Article:

Motlhale, Melitah, Sitas, Freddy, Bradshaw, Debbie et al. (9 more authors) (2022) Epidemiology of Kaposi’s sarcoma in sub-Saharan Africa. Cancer Epidemiology. 102167. ISSN 1877-7821

https://doi.org/10.1016/j.canep.2022.102167

Cancer Epidemiology 78 (2022) 102167

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Epidemiology of Kaposi's sarcoma in sub-Saharan Africa

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ARTICLE INFO

Keywords:
Kaposi's sarcoma
Kaposi's sarcoma-associated herpesvirus
Antiretroviral therapy
Human immunodeficiency virus/acquired immunodeficiency syndrome
Sub-Saharan Africa

ABSTRACT

Kaposi's sarcoma (KS) has become a common AIDS-defining cancer in sub-Saharan Africa. Kaposi's sarcoma-associated human herpesvirus strongly modulated by HIV-related immune suppression are the principal causes of this cancer. No other risk factors have been identified as playing a strong role. HIV prevention programs and good coverage of antiretroviral therapy (ART) in developed countries resulted in a remarkable decline in HIV-KS incidence and better KS prognosis. By contrast, in sub-Saharan Africa, population ART rollout has lagged, but clinical studies have shown positive results in reduction of KS incidence and better KS prognosis. However, the effect of ART rollout in relation to population KS incidence is unclear. We describe the incidence of KS in sub-Saharan Africa, in four time-periods, (1) before 1980 (before HIV/AIDS era); (2) 1981–2000 (early HIV/AIDS era, limited or no ART coverage); (3) 2001–2010 (early ART coverage period); and (4) 2011–2016 (fair to good ART coverage period). We used KS incidence data available from WHO-International Agency for Research on Cancer (IARC) publications and the Africa Cancer Registry Network. National HIV prevalence and ART coverage data were derived from UNAIDS/WHO. A rapid increase in KS incidence was observed throughout sub-Saharan Africa as the HIV epidemic progressed, reaching peak incidences in Period 2 (pre-ART rollout) of 50.8 in males and 20.3 per 100 000 in females (Zimbabwe, Harare). The overall unweighted average decline in KS incidence between 2000 and 2010 and 2011–2016 was 27%, but this decline was not statistically significant across the region. ART rollout coincides with a decline in KS incidence across several regions in sub-Saharan Africa. The importance of other risk factors such as reductions in HIV incidence could not be ascertained.

1. Background

Kaposi's sarcoma is a malignant neoplasm caused by infection with Kaposi's sarcoma associated herpes virus (KSHV) [1]. Prior to the advent of the HIV/AIDS epidemic, Kaposi's sarcoma (KS) was present in Sub Saharan Africa at a larger frequency than the rest of the world [2–4]. Until the 1980s, little focus had been accorded to KS, which was regarded as an indolent tumor with relatively slow clinical progression

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https://doi.org/10.1016/j.canep.2022.102167
Received 9 December 2021; Received in revised form 18 March 2022; Accepted 20 April 2022
Available online 30 April 2022

[5]. With the emergence of the HIV/AIDS epidemic, the clinical severity, incidence and mortality of KS increased significantly, having a profound impact in the region [5–7]. The impact included increases in incidence in younger age groups, a narrowing of the male-female ratio, and an increase in KS into regions where it was not endemic [8,9]. KS is now predominantly an AIDS defining malignancy and one of the commonest cancers in sub-Saharan Africa.

Epidemic KS has been described due to coinfection with HIV and KSHV. KSHV is a necessary cause of KS [5,10]. The seroprevalence of KSHV in Africa is relatively high (20–80%) [6,8,11]. Sub-Saharan Africa accounts for approximately 70% of the global burden of HIV infection [12,13]. Co-infection with HIV and KSHV greatly increases the likelihood of developing KS [14]. Being male and age are factors related with risk of KS where it affects older people in endemic and classical, younger people in epidemic KS. Studies have further hypothesized that (non-viral) demographic and lifestyle risk factors for all KS types include infection with helminths and alcohol consumption [14–26]. The role of ethnicity in the etiology of KS is geographically bound by latitude north and south of central-east Africa and seems to be even less relevant in the presence of HIV than it was for the development of the classical or endemic KS before the HIV pandemic [9]. In the absence of HIV infection, risk factors associated with endemic KS remain unclear, this includes the male to female difference [19].

In sub-Saharan Africa, antiretroviral therapy (ART) is used to manage HIV / and AIDS related conditions including epidemic KS [19]. Since the introduction of ART, KS clinical outcomes have improved significantly with a combination of ART and chemotherapy [27]. In sub-Saharan Africa, complete remission of KS has been reported in about 20–80% of patients who were ART compliant [28,29]. The median time for remission in patients with KS due to ART has been reported to be between three to nine months [30]. ART is a cost effective intervention in decreasing the burden of KS, and offers great potential for improvements on survival, and quality of life for those with HIV-associated KS [31]. ART has also been shown to be an important way to reduce the risk of developing KS among people living with HIV/AIDS (PLWHA) in high income countries both in clinical follow-up and population studies [32]. The HIV burden, late rollout of ART, socio-economic issues and intervention implementation challenges in sub Saharan Africa could possibly explain the differential intervention outcomes between high income countries [12,33]. Clinical studies from Kenya, Uganda and South Africa indicate that ART is effective in reducing the incidence of KS [15,28,32].

In most sub-Saharan African countries, public sector ART programs were rolled-out in the mid-2000s. By 2017 approximately 11.8 million (46%) people living with HIV or AIDS in sub-Saharan Africa were receiving treatment [27]. ART coverage estimates are regularly compiled by the most recent report received by World Health Organization (WHO) and / or the Joint United Nations Program on HIV/AIDS (UNAIDS). The ART coverage estimates are calculated using statistical modeling methods [34].

WHO updated the ART guidelines for adults and adolescents in 2009. All adults and adolescents, including pregnant women with HIV infection and a CD4 count at or below 350 cells/mm^3 were enrolled for treatment, regardless of whether or not they have clinical symptoms. Those with WHO clinical stage 3 or 4 were to start treatment, irrespective of CD4 cell count. Old guideline thresholds for treatment initiation was $<$ 200 cells/mm^3 [35]. In 2016, WHO launched revised, more inclusive guidelines for ART eligibility [27]. Since 2017, all people living with HIV or AIDS are recommended to receive ART, irrespective of CD4 count [27,36]. Most sub-Saharan African countries are formally rolling out ART programs, and most programs are now widening eligibility criteria to cover a broader group of HIV infected individuals outside of hospital systems.

There have been several review papers on KS pre and post the advent of HIV/AIDS (circa 1980) covering incidence or relative frequency of KSHV, associated risk factors in sub-Saharan Africa countries, and descriptions of the epidemiological and clinical characteristics of different forms of KS [1,15,19,27,37]. One review in 2010 focused on the epidemiology and transmission of KSHV as well as the clinical characteristics and therapy of HIV-associated KS in sub-Saharan Africa, with concerns raised about ART population coverage [38]. However, the effect of ART rollout on KS in sub-Saharan Africa at a hospital or population level has not been systematically documented.

We hypothesized that ART rollout should cause a decline in population-based incidence of Kaposi sarcoma in sub-Saharan Africa by comparing KS incidence to time periods pre and post rollout of ART.

2. Methods

This is a synthesis of literature on KS incidence and trends in relation to ART rollout in sub-Saharan Africa. We used KS incidence data available from WHO-International Agency for Research on Cancer (IARC) publications and the Africa Cancer Registry Network (AFCRN). National HIV prevalence and ART coverage data were derived from UNAIDS/WHO. Data on ART were gathered per sub-Saharan Africa country together with available HIV prevalence and available KS incident data. We reviewed published English articles on KS and ART related studies to assess the incidence of KS and the effect of ART over time in sub-Saharan Africa. Countries from North Africa were excluded because their climate conditions and cultural backgrounds have been considered to be more Mediterranean than African [34]. Conference abstracts were excluded. This review reflects on KS trends pre- and post-ART in sub-Saharan Africa.

2.1. KS age standardized incidence rates

KS incidence and trend data were derived from sub-Saharan African cancer registry reports in IARC Cancer Incidence in Five Continents (CI5) Volumes I-XI, two IARC Monographs on Cancer in Africa [39–41] and cancer registry reports published by the AFCRN [42,43]. KS age standardized (world) incidence rates (ASIR) per 100 000 persons were summarized for four time-periods, (1) before 1980 (before HIV/AIDS era); (2) 1981–2000 (early HIV/AIDS era, limited or no ART coverage); (3) 2001–2010 (early ART coverage period) and; (4) 2011–2016 (fair to good ART coverage period). Cancer registry data published by IARC and AFCRN were classified as being population-based (i.e. representing reasonable quality cancer registries and a good indication of KS incidence thus appearing in CI5 series (CI5 Vol VIII (1993–1998) [39], CI5 Vol X (2003–2007) [40], and CI5 Vol XI (2008–2012) [41]) and those published by AFCRN (Cancer in Africa Epidemiology and Prevention (1960–2000) [42], Cancer in Africa (2001–2014)(45) and Cancer in sub-Saharan Africa AFCRN Vol III [43]). GLOBOCAN reports (GLOBOCAN 2008 and 2012 reports [34,44], which in sub-Saharan Africa interpolate several countries' data, were only used for regional summary statistics.

2.2. Adult (15–49 years) HIV/AIDS prevalence, ART rollout and ART coverage percentage

Adult HIV prevalence data were drawn from country specific UNAIDS/WHO epidemiological fact sheet 2004 updates [45]. ART rollout and coverage data were drawn from data provided by UNAIDS/WHO website [46,47].

2.3. Regions

Data are presented for each country and within five African regions as defined by the United Nations Population Division [34]. Northern (excluded here for reasons mentioned previously, and for not falling in sub-Saharan Africa), Eastern, Southern, Middle (Central) and West Africa.

2.4. KS trends

Trends of the ASIR of the incidence of KS over the four time periods were presented graphically for males and females (Figs. 1 and 2). Fig. 3 illustrates the relationship between ART coverage and decline in KS incidence between 2001 and 2010 (early ART coverage period) and 2011–2016 (fair to good ART coverage period).

3. Results

Registries from eight of the 46 sub-Saharan African countries appeared in CI5 volumes I-XI and AFCRN reports and they were classified as fairly good quality registry data. Cancer registration coverage per region was poor with one country reporting out of the eight countries in Southern Africa, four countries out of the 14 countries in Eastern Africa, no country reporting in Central Africa (eight countries) and three countries reporting out of 16 West African countries.

3.1. ART Coverage (2018)

ART coverage increased from late 1990s, early 2000s to 2018, 30 countries have high (above 50%) ART rollout rates by 2018. In 2018 the lowest ART coverage was reported in Madagascar (9% in 2018) and the highest in Namibia at 92% [46,47].

3.2. Adult HIV prevalence, and ART roll out

The adult prevalence of HIV varies across sub-Saharan Africa, with a prevalence of $< 0.1\%$ in Comoros and 27.3% in Eswatini in the year 2018. Southern Africa has the highest burden of HIV compared to other regions. The earliest national rollout of ART in sub-Saharan Africa was in 1998 (Senegal); most countries rolled out ART in early 2000s and later programs started in 2006 (Chad).

3.3. Reported KS ASIR incidence per 100 000 from before 1980–2016

Table 1 reports the countries that reported KS ASIR to CI5. Before 1980, two population-based registries; Zimbabwe (Bulawayo) and Uganda (Kampala) reported KS incidence data for this period. Between 1981 and 2000, six registries reported KS cases and were published in CI5: Malawi, France La Reunion, Uganda (Kyadondo), Zimbabwe (Harare), The Gambia, and Mali (Bamako). For the period between 2001 and 2010, seven registries reported KS cases and were published in CI5: South Africa (Eastern Cape), Malawi, Uganda (Kyadondo), Zimbabwe (Harare), The Gambia, Mali (Bamako) and Nigeria (Ibadan). Seven registries published KS cases in CI5 between 2011 and 2016: South Africa (Eastern Cape), France La Reunion, Uganda (Kyadondo), Zimbabwe (Bulawayo), Zimbabwe (Harare), The Gambia and Mali (Bamako).

Table 2 reports on KS age standardized incidence rates (ASIR) for sub-Saharan African countries for 4 time-periods (pre-1980, 1981–2000,

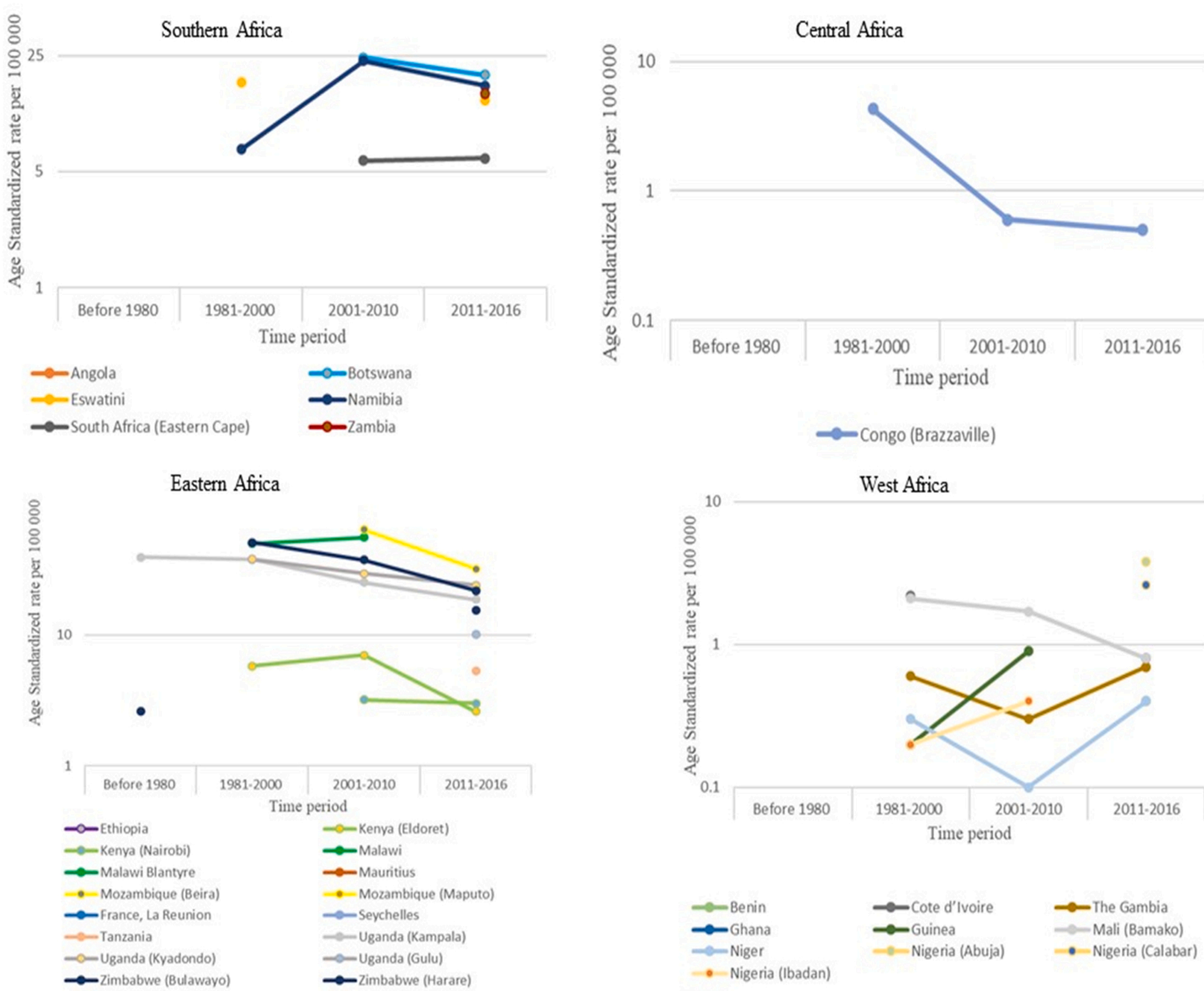

Fig. 1. KS ASIR per 100,000 trends in males (before 1980–2016) in sub-Saharan African countries. Cancer in Africa (2001–2014) [48]. Cancer in sub-Saharan Africa AFCRN Vol III [43]. Population based cancer registries. CI5 Vol VIII (1993–1998) [39]. CI5 Vol X (2003–2007) [40]. CI5 Vol XI (2008–2012) [41].
Data source: Cancer in Africa Epidemiology and Prevention (1960–2000) [42].

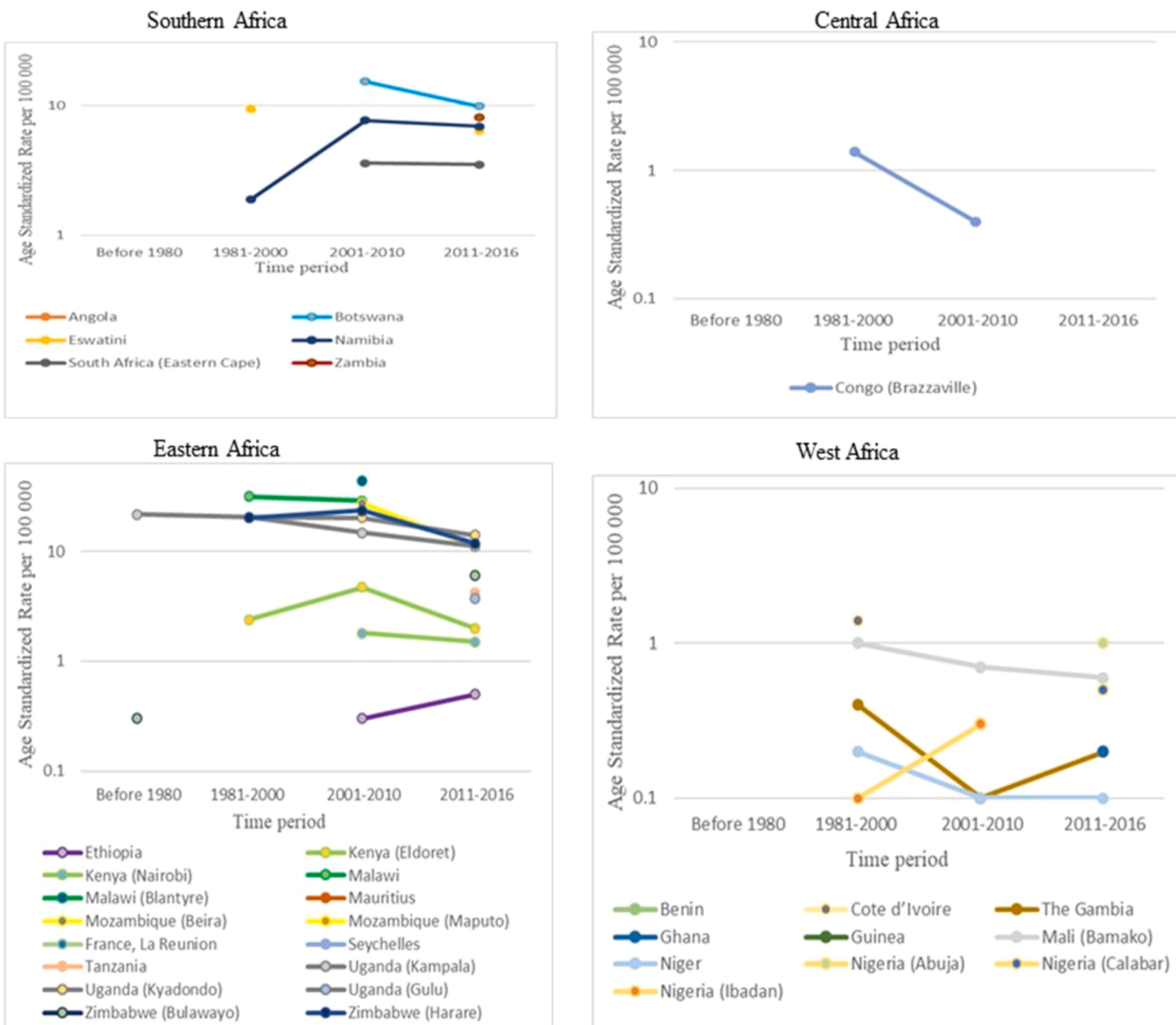

Fig. 2. KS ASIR per 100,000 trends in females (before 1980–2016) from sub-Saharan African countries. Cancer in Africa (2001–2014) [48]. Cancer in sub-Saharan Africa AFCRN Vol III [43]. Population based cancer registries. CI5 Vol VIII (1993–1998) [39]. CI5 Vol X (2003–2007) [40]. CI5 Vol XI (2008–2012) [41]. Data source Cancer in Africa Epidemiology and Prevention (1960–2000) [42].

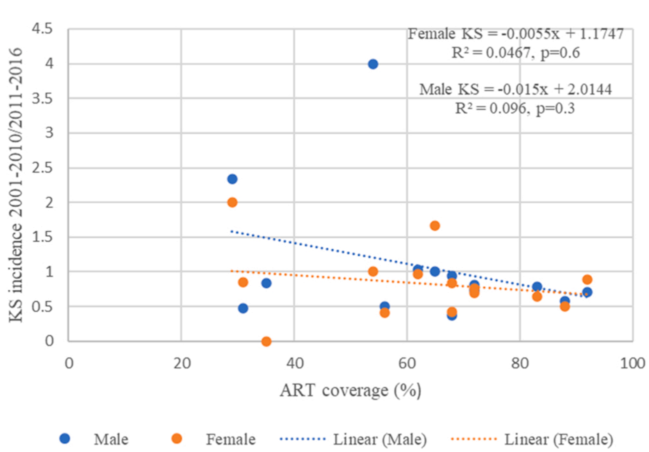

Fig. 3. Relationship between ART coverage and decline in KS incidence between 2001 and 2010 (early ART coverage period) and 2011–2016 (fair to good ART coverage period). Cancer in Africa (2001–2014) [48]. Cancer in sub-Saharan Africa AFCRN Vol III [43]. Population based cancer registries. CI5 Vol VIII (1993–1998) [39]. CI5 Vol X (2003–2007) [40]. CI5 Vol XI (2008–2012) [41].
Data source: Cancer in Africa Epidemiology and Prevention (1960–2000) [42].

Table 1
Countries that reported KS ASIR to C15 pre- and post- HIV/AIDS epidemic.

Country ASIR published in CI5	Pre- and post- HIV/AIDS epidemic			
	Before 1980	1981–2000	2001–2010	2011–2016
Zimbabwe	✓	✓	✓	✓
Uganda	✓	✓	✓	✓
Malawi		✓	✓	
France La Reunion		✓		✓
The Gambia		✓	✓	✓
Mali		✓	✓	✓
South Africa			✓	✓
Nigeria			✓	

2001–2010 and 2011–2016). Figs. 1 and 2 shows KS ASIR trends over the four time periods. KS incidence rates varied over 10–20-fold amongst countries, from 2.6 to 39.3 in males and 0.3–21.8 in females; pre-1980, 0.0–32.0 in males and 0.0–11.8 per 100 000 in females for 2011–2016. In the pre-1980 period, KS was so rare that it was often combined with skin cancer or other miscellaneous categories or not classified in cancer registry reports [39].

Table 2
The burden of KS in sub-Saharan African countries in the regions over pre- and post- HIV/AIDS epidemic ART rollout periods (<1980, 1981–2000, 2001–2010 and 2011–2016).

Sub-Saharan Africa regions / countries	Latest adult (15–49) HIV prevalence% (2018)[b]	Introduction of ART (Year)[c]	Latest estimated coverage of ART % (2018)[d]	Before 1980 KS ASIR per 100 000[e]		1981–2000 KS ASIR per 100 000 [f]		2001–2010 KS ASIR per 100 000 [g]		2011–2016 KS ASIR per 100 000 [h,i]	
				Male	Female	Male	Female	Male	Female	Male	Female
Southern Africa[a]								**11.5**	**5.1**	**7.6**	**4.7**
Angola	2	2003	27			0.0	0.0				
Botswana	20.3	2002	83					24.3	15.4	19.1	9.9
Eswatini	27.3	2003	86			17.2	9.5			13.5	6.4
Lesotho	23.6	2004	61								
Madagascar	0.3	2003	9								
Namibia	11.8	2003	92			6.8	1.9	23.2	7.7	16.4	6.9
South Africa (Eastern Cape)	20.4	2004	62					5.8	3.6	6.0	3.5
Zambia	11.8	2002	78							14.8	8.1
Eastern Africa[a]								**14.9**	**6.8**	**15.1**	**7.6**
Burundi	1	2003	80								
Comoros	< 0.1	2005	79								
Eritrea	0.7	2005	51								
Ethiopia	1	2005	65					0.6	0.3	0.6	0.5
Kenya (Eldoret)	4.7	2003	68			5.8	2.4	7.0	4.7	2.6	2.0
Kenya (Nairobi)								3.2	1.8	3.0	1.5
Malawi	9.2	2004	78	NC	NC	49.9	31.7	55.5	28.9		
Malawi (Blantyre)								91.8	43.6		
Mauritius	1.3	2001	22			0.0	0.0	0.0	0.0	0.0	0.0
Mozambique (Beira)	12.6	2004	56					63.6	27.5	32.0	11.2
Mozambique (Maputo)										22.7	11.6
France, La Reunion		2004				0.6	0.0			0.2	0.0
Rwanda	2.5	2003	87								
Seychelles		2001						0.0	0.0	0.0	0.0
Tanzania	4.6	2004	71							5.3	4.2
Uganda (Kampala)	N/A	2004	72	39.3	21.8	37.7	20.5	25.2	14.8	18.6	11.2
Uganda (Kyadondo)						37.9	20.4	29.5	20.2	24.0	14.1
Uganda (Gulu)										10.1	3.7
Zimbabwe (Bulawayo)	12.7	2004	88	2.6	0.3					15.5	6.0
Zimbabwe (Harare)						50.8	20.3	37.3	23.5	21.8	11.8
Central Africa[a]								**4.1**	**0.6**	**1.2**	**0.4**
Cameroon	3.6	2003	52								
Central African Republic	3.6	2003	36								
Chad	1.3	2006	51								
Congo (Democratic Republic)		2002	57								
Congo (Brazzaville)	2.6	2003	35			4.3	1.4	0.6	0.4	0.5	0.0
Equatorial Guinea	7.1	2005	34								
Gabon	3.8	2002	67								
Sao Tome & Principe	N/A	2005	N/A								
West Africa[a]								**1.9**	**1.2**	**0.9**	**0.6**
Benin	1	2002	61							0.4	0.0
Burkina Faso	0.7	2003	62								
Cape Verde	0.6	2004	89								
Cote d'Ivoire	2.6	2004	55			2.2	1.4			0.7	0.5
The Gambia	1.9	2004	29			0.6	0.4	0.3	0.1	0.7	0.2
Ghana	1.7	2004	34							0.8	0.2
Guinea	1.4	2003	40			0.2	0.0	0.9	0.3		
Guinea-Bissau	3.5	2005	33								
Liberia	1.3	2004	35								
Mali (Bamako)	1.4	2004	31	NC	NC	2.1	1.0	1.7	0.7	0.8	0.6
Mauritania	0.2	2003	54								
Niger	0.3	2005	54	NC	NC	0.3	0.2	0.1	0.1	0.4	0.1
Nigeria (Abuja)	1.5	2002	53							3.8	1.0
Nigeria (Calabar)										2.6	0.5
Nigeria (Ibadan)						0.2	0.1	0.4	0.3		
Senegal	0.4	1998	63	NC	NC						
Sierra Leone	1.5	2005	41								
Togo	2.3		60								

[a]GLOBOCAN 2008 and 2012 reports [34,44].
[b,c]UNAIDS/WHO epidemiological fact sheet 2004 update [45].
[d]UNAIDS website and WHO website [46,47].
[e,f,g,h]Population based cancer registries; AFCRN reports. Cancer in Africa Epidemiology and Prevention (1960–2000) [42]. Cancer in Africa (2001–2014) [48]. Cancer in sub-Saharan Africa AFCRN Vol III [43].
[i]Population based cancer registries; CI5 reports. CI5 Vol VIII (1993–1998) [39]. CI5 Vol X (2003–2007) [40]. CI5 Vol XI (2008–2012) [41].
N/A: Not applicable
NC: KS not classified.

3.3.1. *Southern Africa*

In the Southern African region, there was a lack of data on incidence rates of KS pre-1980. In 2008, GLOBOCAN reported that the KS incidence rates (per 100 000) for Southern Africa were 11.5 and 5.1 among males and females, respectively. GLOBOCAN 2012, reported a decrease on KS incidence rates (7.6 and 4.7 among males and females respectively). High incidence rates were reported in Swaziland/Eswatini [1981–2000]; males 17.2 and females 9.5. The ASIR decreased to 13.5 among males and 6.4 in females by 2011–2016. In Namibia, the incidence rates were lower for the 1981–2000 period [6.8 males, 1.9 females], there was a pronounced increase in the 2001–2010 period [23.2 males, 7.7 females].

3.3.2. *Eastern Africa*

Before 1980, only two registries (Uganda and Zimbabwe) out of the 14 countries in Eastern Africa reported KS age standardized incidence rates to IARC. There are still large gaps in data availability with no data reported for some countries. GLOBOCAN 2008 and 2012 reports indicate that this region shoulders most of the KS burden in sub-Saharan Africa. For 2001–2010, the ASIR for males was 14.9 and 6.8 for females and the rates increased to 15.1 for males and 7.6 for females [2011–2016]. Mozambique and Zimbabwe reported high incidence rates. In Mozambique (Beira), the ASIR for KS was 63.6 for males and 27.5 for females [2001–2010] and decreased to 32.0 for males and 11.2 females [2011–2016]. In Zimbabwe (Harare), the KS incidence rate was high 50.8 for males and 20.8 for females [1981–2000]. The reported rates decreased to 37.3 for males and 23.5 for females [2001–2010] and 18.4 for males and 10.3 for females [2011–2016].

3.3.3. *Central Africa*

GLOBOCAN reported that the KS ASIR for Central Africa were 4.1 and 0.6 among males and females respectively in 2008. GLOBOCAN 2012, reported a decrease on KS incidence rates (1.2 and 0.4 among males and females respectively). The only country that reported over all time periods was Congo (Brazzaville) and was characterized by a decrease in KS incidence rates over time. KS incidence varied from 4.3 for males and 1.4 for females [1981–2000] to 0.6 for males and 0.4 for females [2001–2010] and during 2011–2016 the ASIR for males was 0.5 and 0.0 for females.

3.3.4. *West Africa*

This region reported the lowest KS ASIR and the rates decreased over time. The ASIR was 1.9 for males and 1.2 for females [2001–2010] and the rates decreased to 0.9 for males and 0.6 for females [2011–2016] according to the GLOBOCAN reports in 2008 and 2012. Mali (Bamako) reported KS rates ranging from 2.1 for males and 1.0 for females [1981–2000] to 1.7 for males and 0.7 for females [2001–2010] and during 2011–2016 the ASIR declined for males to 0.8 and to 0.6 for females.

In summary, in the 16 registries from 14 countries that had sufficient serial data on KS, two showed no increase or decrease, 10 showed a decline and four showed an increase in KS incidence between 2000 and 2010 (early ART coverage period) and 2011–2016 (fair to good ART coverage period). GLOBOCAN reports on regional KS incidence estimates which vary from country to country within each region. With the understanding that these data are limited, incomplete and “ecological”, Fig. 3 illustrates the geographical association between percentage ART coverage (latest data available in 2018) and KS incidence in the early vs. more recent ART periods. The overall unweighted average decline in KS incidence between the early ART and later period was 27%, but this decline was not statistically significant across the region. Fig. 4 illustrates the relationship between the latest adult (15–49) HIV prevalence (%) and KS incidence between 2011 and 2016. There was a moderate positive correlation between HIV prevalence and KS incidence for males and females.

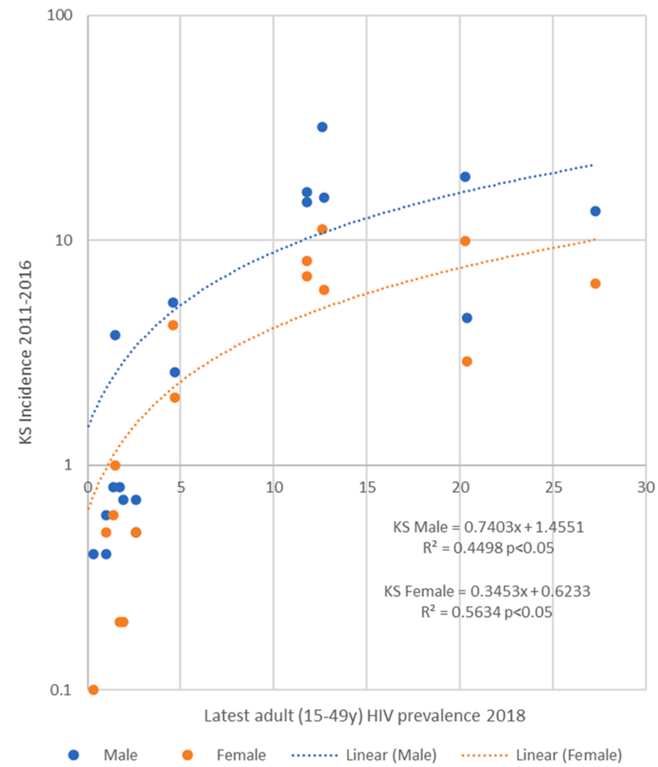

Fig. 4. Relationship between latest adult (15–49) HIV prevalence and KS incidence between 2011 and 2016. Cancer in Africa (2001–2014) [48]. Cancer in sub-Saharan Africa AFCRN Vol III [43]. Population based cancer registries. CI5 Vol VIII (1993–1998) [39]. CI5 Vol X (2003–2007) [40]. CI5 Vol XI (2008–2012) [41].
Data source: Cancer in Africa Epidemiology and Prevention (1960–2000) [42].

4. Discussion

4.1. *Data quality and coverage*

There is a significant under-reporting of cancer incidence in sub-Saharan Africa as there are few population-based cancer registries in the region. Cancer registration has been progressing slowly since the 1980 s and this can be attributed to several factors like insufficient and poor coordination of data sources, lack of adequately trained staff, poor infrastructure and low to no political will in other countries [42,49,50]. The KS incidence data used is from WHO-IARC and from AFCRN publications. These are considered to be reliable data source and cover about 24 countries – however not all of the data reported in the AFCRN are as strictly quality assured as in CI5. Prior to the onset of the HIV/AIDS epidemic in the 1980 s there were clear geographical variations in KS incidence within Africa. These are not obvious from sparse, high quality incidence data but previous work using relative frequencies does illustrate wide variations between central & East Africa compared to areas north and south [51].

4.2. *The effect of ART on KS incidence in sub-Saharan Africa*

During periods 2001–2010 and 2011–2016, 11 out of 16 registries with sufficient trend data showed a decline in KS incidence. Changes in KS incidence between these two periods vary from a 63% decline (Kenya, males) to a 400% increase (Nigeria, males), a crude average decline of 6%. KS trend data from a similar period (2000–2016) from the USA show a decrease in incidence of 35% [52].

The decrease in KS incidence has been small, this was not associated with ART coverage as measured [7,32] and possibly more related to broader changes in the HIV prevalence in many sub-Saharan African countries over the years. One study reported that between 2000 and 2017, the estimated country level HIV prevalence increased in 15 of the 46 sub-Saharan African countries, unfortunately changes in HIV prevalence are not necessarily linear or consistently in the same direction in the region [53]. Another study reported a decline in HIV infections of more than 33% from an estimated 2.2 (2.1–2.3) million in 2005–1.5 (1.3–1.6) million in 2013, ART scale up and wide coverage were attributed to the substantial declines in new HIV infections [12].

Despite ART scale up in African countries HIV/AIDS-associated KS burden remains high in sub-Saharan Africa due to ART coverage gaps and policy variation [27,54]. Total coverage and implementation of 'test and treat all' is still a challenge in many sub-Saharan African countries because of limited resources and logistical issues [27]. In sub-Saharan Africa, the availability of ART has not completely resolved the challenges of epidemic KS [1]. The availability of oncologic care services and the existing underlying comorbidities may also be contributing to the variations [28].

Some of the decline in KS incidence can be attributed to the introduction of ART in sub-Saharan Africa, in the early 2000s and a drop in the HIV prevalence over the years. This is substantiated by epidemiological studies in South Africa and Uganda that reported an increase in KS cases, as the HIV/AIDS epidemic progressed, followed by a subsequent decrease once ART was introduced [19,55,56]. Epidemic KS is an important public health problem in sub-Saharan Africa because of the high KSHV and HIV prevalence [35–37]. KSHV is common in sub-Saharan Africa countries like Cameroon and Uganda where KS was relatively frequent pre-1980, but the virus is also common in countries like Botswana and Gambia where KS was rare before the spread of HIV [57]. KS is more common in males. It is not clear why KS is much more frequent in males. This suggests the need for more studies on the cofactors in the etiology of KS [9], and ideally development of an effective KSHV vaccine.

3. Limitations

Only 2% of the continent's population was covered by cancer registries that complied with the International Agency for Research on Cancer (IARC) quality standards in 2014. This indicates significant lack of population-based registries in Africa [27,31]. We used population-based registry data for cancer incidence, HIV prevalence and ART coverage data to reflect population trends. We acknowledge that the data are geographical, and the role of ART may not be ascertained using such correlation methods, differences in data sources used and large variations in ARV rollout policies.

6. Conclusion

In sub-Saharan Africa, there is limited evidence of a decline in KS incidence after the rollout of ART in some countries. However, epidemic KS continues to be a major public health problem in terms of morbidity and mortality. There is a paucity of literature on the burden of KS, risk factors associated with KS and the impact of ART on KS. There is a need for direct measures of the incidence and risk factors for KS in sub-Saharan Africa and effects of treatments. These could then be used to inform interventions, prevention, and management policies.

The continued recording of high numbers of KS in sub-Saharan Africa contrasts with its decline in developed countries and could be attributed to the ART treatment gap in the sub-Saharan Africa. The long-term effect of ART on KS in resource-limited regions like sub-Saharan Africa still needs to be evaluated to inform prevention and management interventions to improve the overall outcome for individuals living with HIV in this region. This requires continued investment in research of HIV associated malignancies in sub-Saharan Africa [27].

CRediT authorship contribution statement

Melitah Motlhale: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. Freddy Sitas: Conceptualization, Validation, Resources, Supervision, Writing – review & editing. Elvira Singh: Conceptualization, Validation, Resources, Supervision, Writing – review & editing. Debbie Bradshaw, Wenlong Carl Chen, Mwiza Gideon Singini, Chantal Babb de Villiers, Cathryn M. Lewis, Mazvita Muchengeti, Tim Waterboer, Christopher G. Mathew, Freddy Sitas and Elvira Singh and Robert Newton are the members of ERICA_SA collaborative group. All authors read and provided feedback (writing: review and editing) to improve the final version of the manuscript.

Acknowledgement

This study was supported by the South African Medical Research Council and the UK Medical Research Council (with funds from the UK Government's Newton Fund) (MRC-RFA-SHIP 01-2015). The authors are solely responsible for the contents of this publication and do not necessarily represent views of the funders.

Conflict of Interest

The authors declare that there are no conflicts of interest.

References

[1] A. Dalla Pria, D.J. Pinato, M. Bracchi, M. Bower, Open Peer Review Recent advances in HIV-associated Kaposi sarcoma, F1000 Res. 8 (2019) 970.
[2] P. Cook-Mozaffari, R. Newton, V. Berai, D.P. Burkitt, The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic, Br J. Cancer 78 (11) (1998) 1521–1528.
[3] J. Orem, Cancer prevention and control: Kaposi ' s sarcoma, eCancer 13 (2019) 951.
[4] L. Jakob, G. Metzler, K.M. Chen, C. Garbe, Non-aids associated kaposi's sarcoma: clinical features and treatment outcome, PLoS One 6 (4) (2011) 2–7.
[5] G. Sissolak, P. Mayaud, AIDS-related Kaposi's sarcoma: epidemiological, diagnostic, treatment and control aspects in sub-Saharan Africa, Trop. Med. Int. Health 10 (10) (2005) 981–992.
[6] L. Stein, M.I. Urban, D. O'Connell, Q.Y. Xue, V. Beral, R. Newton, et al., The spectrum of human immunodeficiency virus-associated cancers in a South African black population: Results from a case-control study, 1995-2004, Int. J. Cancer 122 (10) (2008) 2260–2265.
[7] T. Dhokotera, J. Bohlius, A. Spoerri, M. Egger, J. Ncayiyana, V. Olago, et al., The burden of cancers associated with HIV in the South African public health sector, 2004-2014: a record linkage study, Infect. Agent Cancer 14 (1) (2019) 1–12.
[8] F. Sitas, R. Newton, Kaposi ' s Sarcoma in South Africa AND, J. Natl. Cancer Inst. Monogr. 28 (2000) 1–4.
[9] M. Dedicoat, R. Newton, Review of the distribution of Kaposi's sarcoma-associated herpesvirus (KSHV) in Africa in relation to the incidence of Kaposi's sarcoma, Br. J. Cancer 88 (2003) 1–3.
[10] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. Volume 100 B. A review of human carcinogens. IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer. 2012.
[11] W. Klaskala, B.P. Brayfield, C. Kankasa, G. Bhat, J.T. West, C.D. Mitchell, C. Wood, Epidemiological characteristics of human herpesvirus-8 infection in a large population of antenatal women in Zambia, J. Med. Virol. 75 (1) (2005) 93–100.
[12] A.B.M. Kharsany, Q.A. Karim, HIV infection and AIDS in Sub-Saharan Africa: current status, challenges and opportunities, Open AIDS J. 10 (1) (2016) 34–48.
[13] UNAIDS, 2011. Global HIV/AIDS response. Epidemic update and health sector progress towards Universal Access. Geneva, Switzerland; 2011.
[14] F. Sitas, H. Carrara, V. Beral, R. Newton, G. Reeves, D. Bull, et al., Antibodies against human herpesvirus 8 in Black South African Patients with cancer, N. Engl. J. Med. 340 (24) (1999) 1863–1871.
[15] E.A. Rogena, K.O. Simbiri, G. De Falco, L. Leoncini, L. Ayers, J. Nyagol, A review of the pattern of AIDS defining, HIV associated neoplasms and premalignant lesions diagnosed from 2000-2011 at Kenyatta National Hospital, Kenya, Infect. Agent Cancer 10 (1) (2015) 1–7.
[16] S.J. Lidenge, T. Tran, F.Y. Tso, J.R. Ngowi, D.M. Shea, J. Mwaiselage, et al., Prevalence of Kaposi's sarcoma-associated herpesvirus and transfusion-transmissible infections in Tanzanian blood donors, Int. J. Infect. Dis. 95 (2020) 204–209.
[17] J. Ziegler, R. Newton, D. Bourboulia, D. Casabonne, V. Beral, E. Mbidde, et al., Risk factors for Kaposi's sarcoma: a case-control study of HIV-seronegative people in Uganda, Int. J. Cancer 103 (2) (2003) 233–240.

[18] K. Wakeham, E.L. Webb, I. Sebina, L. Muhangi, W. Miley, W.T. Johnson, et al., Parasite infection is associated with Kaposi's sarcoma associated herpesvirus (KSHV) in Ugandan women, Infect. Agent Cancer 6 (1) (2011) 15.

[19] E. Rohner, M. Kasaro, S.C. Msadabwe-chikuni, K. Stinson, Z. Mohamed, H. Tweya, Treatment and outcome of AIDS-related Kaposi sarcoma in South Africa, Malawi and Zambia: an international comparison, Pan Afr. Med. J. 28 (261) (2017) 1–8.

[20] G.P. Semango, R.M. Charles, C.I. Swai, A. Mremi, P. Amsi, T. Sonda, et al., Prevalence and associated risk factors for Kaposi's sarcoma among HIV-positive patients in a referral hospital in Northern Tanzania: a retrospective hospital-based study, BMC Cancer 18 (1) (2018) 1–8.

[21] M.S.R. Hutt, The Epidemiology of Kaposi's Sarcoma, Antibiot. Chemother. 29 (1981) 3–8.

[22] F.M. Asiimwe, D.M. Moore, W. Were, R. Nakityo, J. Campbell, A. Barasa, et al., Clinical outcomes of HIV-infected patients with Kaposi's sarcoma receiving nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy in Uganda, HIV Med. 13 (3) (2012) 166–171.

[23] C. Slaught, V. William, S. Grover, E. Bigger, M. Kayembe, S. Chiyapo, et al., A retrospective review of patients with Kaposi's sarcoma in Botswana, Int. J. Dermatol. 58 (6) (2018) 707–712.

[24] A.G. Oettle, Geographical and racial differences in the frequency of Kaposi's Sarcoma as evidence of environmental or genetic causes, Acta Unio Int. Contra Cancrum 18 (1962) 330–336.

[25] K. Stolka, P. Ndom, J. Hemingway-Foday, J. Iriondo-Perez, W. Miley, N. Labo, et al., Risk factors for Kaposi's sarcoma among HIV-positive individuals in a case control study in Cameroon, Cancer Epidemiol. 38 (2) (2014) 137–143.

[26] Y. Chang, E. Cesarman, M.S. Pessin, F. Lee, J. Culpepper, D.M. Knowles, et al., Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's Sarcoma, Science 266 (1994) 1865–1870, 80.

[27] L. Chinula, A. Moses, S. Gopal, HIV-associated malignancies in sub-Saharan Africa: progress, challenges, opportunities, Curr. Opin. HIV AIDS 12 (1) (2017) 89–95.

[28] J. Bohlius, F. Valeri, M. Maskew, H. Prozesky, D. Garone, M. Sengayi, et al., Cohort study in the antiretroviral therapy Era, Inter 135 (11) (2014) 2644–2652.

[29] A. Mosam, F. Shaik, T.S. Uldrick, T. Esterhuizen, G.H. Friedland, D.T. Scadden, et al., A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy-naive patients with HIV-associated Kaposi sarcoma in South Africa, J. Acquir. Immune Defic. Syndr. 60 (2) (2012) 150–157.

[30] P.H. Gonçalves, T.S. Uldrick, R. Yarchoan, HIV-associated Kaposi Sarcoma and related diseases, AIDS 31 (14) (2017) 1903–1916.

[31] E. Amerson, C.M. Woodruff, A. Forrestel, M. Wenger, T. McCalmont, P. LeBoit, et al., Accuracy of clinical suspicion and pathologic diagnosis of Kaposi sarcoma in East Africa, J. Acquir. Immune Defic. Syndr. 71 (3) (2016) 295–301.

[32] A.S. Semeere, N. Busakhala, J.N. Martin, Impact of antiretroviral therapy on the incidence of Kaposi's sarcoma in resource-rich and resource-limited settings, Curr. Opin. Oncol. 24 (5) (2012) 522–530.

[33] M. Lahuerta, F. Ue, S. Hoffman, B. Elul, S.G. Kulkarni, Y. Wu, et al., The problem of late ART initiation in sub-Saharan Africa: a Transient aspect of scale-up or a long-term phenomenon? J. Health Care Poor Underserv. 24 (1) (2013) 359–383.

[34] J. Ferlay, H.R. Shin, F. Bray, D. Forman, C. Mathers, D.M. Parkin, Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008, Int. J. Cancer 127 (12) (2010) 2893–2917.

[35] WHO, Guidelines for Managing Advanced of Antiretroviral Rapid Initiation Hiv Disease and Therapy, WHO, Geneva, Switzerland, 2017.

[36] UNAIDS, 2014. 90–90-90 An ambition to help end the AIDS epidemic. Geneva, Switzerland; 2014.

[37] A. Mosam, H. Carrara, F. Shaik, T. Uldrick, A. Berkman, J. Aboobaker, et al., Increasing incidence of Kaposi's sarcoma in black South Africans in KwaZulu-Natal, South Africa (1983-2006), Int. J. STD AIDS 20 (2009) 553–556.

[38] A. Mosam, J. Aboobaker, F. Shaik, Kaposi's sarcoma in sub-Saharan Africa: a current perspective, Curr. Opin. Infect. Dis. 23 (2) (2010) 119–123.

[39] D.M. Parkin, S.L. Whelan, J. Ferlay, L. Teppo, D.B. Thomas, Cancer Incidence in Five Continents, VIII, IARC Scientific Publications, Lyon, France, 2002.

[40] D. Forman, F. Bray, D.H. Brewster, C. Gombe Mbalawa, B. Kohler, M. Piñeros, E. Steliarova-Foucher, R. Swaminathan, et al., Cancer Incidence in Five Continents, X, IARC Scientific Publications, Lyon, France, 2014.

[41] Bray F., Colombet M., Mery L., Piñeros M., Znaor A., Zanetti R., et al., 2017.Cancer Incidence in Five Continents, Vol. XI. IARC Scientific Publications No. 166. Vol. XI, Lyon: International Agency for Research on Cancer. 2017.

[42] Parkin DM, Ferlay J., Hamdi-Cherif M., Sitas F., Thomas JO, Wabinga H., et al., 2003. Cancer in Africa Epidemiology and Prevention. Lyon, France; 2003.

[43] D.M. Parkin, A. Jemal, F. Bray, A.R. Korir, B. Kamate, E. Singh, et al., Cancer in Sub-Saharan Africa-, UICC III (2019).

[44] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, et al., Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012, Int. J. Cancer 136 (2015) E359–E386.

[45] UNAIDS/ WHO, 2004. Epidemiological fact sheet 2004 update. 2004. p. 〈https://data.unaids.org/publications/fact-sheets01〉.

[46] UNAIDS, 2018. ARV rollout and coverage. 2018. p. 〈https://www.unaids.org/en/regionscountries/countri〉.

[47] WHO, 2019. HIV Country Profile. 2019. p. 〈https://cfs.hivci.org/country-factsheet.html〉.

[48] D.M. Parkin, F. Bray, J. Ferlay, A. Jemal, Cancer in Africa 2012, Cancer Epidemiol. Biomark. Prev. 23 (6) (2014) 953–966.

[49] A.E. Omonisi, B. Liu, D.M. Parkin, Population-based cancer registration in sub-saharan africa: its role in research and cancer control, JCO Glob. Oncol. (6) (2020) 1721–1728.

[50] D.M. Parkin, L.D. Sanghvi, Cancer registration in developing countries, IARC Sci. Publ. 95 (1991) 185–198.

[51] M.S.R. Hutt, Classical and endemic form of Kaposi's sarcoma. a review, Antibiot. Chemother. 32 (1984) 12–17.

[52] D.L. White, A. Oluyomi, K. Royse, Y. Dong, H. Nguyen, E. Chang, et al., Incidence of AIDS-Related Kaposi Sarcoma in all 50 United States from 2000 to 2014, J. Acquir. Immune Defic. Syndr. 81 (4) (2019) 387–394.

[53] L. Dwyer-Lindgren, M.A. Cork, A. Sligar, K.M. Steuben, K.F. Wilson, N.R. Provost, et al., Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017, Nature 570 (7760) (2019) 189–193.

[54] K. Church, F. Kiweewa, A. Dasgupta, M. Mwangome, E. Mpandaguta, F.X. Gómez-Olivé, et al., A comparative analysis of national HIV policies in six African countries with generalized epidemics, Bull. World Health Organ 93 (7) (2015) 457–467.

[55] F. Okuku, E.M. Krantz, J. Kafeero, M.R. Kamya, J. Orem, C. Casper, et al., Evaluation of a predictive staging model for HIV-associated Kaposi sarcoma in Uganda, J. Acquir. Immune Defic. Syndr. 74 (5) (2017) 548–554.

[56] E. Majaya, B.V. Girdler-Brown, M. Muchengeti, E. Singh, The impact of the South African antiretroviral treatment programme on the age-standardised incidence rate of Kaposi sarcoma, 1999–2016: an interrupted time series analysis, Int. J. Infect. Dis. 102 (2021) 20–27.

[57] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, et al., Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424.