 and 2 patients who were not clinically eligible for ART (e.g. stages 3 and 4). For QECH prior to 2011, CD4 counts were not captured in the electronic monitoring system and therefore were not available for analysis. Routine HIV RNA monitoring in Malawi did not begin until 2011. Therefore, limited CD4 count data and no HIV RNA data were available during the time period of our study reflecting practice within the Malawi national HIV program.

The population-based Malawi Cancer Registry (henceforth, the registry) is a founding member of the African Cancer Registry Network and one of only five cancer registries from SSA included in WHO international estimates of cancer [2]. Active case-finding procedures have been described previously [13]. During the study period, QECH in Blantyre housed the sole pathology laboratory for the entire country; a second laboratory open at Kamuzu Central Hospital, Lilongwe in 2011 [14]. Thus, historically

only 18% of cases were pathologically confirmed, with most cancer diagnoses supported by clinical, radiological, and/or laboratory data [13]. Pathology confirmation rate is comparable to that of other cancer registries from SSA [15, 16].

Electronic medical record linkage

In the absence of unique personal identifiers, we used probabilistic algorithms to link electronic medical records (EMR) from ART cohorts with cancer records. All HIV-infected people initiating ART at QECH from 2000 to 2010 or LT from 2007 to 2010 were eligible based on years of registry coverage in Blantyre and Lilongwe, respectively. EMR were matched on first and last name, year of birth, sex, and district of residence as these identifiers were shared across datasets. Consistent with other SSA settings, date of birth was estimated for a substantial proportion of records. Therefore, we allowed for 5-year age discrepancies between record pairs during subsequent iterations of the linkage [10]. Highest-weight classification was used to classify record pairs as matches, potential matches or non-matches, followed by manual adjudication of potential matches (Supplemental Materials p.3) [10]. Potential matches were manually reviewed and validated through clinical review by three senior Malawian investigators using additional oncology treatment data collected by the registry and National Oncology Review Board, when available. Data preprocessing and probabilistic record linkage were performed in KNIME Analytics Platform Version 2.12.1 (Konstanz, Germany). Data pre- and post-processing were conducted in Stata 14 (Stata Corporation, College Station, Texas). Analyses were conducted in SAS software 9.4 for Windows (Cary, NC, USA). The study was approved by the University of North Carolina Institutional Review Board and University of Malawi College of Medicine Research Ethics Committee.

Study design and statistical analysis

We used an observational multi-cohort design. ART-naïve individuals were eligible for analysis if they had a first clinic date occurring between January 1, 2000 and August 30, 2010 at QECH and January 1, 2007 and August 30, 2010 at LT, and were followed for at least 90 days. The event of interest was the first incident primary cancer diagnosed either clinically or pathologically occurring greater than 90 days after ART start. As in other record linkage studies in the United States [17] and Africa [10], the 90 day window accounts for clinical workup of prevalent cancers as patients enter the medical system. Cancers were identified either through registry linkage or EMR.We further classified new cancer as early incident (4 to 24 months after ART start) and late incident (>24 months). Person-years (py) at risk for incident cancer was calculated from 90 days after ART enrollment to the earliest of cancer diagnosis or censor due to ART cessation, clinic transfer, last contact, death, or October 1, 2015 administrative censor. For those lost to follow-up, person-time at risk included a 180-day window past the missed appointment date. Cancer diagnoses that were linked beyond the last date of contact or 180-day window were excluded from primary analyses (n=36). Subsequent multiple primaries of different anatomical site or histology (n=32) and prevalent malignancies defined as a diagnosis prior to enrollment or within 90 days of ART start (n= 3,463) were excluded from incidence rate analysis (Supplemental Figures 1-2). Cancer data were coded using the International Classification of Disease for Oncology (Supplemental Table 1) [18].

Incidence rates (IR) and 95% confidence intervals (CI) were calculated for individual cancer sites, early versus late incidence periods, and WHO stage at clinic enrollment. Rates were age-adjusted to the 2007 Malawi standard population (ages 0-14, 15-24, 25-34, 35-44, 45-54, 55+ years) [19]. We further conducted a sensitivity analysis using only cancer matches with the highest linkage weights to estimate a conservative lower bound on cancer-specific IR (Supplemental Table 3). Age-adjusted rates to the World Standard are also provided (Supplemental Table 4).

RESULTS

Our study included 28,576 new ART users who initiated care at LT (n=15,920) and QECH (n=12,656). Median age at enrollment was 33 years (Table 1). New patients tended to initiate ART at an advanced WHO stage (LT stage 3: 41%, stage 4: 14%; QECH stage 3: 50%, stage 4: 16%).

Overall, 4,346 cancers were identified: 16% were identified through record linkage (LT n=202; QECH n=477), 84% through the EMR (LT n=3351; QECH n=528). The majority of diagnoses did not overlap across data sources (<4%; Supplemental Figures 1-2); information on NHL and NADC was derived exclusively from the match with the registry. Pathological confirmation of cancer diagnosis was low and varied by clinic site: 3% at LT and 19% at QECH, reflecting diagnostic pathology availability in Lilongwe and Blantyre, respectively, during the study period. Prevalence of cancer at time of enrollment was 12%, with prevalent cancers being predominantly ADC.

A total of 23,655 cancer-free individuals at cohort entry were followed for 100,815 py at risk (Table 1). Median time on ART was 3.6 years (interquartile range: 0.4, 6.0 years). Most incident cancers occurred within 4 to 24 months after starting ART (early incident: n=618; late incident n=265); 21% of early incident and 26.4% of late incident diagnoses were identified through linkage to the registry Overall age-adjusted cancer incidence rate for all sites combined was 689.2 (95%CI 610.2, 768.0; Figure 1). Incidence was greatest during the early period of 4-24 months following ART initiation (Table 2).

AIDS-defining cancers

KS, cervical cancer and NHL accounted for 94% of new malignancies among new ART users (Supplemental Table 1). The majority of KS and cervical cancer cases were diagnosed clinically; 10% and 27% received a pathological confirmation of diagnosis at LT and QECH, respectively. Squamous cell carcinoma was the most common type of cervical cancer (42%), followed by non-specified histological types based on clinical diagnosis. All NHL cases were pathologically confirmed.

Overall KS incidence was 634.6 per 100,000 py on ART (95%CI 558.3, 711.0; Figure 1). KS occurred most frequently in the early incidence period of 4-24 months after starting ART for both men and women (Table 2). Early incident KS was greater among men (IR: 525.0; 95%CI 417.5, 615.9) than among women (IR: 399.1; 95%CI 324.5, 473.7; Table 2). Men and women experienced 40% increased incidence of KS at advanced WHO stage relative to early stage (Table 3); however, this association was not observed among clinical stage 4 cases.

Cervical cancer was the second most commonly occurring cancer, with an incidence rate of 36.6 (95%CI 21.4, 51.7; Figure 1). No discernable pattern was observed in early versus late incidence of cervical cancer (Table 2). Women with advanced WHO stage had a 70% higher rate of cervical cancer than women with early stage HIV, but this association was not significant (Table 3). NHL was detected at a low rate in our study (IR 11.7, 95% CI: 0, 27.0).

Non-AIDS-defining cancers

NADC accounted for 6% of the total cancer burden among 2000-2010 ART users (Supplemental Table 1). The highest IR were for cancers of the breast (7.1; 95%CI 0, 17.8), esophagus (6.0, 95%CI: 0.2, 11.8), female reproductive cancers (3.7; 95%CI: 0.6, 6.9) , eye and conjunctiva (1.6; 95%CI: 0.2, 3.1), and bladder (1.5; 95%CI: 0, 2.9) (Figure 1; Supplemental Table 2).

Pathological confirmation varied across NADC sites: esophagus (19%), cervix (27%), breast (53%), anus (75%), lymphomas (100%), oral cavity/pharynx (100%), eye/conjunctiva (100%). Squamous cell carcinoma was the most common type of lip/oral cavity (40%), anus (75%), and eye/conjunctiva (85%) malignancy. Squamous cell carcinoma of the esophagus was also predominant (89%). Among breast cancers, 71% were infiltrating ductal carcinoma. Infection-associated cancers linked to *H. pylori* (stomach), hepatitis B and C virus (liver), schistosomiasis (bladder), and Epstein-Barr virus (Hodgkin lymphoma subtypes) were rarely detected in our study (Figure 1, Supplemental Table 2).

DISCUSSION

Our goal in the Malawi HIV-Cancer Match Study was to characterize the burden and spectrum of cancer among ART users in Malawi, where HIV prevalence is 9% and one in twenty Malawian adults is now on ART [7]. In our study of nearly 29,000 ART users, the overall cancer burden was high and predominantly driven by ADC, even during the early era of improving access to ART. KS was the most common cancer, and ADC were a reason for presenting to care for one in eight patients. The incidence of new KS was most pronounced during the first two years of ART, but remained high over long-term follow-up. Our KS incidence estimates in Malawi are among the highest for ART users in SSA, with other reported rates including 77 per 100,000 py in Zimbabwe, 169 in Zambia [20], 270 in Kenya, 340 in Uganda [21], and 432 in South Africa [9]. High incidence of KS at HIV centers of excellence in Malawi in 2000-2010 are similar in magnitude to ART users with CD4 count of 51-100 (IR: 716) in East African ART populations [21]. High KS burden in Malawi is likely attributable to the 35% to 88% prevalence of the causative virus human herpesvirus-8 (HHV-8) in Southern Africa [22], and typically advanced HIV stage with late presentation to care among ART initiators. This is especially true during the relatively early period of ART scale-up analyzed, which began in Malawi in 2004. KS burden may therefore still decline as the national ART program matures [23] with earlier and more widespread application of ART under 'treat all' guidelines [24].

Reflecting late presentation to care, advanced WHO stage was associated with increased KS incidence, although this association was not observed for those presenting to care with stage 4 disease perhaps owing to differences in competing risk of death and prevalence of individuals who already had KS at ART

initiation. Advanced HIV stage was associated with a 40% increase in KS incidence. Cervical cancer was the second most common cancer, and more advanced WHO stage was not associated with increased incidence of cervical cancer in our study. These findings might suggest KS burden will be more immediately impacted by earlier ART application in SSA than cervical cancer, as also suggested by early epidemiologic data from Uganda and Botswana showing modest incidence declines for KS but not cervical cancer [25, 26].

We also observed a range of NADC even among Malawians with relatively advanced HIV prior to ART initiation. While NADC incidence rates were low overall, our findings highlight the heterogeneous cancer burden among Malawian ART initiators beyond KS and cervical cancer, as also suggested by other regional studies [25-27]. The highest incidence rates observed were for breast, esophageal, other female reproductive, eye and conjunctiva, and bladder cancers. Of these, other female reproductive cancers and bladder cancer have confirmed etiologic associations with infectious pathogens (human papilloma virus and schistosomiasis, respectively), but associations with HIV in SSA are uncertain. For esophageal cancer, there is no known infectious etiology [28], although a Zambia case-control study suggested possible association with HIV [29]. For breast cancer, large studies from high-income countries have repeatedly shown reduced risk among HIV-infected individuals [3]. However, HIV prevalence among breast cancer patients in Botswana is substantially higher than the general population [26]. Our work and that of others thus highlight the need for larger and more definitive epidemiologic studies to define relationships between HIV and cancer which may be unique to SSA, to inform comprehensive, holistic cancer screening and prevention programs in regional ART clinics.

The lower than expected incidence of lymphomas and NADC in our study is likely due to underdiagnosis. Geographical differences in screening and diagnostic confirmation likely contributed to overall completeness of cancer ascertainment by the registry, and therefore record linkage performance. This observation is similar to the overall context of cancer ascertainment in SSA, for which regional limitations have been extensively described [30]. Cancer awareness is often low but improving among patients and clinicians in Malawi, and ability to obtain diagnostic tissue from deep visceral sites is more challenging than from more accessible sites. In addition, a single pathology center in Blantyre provided services to the entire country during the study period, and only approximately one-fifth of all cancer cases were thus pathologically confirmed. Lymphomas may be particularly susceptible to misdiagnosis, and studies from Uganda and Malawi have shown that lymphomas are commonly clinically misdiagnosed as tuberculosis [31, 32]. Our study may also be subject to underreporting of cancer incidence during late patient follow-up. Cancer surveillance after 2010 was limited to central hospitals, therefore diagnoses occurring during follow-up beyond 2010 may be less completely captured by the registry.

The Malawi HIV-Cancer Match Study used probabilistic record linkage algorithms to ascertain cancer outcomes at centers of excellence for HIV care. This is one of the largest epidemiological studies of its kind in SSA to provide a comprehensive overview of the cancer burden among individuals receiving ART. We used information on active patient follow-up to construct a retrospective cohort of approximately 29,000 new ART initiators. Our study leveraged probabilistic methods and extensive clinical review to

link data from Malawi's national cancer registry with existing electronic medical systems supporting ART delivery within large HIV clinics. We performed validation of cancer outcomes through extensive clerical and clinical review of matched cases.

Our study has downstream implications for strengthening health systems in Malawi. Registry data matches are an important mechanism for providing HIV clinics with NADC and other non-communicable disease outcomes. Routine queries of HIV point-of-care clinics and further validation studies may improve cancer registration among HIV-infected populations in SSA. While our study used high quality data from HIV clinics participating in the International epidemiologic Databases to Evaluate AIDS (IeDEA) consortium, improving data quality and completeness of cancer diagnoses outside of HIV centers of excellence is a long-term priority. Interdisciplinary collaboration between HIV and cancer systems is of continued importance to build efficient and complete public health data resources in low-income settings [33].

In conclusion, we provide the first comprehensive baseline description of cancer burden against which to monitor cancer control efforts for HIV-infected populations in Malawi. Our findings demonstrate an ongoing high burden of KS and cervical cancer in a young, urban patient population, and the importance of integrated screening and management of KS and cervical cancer in ART programs. Longer follow-up and additional linkages may be needed to monitor these populations as they age into a demographic group where NADC are most common. Nearly 2.3 million people with HIV over 50 years are African, greater than half the global burden, and demographic shifts are expected to continue under expanded ART guidelines for earlier treatment and the growing number of people accessing ART [34]. In high income countries, the burden and incidence of KS and NHL declined substantially since the introduction of ART [35-37], but the NADC burden has actually increased with growth and aging of HIV-infected populations, as well as declines in competing causes of death [36, 38]. Whether cancer trends in high-income countries will be replicated among HIV populations in Africa remains uncertain. Validation of our findings through companion studies in other parts of SSA is needed, as well as longer-term studies to monitor potential shifts in cancer distribution under expanded ART guidelines. Continued investment in high-quality cancer surveillance will be essential to inform evidence-based national cancer control efforts in SSA. Preparing African healthcare systems for the impending challenges of caring for aging HIV populations, and forthcoming non-communicable disease burden, is essential [39, 40].

CONTRIBUTORS

MJH and SG wrote the first draft of the report. MJH, SC, and SG acquired the data. MJH, SC and AS performed statistical analysis. SG is the principal investigator in the Malawi HIV-Cancer Match Study and supervised the study; SG and JB obtained funding. CD, SP, KM are co-investigators. All authors contributed to the study design, the interpretation of the data and critically reviewed the manuscript for intellectual content, and approved the final version of the report.

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DECLARATION OF INTERESTS

We declare no conflicts of interest.

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Table 1. Characteristics of new ART initiators enrolled at Queen Elizabeth Hospital HIV clinic, Blantyre, and Lighthouse Trust HIV Clinic, Lilongwe, Malawi

	Lighthouse Trust (2007-2010)				Queen Elizabeth Central Hospital (2000-2010)			
	Total cohort		Person-years at risk		Total cohort		Person-years at risk	
	N	%	N	%	N	%	N	%
Total	15920		49981		12656		50834	
Sex								
Male	6713	42.2%	19558	39.1%	5529	43.7%	20591	40.5%
Female	9207	57.8%	30423	60.9%	7127	56.3%	30243	59.5%
Age category (years)								
<16	706	4.6%	2181	4.5%	1730	13.7%	6183	12.2%
16-25	1641	10.7%	4881	10.1%	1203	9.5%	4049	8.0%
26-35	6273	40.8%	19980	41.5%	4628	36.6%	18641	36.7%
36-45	4527	29.5%	14422	30.0%	3283	25.9%	14217	28.0%
46-55	1624	10.6%	5013	10.4%	1321	10.4%	5799	11.4%
56+	595	3.9%	1652	3.4%	491	3.9%	1945	3.8%
missing	554	-	1851	-		-		-
Age at enrollment, years, median (IQR)	33.3 (27.9, 39.8)				33.5 (16.7, 40.9)			
WHO stage								
1 or 2	4852	30.5%	17693	35.4%	4181	33.0%	18793	37.0%
3	6499	40.8%	19362	38.7%	6261	49.5%	26123	51.4%
4	2207	13.9%	4855	9.7%	2010	15.9%	5477	10.8%
Not applicable/unknown	2362	14.8%	8070	16.1%	204	1.6%	441	0.4%

Table 2. Cancer incidence rates by timing of diagnosis after ART initiation

	Men		Women	
	Incidence Rate	(95% CI)	Incidence Rate	(95% CI)
All sites, total	765.5	(621.7, 909.3)	643.3	(543.6, 743.0)
Early incidence	534.7	(417.5, 651.9)	399.1	(324.5, 473.7)
Late incidence	230.8	(147.5, 314.2)	244.2	(178.0, 310.4)
Kaposi sarcoma				
Early incidence	525.0	(407.9, 642.1)	371.7	(298.2, 445.2)
Late incidence	203.4	(126.3, 280.5)	202.8	(140.0, 265.6)
Cervical cancer				
Early incidence	-		13.7	(7.7, 19.7)
Late incidence	-		22.9	(9.0, 36.8)

Incidence rates are per 100,000 person-years on ART and are age-adjusted to the 2007 Malawi standard population. Cancer sites include invasive cases only. Early incidence is defined as 4 to 24 months after start of ART; late incidence is defined as >24 months after start of ART.

95%CI : 95% Confidence Interval.

Table 3. Cancer incidence rates by WHO clinical stage at time of cohort enrollment

	Incidence Rate	(95% CI)	IRR	(95% CI)
Kaposi sarcoma				
stage 1 or 2	145.3	(109.0, 181.6)	1.	
stage 3	202.8	(150.3, 255.4)	1.4	(1.1, 1.7)
stage 4	150.2	(106.5, 193.9)	1.0	(0.8, 1.3)
Cervical cancer				
stage 1 or 2	12.6	(6.0, 19.1)	1.	
stage 3	21.3	(8.0, 34.7)	1.7	(0.9, 3.2)
stage 4	1.0	(0.0, 2.4)	0.1	(0.0, 0.3)

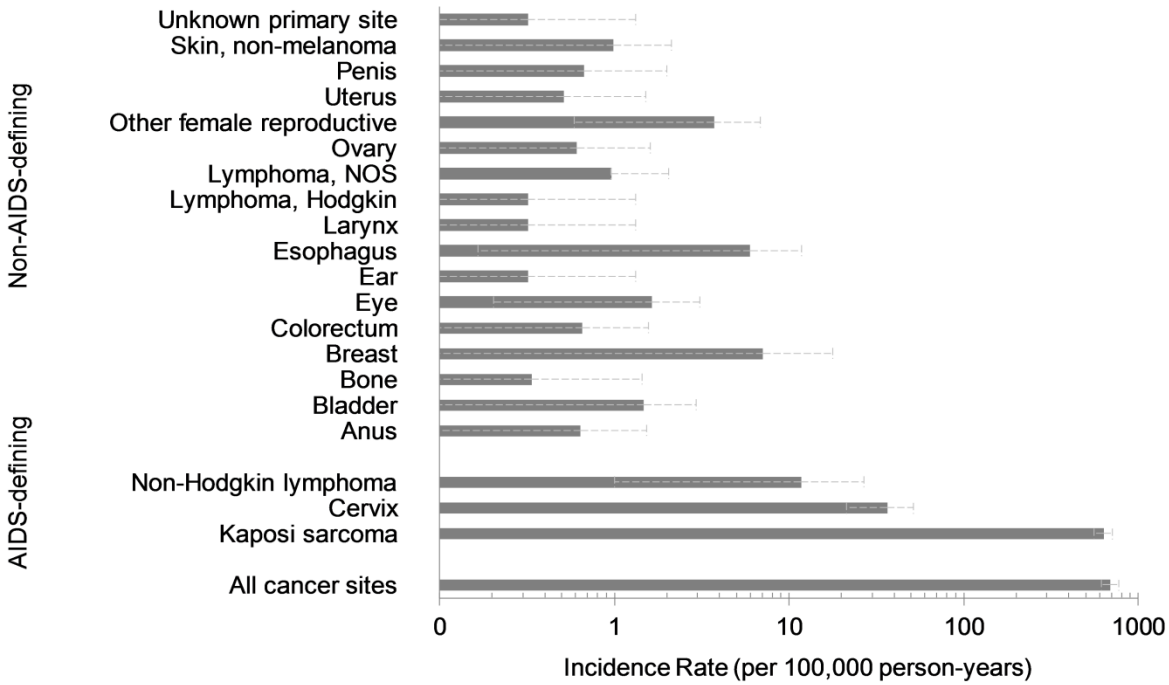
Incidence rates are per 100,000 person-years on ART and are age-adjusted to the 2007 Malawi standard population. Cancer sites include invasive cases only. Cases with missing WHO stage at enrollment were excluded (Kaposi sarcoma n=229; cervical cancer n=2).

95%CI : 95% Confidence Interval. IRR: Incidence Rate Ratio.

Figure Title:

Figure 1. Age-adjusted cancer incidence rates among new ART users in Malawi, 2000-2010.

Figure 1


Non-AIDS-defining
AIDS-defining
Unknown primary site
Skin, non-melanoma
Penis
Uterus
Other female reproductive
Ovary
Lymphoma, NOS
Lymphoma, Hodgkin
Larynx
Esophagus
Ear
Eye
Colorectum
Breast
Bone
Bladder
Anus
Non-Hodgkin lymphoma
Cervix
Kaposi sarcoma
All cancer sites
0
1
10
100
1000
Incidence Rate (per 100,000 person-years)