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Challenges in the Detection, Prevention, and Treatment of HIV-Associated Malignancies in Low- and Middle-Income Countries in Africa

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Abstract

Cancers associated with immunosuppression and infections have long been recognized as a major complication of HIV/AIDS. More recently, persons living with HIV are increasingly diagnosed with a wider spectrum of HIV-associated malignancies (HIVAM) as they live longer on combination antiretroviral therapy. This has spurred research to characterize the epidemiology and determine the optimal management of HIVAM with a focus on low-and middle-income countries (LMICs). Given background coinfections, environmental exposures, host genetic profiles, antiretroviral therapy usage, and varying capacities for early diagnosis and treatment, one can expect the biology of cancers in HIV-infected persons in LMICs to have a significant impact on

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chronic HIV care, as is now the case in high-income countries. Thus, new strategies must be developed to effectively prevent, diagnose, and treat HIVAM in LMICs; provide physical/clinical infrastructures; train the cancer and HIV workforce; and expand research capacity—particularly given the challenges posed by the limitations on available transportation and financial resources and the population's general rural concentration. Opportunities exist to extend resources supported by the President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis, and Malaria to improve the health-care infrastructure and train the personnel required to prevent and manage cancers in persons living with HIV. These HIV chronic care infrastructures could also serve cancer patients regardless of their HIV status, facilitating long-term care and treatment for persons who do not live near cancer centers, so that they receive the same degree of care as those receiving chronic HIV care today.

Keywords

HIV/AIDS; low- and middle-income countries; developing countries; Africa; cancer screening; cancer therapy; infrastructure; health workforce; cancer prevention; cancer diagnosis; training; research

INTRODUCTION

Congenital and acquired immunodeficiencies have long been known to modify the incidence and clinical course of a variety of cancers. The etiologies of most, but not all, such cancers have been associated with infectious agents. Cancers associated with immunosuppression and/or infection, notably Kaposi sarcoma (KS), were among the first well-recognized complications of HIV infection and AIDS in 1981. In this review, we examine the association of HIV disease with cancer in low- and middle-income countries (LMICs), concentrating on sub-Saharan Africa (SSA). We explore the historical factors that have shaped the HIV–cancer co-epidemic and the implication of the wider availability of combination antiretroviral therapy (ART) on cancer burden; we examine critical gaps in infrastructure for cancer diagnosis, screening, training, and treatment in SSA and research and training priorities and challenges (Table 1). We conclude that addressing these gaps is an urgent priority that will have a broad impact on the optimal chronic management of cancers in HIV.

LANDSCAPE: HISTORY

Cancer has been recognized as an important comorbidity of HIV infection since the start of the global pandemic and was heralded by an outbreak of KS among previously healthy young men in the United States.¹ A diagnosis of KS in a person with HIV was subsequently considered an indication of progression to AIDS, and KS became one of the first AIDS-defining conditions and the first AIDS-defining cancer (ADC). Two other cancers, invasive cervical cancer and a subset of aggressive non-Hodgkin lymphoma (NHL), were later included in the category of ADCs by the Centers for Disease Control and Prevention.^{2,3} The aggressive NHLs include diffuse large B-cell lymphomas, Burkitt lymphoma (BL), and primary central nervous system lymphomas.⁴ KS, cervical cancer, and central nervous system lymphomas are all attributable to infection with oncogenic viruses [human herpes

virus 8 (HHV-8), human papillomavirus (HPV), and Epstein–Barr virus (EBV)]. A proportion of diffuse large B-cell lymphomas and BL are also EBV associated.

Before the HIV epidemic, 2 of the ADCs (KS and BL) were endemic in some countries in equatorial Africa⁵ and the high prevalence of the etiological oncogenic viruses in these populations posed an increased risk. Unsurprisingly, after the emergence of HIV, KS has become one of the most frequently reported cancers among persons living with HIV (PLHIV) in SSA.⁶ As ART has become widely available in resource-rich regions, the prevalence of virus-associated cancers, such as KS and, to a lesser extent, aggressive NHLs, has declined dramatically, whereas the prevalence of cervical cancer has risen modestly,⁷ suggesting a dynamic clinical milieu.

Other cancers have been reported in excess among people with HIV. These cancers, referred to collectively as non-ADCs, are increasingly recognized as a threat to the health of PLHIV and include some with viral associations, such as anal cancer (associated with HPV), liver cancer [associated with hepatitis B virus (HBV) and hepatitis C virus (HCV)], and Hodgkin disease (associated with EBV).

The bulk of our knowledge on the epidemiology of HIV-associated cancers comes from high-income countries (HICs), that is, the United States, Australia, and those in Western Europe, where about 10% of PLHIV live. Beyond a few limited studies, our knowledge of the epidemiology of HIV-associated cancers in LMICs remains incomplete. The reasons for sparse data on the burden of HIV-associated malignancies (HIVAM) in LMICs include weaknesses in health-care infrastructure for diagnosing cancers and limited epidemiological expertise in LMICs. Thus, many cancers go undiagnosed or untreated, and accurate comprehensive information from cancer registries cannot be obtained. These weaknesses make it difficult to carry out record linkage studies of HIV and cancer databases as has been done in HICs.⁸ Despite the limitations in available data, the incidence patterns of HIVAM in SSA are consistent with a substantial burden relative to HICs (Fig. 1). There is an urgent need to obtain systematic population-based information about HIV-associated cancers from countries where the preponderance of the global HIV resides.

EVOLUTION

The evolution of the incidence and spectrum of HIV-associated cancers in LMICs will be influenced by many external factors. Primary among these is the successful rollout of ART by initiatives, such as the President's Emergency Plan for AIDS Relief (PEPFAR) and The Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM). By significantly increasing the access of LMIC populations to life-extending ART,^{9–12} these initiatives will lead to reduced mortality from infectious complications of HIV¹³ and an increase in the mean age of PLHIV, which will likely be accompanied by a corresponding increase in the incidence of selected malignancies, particularly those more common among older persons.^{14–18} As many as 11% of individuals on ART in Africa are older than 50 years,¹⁹ a time when there is a marked increase in cancer risk as a function of age.²⁰

These changes present opportunities for prevention through well-implemented cancer screening programs, strengthening of immunizations against oncogenic viruses, and other

initiatives for early cancer detection. Cancer prevention initiatives that harness HIV treatment and prevention programs are likely to be the most cost effective and also to have the broadest impacts.²¹⁻²³ The increased professional and public awareness of cancer in LMICs as a treatable and preventable comorbidity in people with controlled HIV infection is likely to have spin-off benefits to the general population by strengthening general oncologic practice and cancer registration, increasing our understanding of the spectrum of cancers, and characterizing trends in cancer incidence.²⁴

Excellent examples of such programs can be found in cervical cancer screening initiatives, including those that are now supported by PEPFAR. Programs for early detection of other ADCs, such as KS, particularly in SSA, are likely to allow better treatment outcomes by increasing the proportion of patients detected at a stage early enough to limit the need for chemotherapy. The incidence of anal cancer is rapidly increasing among PLHIV, particularly among gay, bisexual, and other men who have sex with men (collectively referred to as MSM). Screening strategies to detect and treat anal lesions could thus positively affect outcome of anal cancer in PLHIV.

Although it is difficult to predict the trajectory of cancers in HIV-infected populations in LMICs, it is likely that the trends will be shaped by interactions between long-term immunosuppression, because ART does not restore immune competence fully; the prevalence of other risk factors, such as tobacco use; chronic infections (eg, HBV, HPV, and HCV); other environmental exposures (eg, ultraviolet light) and aging; and host genetic predisposition to cancers. These factors are likely to affect the risk of cancers at disparate body sites, including the oral cavity, salivary glands, nasopharynx, esophagus, stomach, colon, anus, lung, bronchus, penis, and eyes.^{8,25-28} Dramatically increased rates of primary hepatocellular carcinoma have been reported in multiple studies in several LMICs, further highlighting the possible interaction between HIV-related immunosuppression and known hepato-carcinogenic exposures, including HBV and HCV.^{29,30}

Elevated risk of ocular surface squamous cancer (OSSC) in PLHIV has been reported in many countries in SSA outside of South Africa and in India.³¹ The existence of an infectious risk factor for OSSC is unknown, but some studies have suggested an association with cutaneous types of HPV.^{32,33} Although data are limited, there is some evidence that among PLHIV in LMICs lung cancer risk is increased.³⁴ The reasons for this increase are not clear but may include smoking (which is concerning because LMICs, particularly in Africa, have been targets for aggressive marketing by the tobacco industry), inflammation from chronic infection, or environmental pollution.³⁵⁻³⁷

Cancers are difficult to treat in low-resource settings, even in a non-HIV context. Expanded screening programs are likely to increase the number of diagnosed cases of cancer in regions where resources are not sufficient to handle the existing cancer burden. Thus, screening and prevention programs will need to be accompanied by expansion of treatment capacity. Access to chemotherapy depends on a consistent drug supply and the ability of patients to pay. Radiation therapy is available at only a few centers in a few LMICs. Beyond relatively uncomplicated procedures suitable for certain cancers, access to cancer surgery is also limited in LMICs. The increase in the burden of cancers arising from a surge in the

population of PLHIV who are living longer because of ART is likely to be substantial. Therefore, given the resource limitations outlined above, this increase is likely to overwhelm current health-care infrastructures, even in those LMICs that have operational oncology services, unless urgent steps are taken to buttress capacity.¹⁵

CANCER INFRASTRUCTURE IN LMICs

Diagnosis and treatment of cancer requires a health system with functional, interactive, and responsive physical and human resources to identify, diagnose, and treat cases. The infrastructure necessary for the provision of cancer services is underdeveloped in LMICs, especially those in SSA.³⁸ Although few studies have directly addressed this issue, we suggest that the infrastructure for cancer should comprise 4 elements: physical infrastructure, qualified staff, supportive policies, and supportive laws.

The main components of the physical infrastructure include buildings, such as purpose-built or adapted oncology hospitals, training institutions, laboratories, imaging units, radiation therapy centers, and medical stores; communication infrastructure, such as roads, telephone systems, and Internet availability; and utility support, including water, sewerage, and electricity. Intuitively, countries with better established physical infrastructure have better cancer services, including stable routine facilities for cancer surveillance, diagnosis, treatment, follow-up, and palliation.

The components of qualified and experienced staff include effective team interactions and a goal-driven staff working in multidisciplinary departments. To be effective, research must be integral to practice and should serve to consolidate local knowledge for cancer care. Cancer centers also play an important role in the education of health-care professionals and the public about cancer.

Supportive policies articulated through various documents, including National Cancer Control Plans, acts of parliament, and government white papers, are useful for bringing stability to cancer work, including supporting training plans, conducting monitoring and evaluation, and guiding utilization of scarce resources.

Finally, progressive policies must be backed by the establishment of a regulatory environment to guide expenditures and improve accountability. We suggest that the establishment of additional cancer centers, which are still a rarity in LMICs, is a necessary starting point to guide and shape the development of an effective cancer infrastructure in LMICs.³⁹

Because there are only a few established cancer centers in most LMICs, cancer services are usually obtained from general hospitals in general surgical or medical departments. Some of these hospitals are at regional or district levels, but there is generally little or no information about quantity or quality of the services provided. Most often, the cancer centers that do exist are located in large urban centers, whereas the majority of the population lives in rural areas. Despite their urban location, the hospitals often lack reliable routine pathology, imaging, oncology nursing, and specialized pharmacy departments or have units that offer a low quality of service. Because these hospitals lack multidisciplinary staff, cases are not

evaluated by a multi-disciplinary team (like tumor boards) that would optimize treatment and significantly improve patients' quality of care.⁴⁰ Rural patients who make it to these hospitals find themselves in an unfamiliar environment, which is difficult to navigate, and have to confront numerous hurdles, including unaffordable co-payments for services, transportation difficulties, and stigmatization.^{38,41-53}

The lack or limited scope of pathology services, which are central to cancer diagnosis and care, is a major gap in most countries in SSA, where there is typically only one pathologist for every 500,000 to 1 million people. The corresponding number in HICs is 1 pathologist for every 20,638 people. By necessity, the few pathologists available in SSA have to provide a broad range of services, may lack specialized training, and may not work in well-functioning laboratories with standard operating procedures for handling and processing of pathology specimens.^{54,55} The low quality of pathology services in LMICs has been noted in numerous studies.^{54,56} This constraint not only results in poor clinical care because of low diagnostic accuracy but also limits the ability of researchers working in those settings to contribute to high-impact research and knowledge generation.⁵⁷ Other specialties crucial to oncologic practice are similarly underdeveloped and critically understaffed. This state of affairs is the result of inadequate investment in cancer care, perpetuated in part by the lack of data, which creates the wrong impression that cancer is comparatively rare in these countries.⁵⁸⁻⁶⁰ Efforts to improve cancer registration coverage of SSA populations, such as the African Cancer Registry Network (<http://afcrn.org/>), will contribute to redressing this situation.⁵⁸⁻⁶⁰

Despite the challenges noted above, this is an opportune moment to introduce changes to prepare LMICs to confront the looming HIV-related cancer epidemic. We suggest that the basic solution lies in establishing efficient and effective cancer centers that can collect initial information about cancer and conduct training activities to develop qualified and well-trained staff, who will then become leading advocates for policy and regulatory change. Cancer centers can foster harmony and create stable working environments that will lead to long-term staff commitment.³⁸ They can also serve as the hub, with the spokes representing the outlying hospitals (and perhaps HIV clinics) that can provide simpler chronic care, including ongoing chemotherapy for persons who cannot travel to the cancer center often. This approach can encourage the development and integration of complementary services, guide training, assist with the retention of qualified staff through the provision of incentive schemes, and support the systematic collection of data that will inform policy and resource allocation.

The unprecedented investments in malaria and HIV in LMICs through programs, such as PEPFAR and GFATM, have led to improvements in health-care infrastructure and personnel. These include upgrades to laboratory infrastructure, disease surveillance, infection control, monitoring adherence to treatments, and training and retention of key staff.⁶¹ These investments and the unprecedented success they have garnered in LMICs increase our confidence that now is the time for action against cancer.^{62,63} They also present opportunities to galvanize and leverage efforts to introduce cancer surveillance, diagnosis, treatment, and prevention services.²² Examples of groups building on a foundation nested within PEPFAR- or GFATM-supported program include the Uganda Cancer Institute/Fred

Hutchinson Cancer Center Alliance in Kampala, Academic Model Providing Access to Healthcare Program (AMPATH)-Oncology in Kenya, and clinical trials groups, such as the AIDS Malignancy Consortium and the AIDS Clinical Trials Group, funded by the National Institutes of Health.^{64,65} These programs are working to develop and enhance international clinical and research capacity in AIDS-associated cancers through training, protocol development, and enhancements to physical infrastructure. Local, regional, and international nongovernmental organizations, including patient advocacy groups, are being formed with a mission to promote cancer awareness and improve cancer diagnosis and treatment and can be tapped to foster the development of an enabling policy and regulatory framework.

Strategic investments, such as the creation of histopathology core laboratories, could simultaneously support cancer care, research, and registration.^{54,55} The creation of histopathology core laboratories could provide stable structured training and mentoring programs and introduce best practices in pathology. The laboratories would meet the need for high-quality histopathology clinical care and research, including discovery and biomarker validation. Following the same principle, model cancer centers could be established to improve clinical cancer care, treatment, and surveillance; train multidisciplinary health-care professionals; and educate the public.³⁸ With such strategic investment, nascent cancer centers would be able to establish physical footprints that would strengthen the cancer research infrastructure and foster the training and mentoring of local champions for long-term sustainability.

RESEARCH PRIORITIES AND CHALLENGES

Epidemiological Research: Trends in Cancers Among PLHIV in LMICs

The expansion of access to ART, particularly for PLHIV who still have relatively high CD4⁺ T-cell counts and associated longevity, creates opportunities for new research initiatives to study the frequency and types of cancers that may emerge in PLHIV in LMICs.^{6,7,15,52} These studies could be conducted using the well-established HIV/AIDS–cancer record linkage methodology or via cohort or cross-sectional studies.^{66–69} Etiological studies should also shed light on the interactions between different viral agents and other environmental factors on cancer development in this setting. This may be particularly relevant to childhood cancers.

Pathogenesis: Investigate the Pathogenesis of Unusual HIV-Associated Cancers More Common in LMICs

Much is known about the etiology and pathogenesis of ADCs. The significant proportion of ADCs attributable to oncogenic viruses, including EBV, HPV, and HHV-8, highlight the enhanced risk of infection-related cancers in people with HIV. Several mechanisms may explain the increased incidence of cancer in PLHIV. First, reactivation of oncogenic viruses because of their escape from immune surveillance has been implicated as a primary mode of carcinogenesis. Second, HIV integration at genomic loci near oncogenes and tumor suppressor genes could affect cell proliferation.⁷⁰ Third, some HIV-encoded proteins (eg, Tat) have been implicated in interactions with known cancer suppressor genes, such as p53.⁷¹ Fourth, HIV replication may contribute to carcinogenesis by directly or indirectly

producing proteins that promote inflammation or angiogenesis. One such example is the interaction between HIV tat and HHV-8 viral interleukin-6 to promote angiogenesis.⁷² Finally, HIV replication creates a pro-inflammatory state through its expression of cytokines, inhibition of T-regulatory cells, T-cell activation, B-cell activation, or immune exhaustion. The potentiation of this inflammatory milieu may also contribute to cancer pathogenesis.⁷³

Similar data are needed for cancers that are less frequently diagnosed among PLHIV, such as OSSC.⁷⁴ There is currently no consensus on an association between HPV infection and OSSC or whether invasive tumors are preceded by dysplastic precursors. If such lesions were found, detection and prevention strategies analogous to those for cervical and anal cancers might prove effective. An association between HIV infection and cancers like hepatocellular carcinoma that are well known in LMICs has been described,²⁶ but none of the studies has been adequately powered statistically to investigate this association and its interaction with potentially modifiable risk factors, such as HBV and HCV infections, alcohol intake, and aflatoxin.

Clinical Research: Conduct Cancer Screening, Diagnosis, and Prevention

In LMICs, many cancers are diagnosed at late stages when palliative care is the only option. Although late diagnosis is not unique to HIVAM, patients and care providers may fail to recognize cancer signs and symptoms (eg, fevers, lymph node enlargement, lung infiltrates), attributing them instead to opportunistic infections, such as tuberculosis.^{75,76} Research into early diagnosis of cancer, cancer precursors, or modifiable risk factors for cancer development has the potential to significantly reduce HIV-associated cancer morbidity and mortality. Examples of key research priorities include the following: (1) identification of optimal methods to detect and ablate cervical cancer precursor lesions in women with HIV; (2) evaluation of methods to enhance clinical recognition of early KS lesions, the implementation of pharmacologic methods to inhibit HHV-8 viremia in individuals at high risk for KS development, and the implementation of novel, field-implementable low-cost methods to definitively diagnose KS in areas lacking access to pathology laboratories and trained pathologists; and (3) investigation of methods to rapidly and definitively diagnose and discriminate among the multiple potential causes of lymphadenopathy in PLHIV.⁷⁷

Clinical Research: Develop Resource-Appropriate Strategies for Treatment of HIV-Associated Cancer

In HICs, effective therapeutic strategies have been identified for HIVAM in adults. Whether the same approaches are optimal for cancer management in LMICs has not been systematically determined and should be a major focus of research. Although there is no reason, a priori, to expect that established treatments for invasive cancer in HICs will be less likely to induce tumor regression in LMICs, their overall efficacy in these settings will likely depend on the availability of resources to administer complex therapy, the ability to provide appropriate supportive care and manage complex drug interactions, and the economics of providing costly cancer therapeutics and managing their side effects. Thus, research is urgently needed to evaluate and compare existing therapeutic approaches to treatment of ADC/HIVAM, including reduced-dose regimens that may be associated with lower

objective response rates but also a reduced incidence of adverse effects, which may have a significant impact on both quality of life and overall survival.⁷⁸ Among HIV-infected children with cancer, there have been no systematic investigations to identify optimal therapeutic strategies in either HICs, where such tumors are rare, or LMICs, particularly in SSA, where pediatric HIV infection, KS, and BL are relatively common.⁷⁹⁻⁸¹ Prospective evaluations of optimal management strategies for pediatric patients with HIV in LMICs should be a high priority.

Operational Research: Integrate Cancer Care With HIV Treatment and Evaluate Cost-Effectiveness and Comparative Efficacy of Cancer Prevention and Treatment Strategies

Given the increasing number of people living with HIV, their growing cancer burden, and the increasingly constrained resources of the international community for care, strategies for more efficient and effective delivery of care of HIVAM are needed. Operational research could help define how cancers could be detected at earlier stages by engaging HIV clinics, how the laboratory infrastructure created by HIV care can be applied to cancer diagnosis, and whether the initial or subsequent care of HIVAM can be accomplished by nononcologists practicing in HIV clinics. These studies should be coupled with economic analyses to inform the use of limited resources and with formal evaluations of the interactions of cancer therapy with ART and drugs commonly used in LMICs to treat HIV comorbidities.

RESEARCH TRAINING PRIORITIES AND CHALLENGES

Comprehensive and sustained training is needed to develop the health-care workforce and scientific leaders who will meet the challenges of cancer care in LMICs. The critical shortage of skilled personnel is one of the greatest difficulties facing health-care delivery in SSA today, and cancer specialists are particularly rare in most LMICs.^{20,82} For example, Kenya has had only 5 public cancer physicians in the entire country and Uganda has had fewer than 8 oncologists in the sole national cancer center serving a population of 32 million.^{65,83} Targeted training in the diagnosis and management of HIVAM is needed to meet the growing patient demand for these services. This training should be offered to a range of health-care professionals, including physicians, surgeons, nurses, radiotherapists, pathologists, pharmacists, palliative care providers, and other ancillary staff. To complement the expansion in local specialist care and research capacity, there is also a need to train local health managers, logistical experts, and policy experts to build strong multidisciplinary and well-supported local institutions in LMICs.

To improve cancer training of clinicians and researchers in LMICs, cancer centers designated as “centers of excellence” should be established and linked to regional-level institutions to facilitate sharing of training resources and specialized expertise. The network approach lends itself to creation of educational hubs for cancer training, reduction of duplication in closely located regions, and increased regional responsiveness to the development and conduct of training programs ranging from subspecialist fellowships to train-the-trainer activities.^{84,85} The well-established HIV care infrastructure in SSA would be a catalyst to support the training of cancer care professionals generally.⁸ In particular, PEPFAR’s mandate to train care providers in the management of HIV and its complications

represents an opportunity to expand the cadre of health-care workers who are knowledgeable about the diagnosis and management of cancer. Other important areas that need addressing include the development of standardized clinical guidelines for the management of HIVAM, a harmonized approach for disseminating knowledge, and a general strategy for supporting the underserved regions with less-experienced providers. To be successful and sustainable, these guidelines and harmonization activities should be developed in collaboration with trained experts and be based on evidence generated by research conducted in LMICs. They should include resource-appropriate diagnostic and treatment recommendations. Although we acknowledge that the crafting of such recommendations will be complex and that critics may ask why patients in LMICs should receive anything less than optimal cancer treatment, the success of these activities will be measured by the substantial and steady progress that they have the potential to achieve, even with the use of lower cost options. The development of more practical, affordable, and sustainable approaches to cancer prevention and therapies holds the promise of saving many lives now lost because of the unattainability of HIC standards of cancer care.

The development of research capacity in LMICs will require the extended training and support of aspiring investigators. International partnerships between institutions with established research infrastructures and those without have proven successful in building research capacity, as exemplified by several collaborations between universities in HICs and cancer centers in SSA.^{86,87} Essential elements of these investigator training programs include the following: (1) didactic training in cancer epidemiology, biostatistics, and research methodology, including research integrity and human subjects protection; (2) exposure to research through participation in collaborative research projects at the home institution; and (3) career paths at the home institution that support the development and retention of HIVAM specialists. Establishing a system of mentorship and career development is also critical to the professional growth and retention of clinical scientists.⁸⁸⁻⁹⁰ However, most academic medical centers in LMICs report an inadequate number of potential mentors for their junior faculty and postdoctoral trainees.⁹¹ Facilitated peer-mentoring programs, in which peer mentees develop their own mentoring groups, may offer an approach to leverage the limited number of senior faculty available for mentoring while building a robust culture and practical experience in mentoring for the next generation of researchers in resource-limited settings. Although these strategies provide a map to begin essential training for providers and researchers in HIVAM, building and maintaining a dedicated oncology workforce in LMICs will ultimately require years of sustained commitment and funding for cancer training by local governments and international agencies.

CONCLUSIONS

The evolving global response to the HIV epidemic has resulted in millions of persons in LMICs gaining access to ART. Although KS declines with ART, living longer in an immunosuppressed state may increase the risk for many other cancers, such as cervical cancer, primary hepatocellular carcinoma, and lung cancer. In this dynamic environment, the evidence base for the causes, optimal screening strategies, and feasible therapies of HIVAM in LMICs remains limited. Diagnosis and therapy for HIVAM have remained focused on

HIC needs, with a host of unresolved dilemmas facing LMICs. We urge a focus on the challenges of cancer and HIV/AIDS in LMICs to illuminate modifiable cofactors, elucidate feasible screening strategies, and develop therapies that can be implemented effectively. The lack of a basic cancer diagnostic and treatment infrastructure is a daunting challenge, especially for patients who live far from cancer services,⁹² and the mission of the core infrastructures that have been developed for HIV care in LMICs through PEPFAR and GFATM can and should be expanded to include HIVAM and malignancies in general.

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FIGURE 1.

Incidence of ADCs in the general population of African countries compared with the United States (data from IARC, Globocan 2012). ICC, invasive cervical carcinoma. Note: Nations/territories from left to right: Malawi, Zimbabwe, Mozambique, Zambia, Swaziland, Tanzania, Uganda, Comoros, Lesotho, Burundi, Kenya, Rwanda, Madagascar, Mali, Senegal, South Sudan, Botswana, South Africa, Guinea, Ghana, Cameroon, Somalia, Angola, Democratic Republic of Congo, Western Sahara, Ethiopia, Nigeria, Guinea-Bissau, Sierra Leone, Liberia, Mauritania, equatorial Guinea, Benin, Cape Verde, Gambia, Central African Republic, Republic of Congo, Togo, Burkina Faso, Gabon, Eritrea, Chad, Namibia, Côte d'Ivoire, Djibouti, Morocco, La Réunion, Libya, Sudan, Algeria, Niger, Tunisia, Egypt, United States.

TABLE 1

Perceived Gaps and Recommendations in Research, Training, and Infrastructure Development

Area	Specific Focus	Perceived Gaps	Recommendations
Surveillance	Knowledge of HIVAM epidemiology	Systemic population-based information on cancer incidence and survival not widely available	Support and expand population-based cancer registration
			Integrate cancer incidence and outcome measurement into large studies and sentinel surveillance of HIV-infected persons
Diagnosis	Pathology services	Core cancer diagnostic facilities are underresourced and often limited to basic histopathology. Variable quality and inconsistent turnaround times limit utility of diagnostic pathology in cancer care and research	Develop a core set of diagnostic pathology services necessary to diagnose most common HIVAM in resource-limited settings
			Identify models to assure proficiency, quality, and sustainability
	Early detection	Majority of cancers present at very late stage	Increase community awareness of cancer through public health campaigns Integrate cancer detection into HIV clinical care Improve access to cancer care outside major urban centers
Prevention	Cancer screening programs	Programs to reduce mortality of “preventable” cancers not validated in HIV-positive persons nor widely implemented in resource-limited settings	Focused research to determine approaches for preventing cancer in HIV
	Comprehensive tobacco programs	Nonuniversal adoption of comprehensive tobacco control legislation Few population-based tobacco cessation programs	Implementation research to identify optimal strategies for using screening for preventable cancers in HIV Encourage passage and implementation of WHO comprehensive tobacco control legislation Develop community-level interventions for tobacco cessation
Treatment	Availability of essential medications	Majority of chemotherapeutic agents are widely unavailable or prohibitively priced	Expand and update WHO essential medications list to include a wider range of chemotherapeutic agents Adopt strategies for affordable pricing of antiretrovirals to chemotherapeutics
	Radiotherapy	Limited availability of radiotherapy to majority of population in resource-limited settings	Increase number of radiotherapy units in LMICs Identify sustainable plans for equipment maintenance Train health-care workers in radiation oncology

Area	Specific Focus	Perceived Gaps	Recommendations
	Surgical oncology	Few surgical oncologic specialty units necessitate that cancer care be provided by surgeons with minimal cancer-specific training	Increase number of surgical oncology units and extend capacity of general surgeons to diagnose and treat cancer
	Supportive care	Availability of transfusion medicine, infectious disease, pain control/palliative care, and nutrition limits ability to deliver effective cancer care	Develop core set of supportive services for cancer care that can be adopted in LMICs
	Care plans	Few resource-adapted care guidelines for HIVAM exist or have been validated	Develop specific HIVAM care guidelines for use in LMICs and establish efficacy in clinical trials
Physical infrastructure	Cancer treatment centers	Few dedicated and/or comprehensive cancer treatment facilities in LMICs	Extend HIV care infrastructure to allow treatment of specific HIVAM
			Invest in centralized specialty cancer treatment facilities in major population centers
	Linear accelerators	Few LMICs have access to radiotherapy units and those that do often face antiquated equipment	Model number and distribution of radiotherapy units needed to provide care for HIVAM and establish plan for modernizing and expanding existing facilities
	Diagnostic radiology	Majority of cancer patients in LMICs have regular access only to plain films and ultrasound radiologic technologies	Identify core set of diagnostic and interventional radiologic services necessitated by HIVAM in LMICs
	Medical informatics	Care for oncology patients in LMICs is commonly documented on paper records which often are isolated from HIV clinics, primary providers, or other members of the care team	Adapt and adopt electronic medical record systems used for care of patients with HIV in LMICs
Human capacity	Physicians	Few dedicated physicians trained in oncologic disciplines available in LMICs	Increase the number of medical, pediatric, surgical, gynecologic, and radiation oncologists
	Nurses	Few dedicated nurses trained in oncologic disciplines available in LMICs	Increase the number of nurses with experience in the care of patients with cancer
	Pharmacists	Few dedicated pharmacists trained in oncologic disciplines available in LMICs	Increase the number of pharmacists with experience in the care of patients with cancer
Comprehensive cancer planning	Cost-effective cancer care strategies	Feasibility of treating cancer in LMICs questioned because of perception of expense	Conduct cost-effectiveness analyses to prioritize and advocate for cancer treatment
Research	Translational and clinical research teams	Research teams with expertise in cancer-specific research are not widely available in LMICs	Continue and expand efforts to train research teams in HIVAM
	Human subjects protection	Limited experience in conducting cancer research in LMICs hampers effective review by Institutional Review Boards in the United States and LMICs	Conduct capacity-building exercises to increase cancer-specific regulatory functions
	Laboratory assays	Length and complication of regulatory approvals for cancer studies in LMICs are becoming prohibitive to effective research	
		Supportive and correlative laboratory	Leverage substantial laboratory capacity

Area	Specific Focus	Perceived Gaps	Recommendations
		assays for contemporary cancer research not widely available, necessitating costly or prohibited expatriation of research specimens	for HIV research in LMICs to accommodate HIVAM studies
	Investigational drug availability	Most promising investigational agents for cancer treatment are not widely available in LMICs and importation can be prohibitive	Develop centralized system for procurement and distribution of investigational cancer therapeutics in LMICs by learning from best practices in HIV research
	Safety monitoring	Infrastructure for rapid identification and mitigation of SAE in cancer clinical trials not widely available	Leverage HIV research systems to empower cancer SAE reporting

SAE, serious adverse events; WHO, World Health Organization.