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HIV-associated malignancies in sub-Saharan Africa: progress, challenges, opportunities

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Abstract

Purpose of review—Summarize recent developments for HIV-associated malignancies (HIVAM) in low- and middle-income countries (LMIC) with particular focus on sub-Saharan Africa (SSA).

Recent findings—Antiretroviral therapy (ART) scale-up is leading to epidemiologic transitions in LMIC similar to high-income countries, with aging and growth of HIV-infected populations, declining infectious deaths, increasing cancer deaths, and transitions from AIDS-defining cancers (ADC) to non-AIDS defining cancers (NADC). Despite ART scale-up, HIVAM burden remains high including enormous ADC burden in SSA. For Kaposi sarcoma (KS), patients treated with ART and chemotherapy can experience good outcomes even in rural SSA, but KS heterogeneity remains insufficiently understood including virologic, immunologic, and inflammatory features which may be unique to LMIC. For cervical cancer, scale-up of prevention efforts including vaccination and screening is underway, with benefits already apparent despite continuing high disease burden. For non-Hodgkin lymphoma (NHL), curative treatment is possible in the ART era even in SSA, and multifaceted approaches can improve outcomes further. For many other prevalent HIVAM, care and research efforts are being established to guide treatment and prevention specifically in LMIC.

Summary—Sustained investment for HIVAM in LMIC can help catalyze a cancer care and research agenda which benefits HIV-positive and HIV-negative patients worldwide.

Keywords

HIV-associated malignancies; low- and middle-income countries; sub-Saharan Africa; Kaposi sarcoma; cervical cancer; non-Hodgkin lymphoma

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Conflicts of interest

We have no conflicts of interest to declare.

Introduction

Just as the worldwide HIV pandemic disproportionately affects populations in low- and middle-income countries (LMIC), especially sub-Saharan Africa (SSA), so too does the parallel epidemic of HIV-associated malignancies (HIVAM) which are often the most common cancers overall in highly HIV-endemic countries. For HIV itself, the last two decades have witnessed a remarkable global effort for prevention, treatment, and research, resulting from worldwide advocacy and multilateral investment, with a reach that now extends to some of the remotest villages in some of the world's poorest countries. A comparable effort for HIVAM is taking shape. In this review, we summarize recent developments for HIVAM in LMIC, highlighting progress, challenges, and opportunities in this emerging field.

Epidemiology

The global HIV epidemic is concentrated in LMIC, and SSA specifically, with 69% of the worldwide HIV-infected population living in this region in 2015 [1]. In SSA, public sector ART provision in most countries began in the mid-2000s, with 11.8 million individuals now receiving ART or 46% or those living with HIV. Importantly, with accumulating evidence demonstrating individual- and population-level benefits of earlier ART, World Health Organization (WHO) guidelines for ART eligibility in LMIC have become progressively more inclusive. All HIV-infected individuals are now recommended to receive ART irrespective of CD4 count [2], although many countries have yet to implement treating all HIV-positive people due to resource limitations and logistical issues. As a result, despite dramatic increases in ART availability worldwide, the coverage gap in most LMIC remains considerable. Moreover, achievements in ART scale-up are fragile and conditional on ongoing commitments by governments and external donors, with potential for gains to be reversed if commitments are not firm. Finally, despite ambitious targets and incremental progress to provide earlier ART, HIV-infected individuals in LMIC still typically initiate ART with advanced immunosuppression [3], accruing significant risk of morbidity compared to asymptomatic patients treated before CD4 count depletion or HIV-related complications. LMIC therefore have substantial HIV-infected populations who still cannot access timely HIV diagnosis and treatment, similar to early years before public sector ART availability, along with large numbers of patients having well controlled HIV on long-term ART, for whom epidemiologic transitions toward chronic non-communicable disease (NCD) complications of HIV are occurring as in resource-rich settings.

With respect to HIVAM epidemiology, data from high-income countries demonstrate that the proportion of HIV-related deaths due to cancer is increasing [4], HIVAM are transitioning from AIDS-defining cancers (ADC) to non-AIDS defining cancers (NADC) [5], and CD4 count and HIV control at cancer diagnosis are improving even for patients with ADC [6]. However, several factors make it difficult to fully assess the degree to which trends in resource-rich settings are replicated in LMIC, even aside from less mature ART coverage. There are severe deficits in cancer registration in LMIC, particularly SSA and even for registries contributing to WHO global cancer estimates, including low population coverage, significant urban bias, and low data quality [7**]. Even in well enumerated HIV cohorts

retained in care on chronic ART, ascertainment of cancer diagnoses is poor [8*]. Diagnostic pathology in SSA is also limited, and often under-utilized when it exists [9]. Even for superficial tumors which can be visualized and often are diagnosed clinically in SSA, like Kaposi sarcoma (KS) and ocular surface squamous neoplasia (OSSN), clinical diagnosis performs poorly compared to pathology with positive predictive value less than 80% [10*, 11*]. For more visceral tumors, not only pathology limitations but inadequate surgical or interventional capabilities to obtain diagnostic tissue results in these tumors also being underrepresented. In Malawi, investments to build and improve pathology infrastructure led to the 'discovery' of HIV-associated multicentric Castleman disease (MCD), which is scarcely reported from SSA and in Malawi was often misdiagnosed as lymphadenitis due to tuberculosis or HIV [12, 13*]. Finally, because cancer diagnosis and care are highly centralized in LMIC, there is significant referral bias affecting all cancer burden descriptions, such that tumors at the most indolent and fulminant ends of the clinical spectrum may be underrepresented, as patients may die before presenting to tertiary centers when severely ill or forego spending time and money to seek care for mild symptoms. Even in Botswana, a country with a relatively small population and high per capita resource level relative to many of its neighbors, as well as one of the region's most successful national ART programs, a median 13-month delay has been documented from symptom onset to receipt of subspecialty oncology care across diverse cancer patients [14**].

Despite these caveats, data are emerging that ART availability in LMIC may be producing trends which at least partly resemble resource-rich settings. Perhaps not surprisingly, similar trends to high-income countries are most evident thus far in middle-income countries, where ART coverage and cancer diagnostic infrastructure are better than low-income countries. For instance, in Botswana, ART expansion has resulted in significant decreases in age-specific cancer risk for HIV-infected individuals [15**]. However, just as in resource-rich settings, when declining incidence is coupled to growth and aging of HIV-positive populations, HIVAM burden is static without significant declines. Similarly, in both China and Brazil, relative ADC declines and NADC increases are occurring as in high-income countries [16*, 17*]. Conversely, in most of SSA, ADC still dominate with incidence declines most consistently observed for KS, although KS incidence remains high throughout the region and is often among the most frequent cancers overall [15**, 18*, 19*, 20, 21**, 22]. HIVAM are therefore unlikely to recede as a public health problem in LMIC in the near term despite ART scale-up. Studies from SSA have also suggested links between HIV and malignancies without well described associations with HIV in high-income countries. An example is esophageal squamous cell carcinoma which occurs with high frequency in much of SSA for reasons that remain unclear, and which has been associated with HIV in a case-control study from Zambia [23*]. A linkage study between HIV and cancer registries in Uganda also suggested potentially novel associations between HIV and several tumors including kidney, thyroid, uterine, breast, and nasopharyngeal cancers [24]. More definitive regional epidemiologic studies are needed to prove or disprove these associations.

Kaposi sarcoma

As noted above, KS is the most frequent cancer in many SSA countries. Patients with HIV-associated KS in SSA have higher mortality, higher risk of immune reconstitution

inflammatory syndrome (IRIS), and more frequently detectable Kaposi sarcoma-associated herpesvirus (KSHV) in peripheral blood than cohorts in resource-rich settings [25]. For KS, the KART study conducted in Durban remains the only clinical trial completed in SSA in the ART era, and demonstrated better tumor response but similar overall survival at one year for HIV-infected patients with primarily advanced KS treated with ART plus chemotherapy (ABV; doxorubicin, bleomycin, vincristine) compared with ART alone [26]. Two ongoing multinational studies co-sponsored by the AIDS Clinical Trials Group and AIDS Malignancy Consortium are evaluating treatment strategies for limited and advanced KS respectively [27, 28]. The limited KS trial is comparing ART alone to ART plus oral etoposide, and the advanced KS trial is comparing ART for all patients with oral etoposide, intravenous paclitaxel, or intravenous bleomycin plus vincristine. Final results from both studies will inform regional practice. Apart from clinical trials at urban SSA referral centers, we have demonstrated in Malawi that ART with chemotherapy (paclitaxel or bleomycin/vincristine) can produce excellent outcomes even in extremely remote areas, when implemented using standardized algorithms with appropriate levels of support for nurses and clinical officers [29**]. In this cohort, anemia and low body mass index were significantly associated with worse survival.

Associations between anemia and poor outcomes are interesting given Malawi experience with MCD, which has been observed almost exclusively among HIV-infected individuals with excellent long-term HIV control on ART often without evident KS [12, 13*]. Patients with MCD have had severe illness including profound anemia with markedly elevated plasma KSHV levels, and have typically responded to chemotherapy but relapsed shortly after chemotherapy was discontinued with subsequently poor outcomes in the absence of rituximab availability. The association between anemia and worse survival for HIV-associated KS raises questions as to whether concurrent MCD, KSHV-associated inflammatory cytokine syndrome (KICS), or a virologic, inflammatory, and/or immunologic milieu at least partially resembling these disorders, may occur in some KS patients in SSA and contribute to worse outcomes. Work in Uganda has suggested that immune activation via induction of indoleamine dioxygenase may be associated with reduced KS incidence in HIV-positive people [30*], and similar pathways might be implicated in differential outcomes for patients with KS. Overall, heterogeneity among HIV-associated KS patients in SSA, including development of IRIS, remains poorly understood, and numerous groups are working to define KS subtypes and clinical implications more clearly. In Malawi, our group demonstrated the possible existence of KS subtypes defined by KSHV transcription either limited to latency loci or extending across the viral genome [31]. Other groups have provided novel descriptions of pediatric KS [32**–34], a distinct form of KS frequently characterized by lymphadenopathy and peripheral blood cytopenias, which is highly geographically restricted to SSA where HIV and KSHV are prevalent and both often acquired during childhood [35**].

Cervical cancer

Cancers caused by human papillomavirus (HPV), particularly cervical cancer, exact an enormous toll in LMIC, and are unique among HIVAM in having established preventive interventions, including immunization against HPV and screening for dysplasia. Efforts to

optimize delivery of these measures in LMIC are ongoing, and in SSA are often piggybacked onto infrastructure developed for HIV care. Similar to ART scale-up, substantial progress can be achieved within relatively short periods with committed support for population-level implementation. In Rwanda, more than 90% coverage with HPV vaccine among school-age girls was achieved within five years of the national program being initiated [36**], and within two years HPV prevalence was lower among vaccinated versus unvaccinated girls [37**]. Just as in resource-rich settings, community education is paramount to optimize vaccine uptake, as evidenced in Kenya where higher teacher knowledge about HPV may be an important factor facilitating success of school-based immunization [38*]. Even with widespread availability of HPV vaccination, effects on HPV-associated cancer incidence will not be immediate. Moreover, the quadrivalent vaccine which has been most widely adopted is less immunogenic in HIV-infected women with severe immunosuppression [39], and vaccination has yet to be applied in most LMIC to at-risk populations other than school-age girls, including boys. The quadrivalent vaccine also provides limited protection against oncogenic HPV subtypes other than 16 and 18, with non-16/18 subtypes being responsible for approximately 20% of cervical cancer globally [40], although the proportion of cases attributable to 16/18 versus non-16/18 HPV subtypes does not appear to differ in SSA by HIV status [41**].

Vaccine scale-up must be accompanied by screening scale-up, for which high-level evidence exists that this can be implemented on a large scale using visual inspection with acetic acid (VIA) or HPV testing, with consequent mortality reductions related to cervical cancer [42, 43]. Substantial progress in scaling up VIA has been made in many LMIC countries, for example Zambia, where a large national screening program has found an extremely high burden of high-grade dysplasia and cancer especially among women with HIV [44**, 45**]. Other methods to optimize screening are under evaluation, including evaluations of HPV testing specifically among HIV-positive women and use of self-collected specimens [46, 47]. As these efforts move forward, best practices for cervical cancer screening in LMIC will become better defined to achieve more immediate declines in disease-specific incidence and mortality, while longer-term effects of population-level HPV immunization are awaited.

Despite vaccination and screening, cervical cancer cases continue to occur, and treatment in SSA is made difficult by scarce or absent radiotherapy in many countries [48], as is typically required for women with stage IB2 or greater tumors who cannot be treated with surgical resection alone. Overall, cervical cancer treatment studies have been few, but the AIDS Malignancy Consortium has recently completed a study evaluating the feasibility of cisplatin-based chemoradiation specifically among HIV-infected women with locally advanced cervical cancer in Zimbabwe [49].

Non-Hodgkin lymphoma

While less frequent than KS or cervical cancer, non-Hodgkin lymphoma (NHL) is most commonly treated with curative intent in LMIC among HIVAM, building on experience in resource-rich settings showing that HIV-positive NHL patients can be treated with similar intensity and achieve similar outcomes to those without HIV in the ART era. Despite availability in LMIC of generic chemotherapy drugs which remain key components of NHL

treatment even in high-income countries, stock outs are common, supportive care is limited including often absent hematopoietic growth factors, infusional and higher-intensity regimens are often impractical, infectious complications during chemotherapy and anti-infective prophylaxis strategies are poorly defined, and newer non-cytotoxic agents including rituximab are often not available. In Malawi, HIV-infected patients with aggressive NHL present with advanced bulky disease and poor performance status, although interestingly with less tumor bulk and shorter symptom durations than HIV-negative patients, perhaps reflecting primary care and referral networks established for HIV which are absent for HIV-uninfected populations [50*]. With appropriate monitoring and dose adjustment, even unselected HIV-infected patients can be treated with standard chemotherapy (CHOP; cyclophosphamide, doxorubicin, vincristine, prednisone), with comparable treatment intensity to HIV-negative patients, reasonably good outcomes, and deaths primarily related to relapsed/refractory NHL, although treatment-related mortality is also considerable. Outcomes are principally determined by NHL disease characteristics (international prognostic index score) rather than HIV status, and neutropenia is by far the most frequent toxicity among HIV-positive patients which might be easily addressed with greater availability of hematopoietic growth factors. Based on our experience and other similar reports from SSA [51–53], continued efforts to diagnose patients earlier, treat them with standardized protocols, improve supportive care, and incorporate newer non-cytotoxic therapies can likely increase cure rates substantially even for HIV-infected patients in highly resource-limited settings [54]. Strategies testing lower-intensity, oral, metronomic approaches are also under evaluation with some promising early experience [55, 56].

Other cancers

Many other HIVAM occur with appreciable frequency in LMIC, and many groups are developing research programs specifically focused on these. For instance, for conjunctival squamous cell carcinoma, efforts to screen HIV-infected patients in Kenya using toluidine blue staining have been described [57*], as well as suggestions that resection followed by brachytherapy may be well tolerated and associated with low recurrence rates in South Africa [58*]. However, given the relatively immature nature of the field overall, there are not major recent studies for other HIVAM in LMIC that would clearly merit inclusion in this review, although it is hoped that more data related to these tumors will soon be forthcoming.

Conclusion

The field of HIVAM in LMIC is in its infancy. Building on remarkable progress for HIV, there are encouraging initial efforts to define unique pathogenesis and best approaches to treatment and prevention for HIVAM in LMIC where burden is greatest. Continued investments for HIVAM in LMIC can also likely catalyze a broader cancer care and research agenda, with substantial benefits to HIV-positive and HIV-negative cancer patients worldwide.

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References

Papers of particular interest, published within the period of review (18 months from 1 Feb 2015 until 1 Aug 2016) have been highlighted as follows: *of special interest **of outstanding interest

1. UNAIDS. AIDSinfo. Available at: http://aidsinfo.unaids.org/. (accessed 1 August 2016)
2. UNAIDS. 90–90–90: An ambitious treatment target to help end the AIDS epidemic. Available at: http://www.unaids.org/en/resources/documents/2014/90-90-90. (accessed 1 August 2016)
3. Avila D, Althoff KN, Mugglin C, et al. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. J Acquir Immune Defic Syndr. 2014; 65:e8–16. [PubMed: 24419071]
4. Bonnet F, Burty C, Lewden C, et al. Changes in cancer mortality among HIV-infected patients: the Mortalite 2005 Survey. Clin Infect Dis. 2009; 48:633–9. [PubMed: 19202627]
5. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011; 103:753–62. [PubMed: 21483021]
6. Yanik EL, Achenbach CJ, Gopal S, et al. Changes in clinical context for Kaposi sarcoma and non-Hodgkin lymphoma among HIV-infected people in the United States. J Clin Oncol. 2016 (in press).
7**. Crocker-Buque T, Pollock AM. Appraising the quality of sub-Saharan African cancer registration systems that contributed to GLOBOCAN 2008: a review of the literature and critical appraisal. J R Soc Med. 2015; 108:57–67. This study critically appraises the quality of cancer registries in sub-Saharan Africa contributing to GLOBOCAN estimates. Population coverage across countries ranged from 2.3% to 100% with heavy urban bias in all registries, and 20 countries and 300 million people having no cancer registration. Data quality from cancer registries included in GLOBOCAN was overall poor. [PubMed: 25721114]
8*. Sengayi M, Spoerri A, Egger M, et al. Record linkage to correct under-ascertainment of cancers in HIV cohorts: The Sinikithemba HIV clinic linkage project. Int J Cancer. 2016; 139:1209–16. This study from South Africa demonstrates marked under-ascertainment of cancer diagnoses within a large HIV cohort, with a more than six-fold increase in estimated cancer incidence after cohort data were linked with data from geographically overlapping cancer registries. [PubMed: 27098265]
9. Adesina A, Chumba D, Nelson AM, et al. Improvement of pathology in sub-Saharan Africa. Lancet Oncol. 2013; 14:e152–7. [PubMed: 23561746]
10*. Amerson E, Woodruff CM, Forrestel A, et al. Accuracy of Clinical Suspicion and Pathologic Diagnosis of Kaposi Sarcoma in East Africa. J Acquir Immune Defic Syndr. 2016; 71:295–301. This study in HIV clinics in Uganda and Kenya found only 77% positive predictive value for clinically suspected Kaposia sarcoma compared to final histologic diagnosis, highlighting a need to improve pathology and abandon clinical diagnosis for this disease. [PubMed: 26452066]
11*. Gichuhi S, Macharia E, Kabiru J, et al. Clinical Presentation of Ocular Surface Squamous Neoplasia in Kenya. JAMA Ophthalmol. 2015; 133:1305–13. This study in Kenya found only 54% positive predictive value for clinically suspected ocular surface squamous neoplasia compared to final histologic diagnosis, suggesting that malignant and benign conjunctival lesions are not reliably distinguished by clinical exam alone. [PubMed: 26378395]
12. Gopal S, Fedoriw Y, Montgomery ND, et al. Multicentric Castleman's disease in Malawi. Lancet. 2014; 384:1158. [PubMed: 25241721]
13*. Gopal S, Liomba NG, Montgomery ND, et al. Characteristics and survival for HIV-associated multicentric Castleman disease in Malawi. J Int AIDS Soc. 2015; 18:20122. This is the first clinical case series of multicentric Castleman disease reported from sub-Saharan Africa, where

HIV and Kaposi sarcoma-associated herpesvirus are both prevalent, demonstrating late diagnosis, frequent misdiagnosis, severe illness, and high mortality for these patients. [PubMed: 26242311]

14**. Brown CA, Suneja G, Tapela N, et al. Predictors of Timely Access of Oncology Services and Advanced-Stage Cancer in an HIV-Endemic Setting. Oncologist. 2016; 21:731–8. This study documents long delays between symptom onset and oncology care (median 13 months) in the high middle-income country of Botswana for a diverse group of cancer patients. Longitudinal engagement in HIV care for HIV-infected cancer patients did not appear to shorten delays in accessing specialized oncology care. [PubMed: 27053501]

15**. Dryden-Peterson S, Medhin H, Kebabonye-Pusoentsi M, et al. Cancer Incidence following Expansion of HIV Treatment in Botswana. PLoS One. 2015; 10:e0135602. This study describes changing cancer incidence in one of the most mature antiretroviral therapy programs from sub-Saharan Africa. Age-specific cancer risk declined in HIV-infected individuals between 2003 and 2008, but growth and aging of the HIV-positive population resulted in unchanged HIV-associated malignancies burden over time. [PubMed: 26267867]

16*. Yang J, Su S, Zhao H, et al. Prevalence and mortality of cancer among HIV-infected inpatients in Beijing, China. BMC Infect Dis. 2016; 16:82. This study decribes 7.7% of HIV-infected inpatients in Beijing being admitted with cancer from 2008 to 2013, with approximately two-thirds of patients having non-AIDS defining cancers, and one-third having AIDS-defining cancers. [PubMed: 26883427]

17*. Castilho JL, Luz PM, Shepherd BE, et al. HIV and cancer: a comparative retrospective study of Brazilian and U.S. clinical cohorts. Infect Agent Cancer. 2015; 10:4. This comparative study of HIV cohorts in the United States and Brazil from 1998 to 2010 demonstrates declining AIDS-defining cancer rates but stable non-AIDS defining cancer rates in both settings. [PubMed: 25685180]

18*. Mutyaba I, Phipps W, Krantz EM, et al. A Population-Level Evaluation of the Effect of Antiretroviral Therapy on Cancer Incidence in Kyadondo County, Uganda, 1999–2008. J Acquir Immune Defic Syndr. 2015; 69:481–6. This ecological analysis from Uganda correlates increasing antiretorival therapy coverage with declining Kaposi sarcoma and gastric cancer rates, but significant declines in other tumor types were not observed. [PubMed: 25844696]

19*. Rogena EA, Simbiri KO, De Falco G, et al. 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. 2015; 10:28. This retrospective review of HIV-associated malignancies from a national hospital in Kenya from 2000 to 2011 found continued predominance of AIDS-defining cancers, particularly Kaposi sarcoma, and conjunctival cancer being the most frequent non-AIDS defining cancer. [PubMed: 26306097]

20. Msyamboza KP, Dzamalala C, Mdokwe C, et al. Burden of cancer in Malawi; common types, incidence and trends: national population-based cancer registry. BMC Res Notes. 2012; 5:149. [PubMed: 22424105]

21**. Semeere A, Wenger M, Busakhala N, et al. A prospective ascertainment of cancer incidence in sub-Saharan Africa: The case of Kaposi sarcoma. Cancer Med. 2016; 5:914–28. This study attempts to overcome cancer registration deficiences in sub-Saharan Africa and provide credible estimates for Kaposi sarcoma incidence within large, well enumerated, HIV cohorts in Uganda and Kenya. From 2007 to 2012, the age-standardized Kaposi sarcoma incidence was more than 300/100,000 person-years, highlighting a continued enormous burden athough incidence was lower among women, ART users, and those with higher CD4 counts. [PubMed: 26823008]

22. Rohner E, Valeri F, Maskew M, et al. Incidence rate of Kaposi sarcoma in HIV-infected patients on antiretroviral therapy in Southern Africa: a prospective multicohort study. J Acquir Immune Defic Syndr. 2014; 67:547–54. [PubMed: 25393941]

23*. Kayamba V, Bateman AC, Asombang AW, et al. HIV infection and domestic smoke exposure, but not human papillomavirus, are risk factors for esophageal squamous cell carcinoma in Zambia: a case-control study. Cancer Med. 2015; 4:588–95. This study from Zambia found a modest association between HIV and esophageal cancer (odds ratio 2.3) which was higher among patients younger than 60 years (odds ratio 4.3), suggesting a potentially novel link which requires confirmation between HIV and another high-frequency tumor in sub-Saharan Africa. [PubMed: 25641622]

24. Mbulaiteye SM, Katabira ET, Wabinga H, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. Int J Cancer. 2006; 118:985–90. [PubMed: 16106415]

25. Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. AIDS. 2013; 27:1603–13. [PubMed: 23462220]

26. Mosam A, Shaik F, Uldrick TS, 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. 2012; 60:150–7. [PubMed: 22395672]

27. ClinicalTrials.gov. Antiretroviral Therapy (ART) Alone or With Delayed Chemo Versus ART With Immediate Chemo for Limited AIDS-related Kaposi's Sarcoma. https://clinicaltrials.gov/ct2/show/NCT01352117. (accessed 1 August 2016)

28. ClinicalTrials.gov. Three Chemo Regimens as an Adjunct to ART for Treatment of Advanced AIDS-KS. https://clinicaltrials.gov/ct2/show/NCT01435018. (accessed 1 August 2016)

29**. Herce ME, Kalanga N, Wroe EB, et al. Excellent clinical outcomes and retention in care for adults with HIV-associated Kaposi sarcoma treated with systemic chemotherapy and integrated antiretroviral therapy in rural Malawi. J Int AIDS Soc. 2015; 18:19929. This study is the first description of integrated antiretroviral therapy and chemotherapy for HIV-associated Kaposi sarcoma in rural sub-Saharan Africa. With standardized protocols, clinical support to providers, and community health worker support to patients, 83% of patients were alive one year after chemotherapy initiation, results which are remarkably similar to patients treated in clinical trials at urban referral centers in the region. [PubMed: 26028156]

30*. Byakwaga H, Hunt PW, Laker-Oketta M, et al. The Kynurenine Pathway of Tryptophan Catabolism and AIDS-Associated Kaposi Sarcoma in Africa. J Acquir Immune Defic Syndr. 2015; 70:296–303. This case-control study describes a potentially novel pathogenic mechanism, immune activation through induction of the enzyme indoleamine 2,3-dioxygenase-1, which may be associated with lower risk of Kaposi sarcoma among HIV-infected Ugandans. [PubMed: 26181812]

31. Hosseinipour MC, Sweet KM, Xiong J, et al. Viral profiling identifies multiple subtypes of Kaposi's sarcoma. MBio. 2014; 5:e01633–14. [PubMed: 25249280]

32**. El-Mallawany NK, Kamiyango W, Slone JS, et al. Clinical Factors Associated with Long-Term Complete Remission versus Poor Response to Chemotherapy in HIV-Infected Children and Adolescents with Kaposi Sarcoma Receiving Bleomycin and Vincristine: A Retrospective Observational Study. PLoS One. 2016; 11:e0153335. This is a retrospective cohort description of Kaposi sarcoma among Malawian children, highlighting unique features of the pediatric form of the disease. Lymphadenopathy and peripheral blood cytopenias were common, and distinct clinical presentations were possibly associated with differential outcomes. [PubMed: 27082863]

33. Cox CM, El-Mallawany NK, Kabue M, et al. Clinical characteristics and outcomes of HIV-infected children diagnosed with Kaposi sarcoma in Malawi and Botswana. Pediatr Blood Cancer. 2013; 60:1274–80. [PubMed: 23487320]

34. Chagaluka G, Stanley C, Banda K, et al. Kaposi's sarcoma in children: an open randomised trial of vincristine, oral etoposide and a combination of vincristine and bleomycin. Eur J Cancer. 2014; 50:1472–81. [PubMed: 24636877]

35**. Rohner E, Wyss N, Heg Z, et al. HIV and human herpesvirus 8 co-infection across the globe: Systematic review and meta-analysis. Int J Cancer. 2016; 138:45–54. This is a systematic review describing assocations between HIV and Kaposi sarcoma-associated herpesvirus worldwide. The study found a two-fold increase in seroprevalence for Kaposi sarcoma-associated herpesvirus in HIV-infected versus HIV-uninfected people across all populations, but marked heterogeneity across studies and specific at-risk populations, highlighting a need to better understand transmission in different age and behavioral groups. [PubMed: 26175054]

36**. Gatera M, Bhatt S, Ngabo F, et al. Successive introduction of four new vaccines in Rwanda: High coverage and rapid scale up of Rwanda's expanded immunization program from 2009 to 2013. Vaccine. 2016; 34:3420–6. This study decribes achievement of more than 90% coverage in Rwanda within five years of the national program for human papillomavirus vaccination among

school-age girls. Keys to the program's success included leadership from the Ministry of Health, and engagement of development partners, civil society organizations, and communities. [PubMed: 26704259]

37**. Franceschi S, Chantal Umulisa M, Tshomo U, et al. Urine testing to monitor the impact of HPV vaccination in Bhutan and Rwanda. Int J Cancer. 2016; 139:518–26. This surveillance study was designed to assess early human papillomavirus vaccine effectivness in the first countries in Asia and Africa respectively to introduce national, school-based immunization programs. Signficant reductions in human papillomavirus prevalence were noted in both countries within two years of program initiation. [PubMed: 26991686]

38*. Masika MM, Ogembo JG, Chabeda SV, et al. Knowledge on HPV Vaccine and Cervical Cancer Facilitates Vaccine Acceptability among School Teachers in Kitui County, Kenya. PLoS One. 2015; 10:e0135563. This Kenya mixed methods study conducted in an area of school-based human papillomavirus immunization found moderate levels of teacher knowledge about the vaccine, and that level of teacher knowledge influenced whether or not they would recommend the vaccine. [PubMed: 26266949]

39. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis. 2014; 59:127–35. [PubMed: 24723284]

40. Clifford G, Franceschi S, Diaz M, et al. Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. Vaccine. 2006; 24(Suppl 3):S3/26–34.

41**. Clifford GM, de Vuyst H, Tenet V, et al. Effect of HIV infection on human papillomavirus types causing invasive cervical cancer in Africa. J Acquir Immune Defic Syndr. 2016 This meta-analysis examined human papillomavirus types among cervical cancer patients in Africa stratified by HIV status, and found similar proportions of cancers attributable to types 16/18 (~70–75%) and other non-16/18 oncogenic types (~15–20%) irrespective of HIV status.

42. Sankaranarayanan R, Esmy PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet. 2007; 370:398–406. [PubMed: 17679017]

43. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med. 2009; 360:1385–94. [PubMed: 19339719]

44**. Parham GP, Mwanahamuntu MH, Kapambwe S, et al. Population-level scale-up of cervical cancer prevention services in a low-resource setting: development, implementation, and evaluation of the cervical cancer prevention program in Zambia. PLoS One. 2015; 10:e0122169. This study describes rapid scale-up of cervical cancer screening in Zamiba using visual inspection with acetic acid from 2006 to 2013. More than 100,000 women were screened with nearly 90% receiving same-day services, yielding detection rates of 17 and 7 per 100,000 women screened for high-grade dysplasia or cancer, and cancer, respectively. [PubMed: 25885821]

45**. Kapambwe S, Sahasrabuddhe VV, Blevins M, et al. Implementation and Operational Research: Age Distribution and Determinants of Invasive Cervical Cancer in a "Screen-and-Treat" Program Integrated With HIV/AIDS Care in Zambia. J Acquir Immune Defic Syndr. 2015; 70:e20–6. This study from Zambia describes a four-fold increased risk of cervical cancer among HIV-positive women screened through the national program. Cervical cancer risk among screened HIV-infected women peaked at age 35 and declined subsequently versus continuous increases with age among HIV-negative women. [PubMed: 26322673]

46. Tsu V, Jeronimo J. Saving the World's Women from Cervical Cancer. N Engl J Med. 2016; 374:2509–11. [PubMed: 27355529]

47. ClinicalTrials.gov. HPV Test-and-Treat-Strategy Versus Cytology-based Strategy for Prevention of CIN2+ in HIV-Infected Women. https://clinicaltrials.gov/ct2/show/NCT01315353. (accessed 1 August 2016)

48. Abdel-Wahab M, Bourque JM, Pynda Y, et al. Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. Lancet Oncol. 2013; 14:e168–75. [PubMed: 23561748]

49. ClinicalTrials.gov. Cisplatin and Radiation Therapy in Treating Patients With HIV-Associated Locally Advanced Cervical Cancer. https://clinicaltrials.gov/ct2/show/NCT01590017. (accessed 1 August 2016)

50*. Gopal S, Fedoriw Y, Kaimila B, et al. CHOP Chemotherapy for Aggressive Non-Hodgkin Lymphoma with and without HIV in the Antiretroviral Therapy Era in Malawi. PLoS One. 2016; 11:e0150445. This is the first prospective study describing CHOP for non-Hodgkin lymphoma in sub-Saharan Africa, which yielded 45% overall survival at 12 months among unselected patients, with outcomes driven principally by lymphoma prognostic characteristics rather than HIV status. [PubMed: 26934054]

51. Bateganya MH, Stanaway J, Brentlinger PE, et al. Predictors of survival after a diagnosis of non-Hodgkin lymphoma in a resource-limited setting: a retrospective study on the impact of HIV infection and its treatment. J Acquir Immune Defic Syndr. 2011; 56:312–9. [PubMed: 21350364]

52. de Witt P, Maartens DJ, Uldrick TS, Sissolak G. Treatment outcomes in AIDS-related diffuse large B-cell lymphoma in the setting roll out of combination antiretroviral therapy in South Africa. J Acquir Immune Defic Syndr. 2013; 64:66–73. [PubMed: 23797692]

53. Coghill AE, Newcomb PA, Madeleine MM, et al. Contribution of HIV infection to mortality among cancer patients in Uganda. AIDS. 2013; 27:2933–42. [PubMed: 23921614]

54. ClinicalTrials.gov. Rituximab Plus CHOP Chemotherapy for Diffuse Large B-cell Lymphoma. https://clinicaltrials.gov/ct2/show/NCT02660710. (accessed 1 August 2016)

55. Mwanda WO, Orem J, Fu P, et al. Dose-modified oral chemotherapy in the treatment of AIDS-related non-Hodgkin's lymphoma in East Africa. J Clin Oncol. 2009; 27:3480–8. [PubMed: 19470940]

56. ClinicalTrials.gov. Intravenous Chemotherapy or Oral Chemotherapy in Treating Patients With Previously Untreated Stage III–IV HIV-Associated Non-Hodgkin Lymphoma. https://clinicaltrials.gov/ct2/show/NCT01775475. (accessed 1 August 2016)

57*. Gichuhi S, Macharia E, Kabiru J, et al. Toluidine Blue 0.05% Vital Staining for the Diagnosis of Ocular Surface Squamous Neoplasia in Kenya. JAMA Ophthalmol. 2015; 133:1314–21. This Kenya study describes high sensitivity but low specificity for toluidine blue staining compared with histopathology, suggesting potential utility as a screening rather than diagnostic tool for ocular surface squamous neoplasia. [PubMed: 26378623]

58*. Lecuona K, Stannard C, Hart G, et al. The treatment of carcinoma in situ and squamous cell carcinoma of the conjunctiva with fractionated strontium-90 radiation in a population with a high prevalence of HIV. Br J Ophthalmol. 2015; 99:1158–61. This study describes the addition of brachytherapy to resection of ocular surface squamous neoplasia in a South African setting with HIV prevalence, which was well tolerated and resulted in low rates of recurrence. [PubMed: 25784215]

Key points

- Antiretroviral therapy is leading to epidemiologic transitions in low- and middle-income countries, with increasing cancer deaths, and transitions from AIDS-defining cancers to non-AIDS defining cancers.
- Despite antiretroviral therapy scale-up, HIV-associated malignancies burden remains high including enormous AIDS-defining cancer burden in sub-Saharan Africa.
- Treatment and prevention that is appropriately tailored to low- and middle-income countries can be effective across a diverse range of geographic settings and specific HIV-associated malignancies.
- Continued investment for HIV-associated malignancies in low- and middle-income countries can catalyze a broad cancer care and research agenda which benefits HIV-positive and HIV-negative people.