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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% of 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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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.