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Capacity building for the clinical investigation of AIDS malignancy in East Africa☆

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Abstract

Purpose: To build capacity in the resource-poor setting to support the clinical investigation and treatment of AIDS-related malignancies in a region of the world hardest hit by the AIDS pandemic.
Methods: An initial MEDLINE database search for international collaborative partnerships dedicated to AIDS malignancies in developing countries failed to identify any leads. This search prompted us to report progress on our collaboration in this aspect of the epidemic. Building on the formal Uganda-Case Western Reserve University (Case) Research Collaboration dating back to 1987, established NIH-supported centers of research excellence at Case, and expanding activities in Kenya, scientific and training initiatives, research capital amongst our institutions are emerging to sustain a international research enterprise focused on AIDS and other viral-related malignancies.
Results: A platform of clinical research trials with pragmatic design has been developed to further enhance clinical care and sustain training initiatives with partners in East Africa and the United States. An oral chemotherapy feasibility trial in AIDS lymphoma is near completion; a second lymphoma trial of byrostatin and vincristine is anticipated and a feasibility trial of indinavir for endemic Kaposi's sarcoma is planned.
Conclusions: In the absence of published reports of evolving international partnerships dedicated to AIDS malignancy in resource constrained settings, we feel it important for such progress on similar or related international collaborative pursuits to be published. The success of this effort is realized by the long-term international commitment of the collaborating investigators and institutions to sustain this effort in keeping with ethical and NIH standards for the conduct of research; the provision of formal training of investigators and research

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personnel on clinical problems our East African partners are faced with in practice and the development of pragmatic clinical trials and therapeutic intervention to facilitate technology transfer and enhance clinical practice.

Keywords: AIDS malignancies; Capacity building; East Africa (Uganda; Kenya); Fogarty training; Clinical trials

1. Introduction

As of December 2003, the World Health Organization estimates that more than 40 million adults and children are living with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) worldwide [1]. Over 95% live in developing countries. About two-thirds reside in sub-Saharan Africa and 17% in Uganda, Kenya and Tanzania [2]. As the third decade of the AIDS pandemic evolves, the spectrum of neoplastic complications in this setting is dynamic [3,4]. Since 1996 and the introduction of highly active antretroiviral therapy (HAART), the survival of patients with AIDS has markedly improved and the incidence of opportunistic infections, Kaposi's sarcoma, primary CNS lymphoma and most recently non-Hodgkin's lymphoma has declined in the industrialized world, where HAART is routinely available [5–10]. In the developing world, however, the incidence of Kaposi's sarcoma, in particular, and non-Hodgkin's lymphoma has increased [11–13]. Equally important is the recognition that other viral-induced, transmissible malignancies cervical cancer, hepatocellular carcinoma and Burkitt's lymphoma have become common causes of morbidity and mortality. Clinicians in Africa must become skilled in the management of these neoplasms because their burden is increasing. It will also be critical to develop the research infrastructure to build capacity to study these diseases, and to identify strategies for their prevention. With this backdrop, a multidisciplinary team of investigators based at the Case Western Reserve University (Case) in Cleveland, Ohio, the Uganda Cancer Institute in Kampala, Uganda, and the Kenyatta National Hospital in Nairobi, Kenya have embarked on a more than 6-year research collaboration dedicated to AIDS malignancy. The institutions in East Africa are national referral and academic health science centers. As AIDS is increasingly recognized as a global problem, the time is ripe for international collaborations of this kind to be developed with the broad goals of enhancing clinical care and ultimately prevention of these neoplasms.

2. Search methods

With this backdrop, we searched (June 21 and June 25, 2004) the MEDLINE database via PubMed for articles published through May 2004 using the exploded Medical Subject Heading terms *AIDS, developing countries; Africa, Africa south of the Sahara and East Africa; health policies, delivery of healthcare, program development, and capacity building; AIDS/HIV diseases, infections, and neoplasms; AIDS malignancies and cancer in HIV infection* with the intent of specifically identifying collaborative partnerships dedicated to the investigation of AIDS malignancies. No articles were identified. Herein, we describe our experience as part of the broader 17-year research collaboration amongst our institutions in this report.

3. Historical overview Uganda-Case Research Collaboration and Kenya Collaboration

The Uganda-Case Research Collaboration began in 1986 after a Presidential invitation to the late Dr. Frederick C. Robbins, Professor Emeritus and Nobel Laureate, to visit Uganda and assist the Ugandan government with the HIV/AIDS epidemic. Funding through the NIH/NIAID [initially in 1988 with an International Collaboration for AIDS Research grant, Preparation for AIDS Vaccine Evaluation (PAVE) and HIVNET PAVE program projects and Tuberculosis Research Unit, Dr. Henry Boom current director]; the Fogarty International Center [AIDS International Training and Research Program (AITRP), Dr. Christopher Whalen, current director]; the United States Centers for Disease Control and Prevention; the World Health Organization; pharmaceutical sponsors have provided continued support for HIV/AIDS research and this collaboration, which now spans 17 years. The Case Fogarty program has also extended training opportunities to Kenyan investigators at the Division of Vector Borne Diseases of the Kenyan Ministry of Health and Kenyan Medical Research Institute. Historically, multidisciplinary research activities of the collaboration focused on the interrelationship of co-infection with tuberculosis and HIV, host immunity, and primary vaccine development [14–25]. In addition to the organizations mentioned above, current and previous collaborators include the Institute of Tropical Medicine, Antwerp; London School of Tropical Medicine and Hygiene; Program for Appropriate Technology in Health; University of California, Berkeley; University of Medicine and Dentistry of New Jersey; University of Arkansas for Medical Sciences; University of California, San Francisco; the Johns Hopkins University.

Valuable on-site resources for clinical and basic science research projects have been developed as part of this collaboration. These facilities include an area of Old Mulago Hospital, the primary teaching hospital for Makerere University School of Medicine, in Kampala; a core clinical laboratory as part of other ongoing international research

activities to provide clinical laboratory services for purposes of supporting phases I–III clinical trials; the Joint Clinical Research Centre, a specialized clinical center for HIV research founded in 1993 as a collaborative effort of the Ugandan Ministries of Health and Defense, and Makerere University. The Uganda-Case Research Collaboration has conducted cohort studies and clinical trials with the Joint Centre since its inception. In 1997, the creation of the Case Center for AIDS Research (CFAR) core facility in Uganda, provided opportunities to extend the scientific activities of the collaboration to include studies in medical mycology and AIDS-related malignancies [2,26–29].

The collaborative research enterprise in Kenya is not yet as mature as in Uganda. Nonetheless, international collaborative activities have evolved amongst investigators in the Division of Vector Borne Diseases at the University of Nairobi College of Health Sciences, Kenya Medical Research Institute, and the Center for Global Health and Diseases (Dr. James Kazura current director) at Case as part of NIAID-funded International Collaboration for Infectious Diseases Research project. Research studies have generated insights into the pathogenesis of important helminth infections in Africa including *Schistosoma mansoni*, *S. haematobium*, *Wuchereria bancrofti*, and echinococcus infection. Studies have also focused on the immune response in falciparum malaria [30–33]. More recently, interaction of malaria and EBV co-infection have been studied [34].

4. East Africa-Case AIDS Malignancy Collaboration

Enabling support from the Case Comprehensive Cancer Center and CFAR has been vital in launching and sustaining our collaborative work in HIV-related malignancies. In 1996, the National Cancer Institute (NCI) awarded a supplemental grant to establish interactive and multi-disciplinary research projects focusing on AIDS malignancies (Table 1). The translational research program in AIDS malignancy at our institution is nested in the Comprehensive Cancer Center in the Developmental Therapeutics program. Cancer Center research pursuits in AIDS malignancy have been augmented by interactive linkages with the CFAR and the Fogarty AITRP. The CFAR AIDS Malignancies Working Group is providing leadership for capacity building and collaborative research in East Africa linked to strong laboratory-based and clinical research programs at Case and University Hospitals of Cleveland. Progress to date by this international team is further substantiated by invitations for members to present at the NCI-sponsored *International Conference on Malignancies in AIDS and Other Immunodeficiencies* and at the re-invigorated African Organization for Research and Training in Cancer at the *4th International Conference on Cancer in Africa* convened in October 2003 in Accra, Ghana [35–41].

5. Spectrum of AIDS malignancy in East Africa

5.1. Uganda

Ugandan investigators have made important contributions in cancer research. African Burkitt's lymphoma was described by Dr. Dennis Burkitt, former Head of Medicine at Mulago Hospital and Makerere University in 1958 [42]. Both Burkitt's lymphoma and Kaposi's sarcoma are endemic in Uganda, and important early descriptive research on these neoplasms was performed at Mulago Hospital [43–48]. In 1969, the Uganda Cancer Institute was founded as a satellite of the United States NCI through the collaborative leadership of Dr. John Ziegler at the University of California at San Francisco and Ugandan investigators. After a long and unfortunate hiatus due to national instability, the Uganda Cancer Institute is re-emerging as an important cancer research institute. The Uganda Cancer Institute is a national cancer referral center and is recognized as the principle facility in Uganda for cancer chemotherapy. Thus, it is an ideal site for clinical trials. The Institute is led by Dr. Edward Katongole-Mbidde. Dr. Mbidde also chairs the AIDS Research Subcommittee of the Uganda National Council

Table 1
Case AIDS malignancy program evolution and capacity building for international studies in East Africa

Year	Case/East Africa capacity building-timeline and significant development(s)	NIH grant numbers
1996	CFAR joins Comprehensive Cancer Center P30 supplement AIDS-associated malignancies	CA43703
1997	CFAR establishes International Clinical Coordinating Center with competitive renewal of P30	AI36219
1998	Developmental Therapeutics Program U01 cooperative agreement competitively renewed (also in 2003)-supports launch protocol CWRU 3Y97 (phase I bryostatin/vincristine study in B-cell neoplasms)	CA62502
1999	Comprehensive Cancer Center joins NCI-sponsored AIDS Malignancy Consortium (CCNJ-AAMCTU)	CA70081
2000	AITRP supplement dedicated to Training in HIV-Related Malignancies in Uganda and Kenya.	TW00011
	CFAR pilot grant-launch protocol CWRU 2498 (dose-modified oral chemotherapy) in Uganda and Kenya	AI36219
2001	R01 grant awarded to sustain protocol CWRU 2498 and initial linkage to OSU-ACSR	CA83528
2003	NCI supplement to OSU-AIDS and Cancer Specimen Resource to establish the Case-East Africa subunit as part of the NCI-sponsored AIDS and Cancer Specimen Resource	CA66531
	LOI #6441-phase II study of byrostatin and vincristine in AIDS-related non-Hodgkin's lymphoma in East Africa approved in concept by CTEP (October 7, 2003)	R01 grant submitted
2004	CFAR pilot grant-support protocol CASE 1704 pilot study of indinavir in endemic Kaposi's sarcoma	AI36219

for Science and Technology and has been an internationally recognized spokesperson for bioethics in HIV/AIDS over the past decade.

The initial description of Kaposi's sarcoma in homosexual men in the United States heralded the onset of the AIDS epidemic in 1981 [49,50]. AIDS was first recognized in Uganda in 1984 and was referred to as ''slim disease'' [51,52]. It was not until the end of the first decade of the AIDS epidemic when it was apparent that the incidence of Kaposi's sarcoma in Uganda had sharply increased [13,53]. Kaposi's sarcoma is now recognized as the most common neoplasm in adult Ugandan men and the second most common neoplasm in women [11,13,53]. There has been a 40-fold increase in the incidence of childhood Kaposi's sarcoma during the AIDS epidemic as well [12]. Cervical carcinoma is the most common cancer in women [11,13,53]. Near the end of the second decade of the AIDS pandemic, non-Hodgkin's lymphoma was observed to increase in incidence [13,53]. During this period, the incidence of Hodgkin's disease and hepatocellular carcinoma has remained stable though the incidence of squamous cell carcinoma of the conjunctiva, a unique tumor in eastern Africa has risen [13]. Squamous cell carcinoma of the conjunctiva is associated with immunodeficiency, and is likely HPV-related [54–57]. These trends in cancer incidence of various viral-related neoplasms are summarized in Table 2.

5.2. Kenya and Tanzania

It is clear that as the AIDS epidemic advances the clinical presentation and natural history of endemic Kaposi's sarcoma is blending with epidemic or AIDS-associated Kaposi's sarcoma in this region [58–61]. Approximately, 11% of lymphoma cases are HIV-seropositive in Kenya [62]. We identified a three-fold increase in the incidence of adult Burkitt's lymphoma coincident with the AIDS era [29].

6. Research priorities for AIDS malignancies in developing countries

6.1. Needs

Heightened interest in international aspects of the AIDS pandemic and global implications of neoplastic complications of underlying HIV infection are assuming increased attention. The International Network for Cancer Research (INCTR) was founded in 1998 by the International Union Against Cancer, the World Health Organization Cancer Control Programme, and the Institut Pasteur in Brussels under the leadership of Dr. Ian McGrath at the NCI [63]. This network was created to grapple with the burgeoning problem of cancer in countries with limited resources. The NCI of the United States assists INCTR to achieve its goals by providing financial, technical and intellectual support. Two of the greatest needs are the development of testable prevention strategies and pragmatic therapeutic intervention.

As knowledge has been gained regarding the pathogenesis of AIDS and other viral-associated malignancies, it is apparent that much neoplastic disease (see Table 2) in this setting is transmissible and theoretically preventable. Leads are emerging in the clinic and from preclinical models in which prevention strategies can be pursued. Examples include the use of anti-herpesvirus nucleoside analogs [64] and protease inhibitors [65,66] to prevent Kaposi's sarcoma and the use of hepatitis B vaccines and human papilloma virus vaccines to prevent hepatocellular and cervical cancer [67,68]. This will require the development of small proof of principle studies; a considerable research infrastructure suitable for large-scale prevention trials, and ultimately, the implementation of safe and cost effective interventions suitable for the resource poor settings.

Equally important is the pursuit of knowledge to enhance the recognition and management of AIDS-related and other viral mediated neoplastic diseases. It is advantageous to

Table 2
Uganda cancer incidence, age standardized rates per 100,000, for AIDS/viral-associated neoplasms (adapted from Parkin et al., 1999 [13])

Tumor type	Virus	1960–1971	1991–1994	1995–1997
Males				
Kaposi's sarcoma	KSHV	3.6	39.3*	39.3
Non-Hodgkin's lymphoma	EBV	3.8	3.6	7.4**
Squamous cell carcinoma conjunctiva	HPV	0.2	1.1*	2.1***
Hodgkin's disease	EBV	1.7	0.8**	1.3
Hepatocellular carcinoma	HBV/HCV	9.2	9.8	5.9***
Females				
Kaposi's sarcoma	KSHV	0.2	17.9*	21.8
Non-Hodgkin's lymphoma	EBV	2.3	2.1	5.7*
Squamous cell carcinoma conjunctiva	HPV	0	1.0*	2.3**
Hodgkin's disease	EBV	0.7	0.2	0.9
Cervical cancer	HPV	19.9	39.7*	44.1
Hepatocellular carcinoma	HBV/HCV	3.4	5.1	6.3

* $p < 0.001$.
** $p < 0.01$.
*** $p < 0.05$.

develop pragmatic clinical trials to serve as the focal point around which standards of clinical practice and research methodologies can be improved. Clinical trials also serve as an important vehicle for training. Hypothesis-driven studies of mechanistic and pathogenic laboratory correlates can be nested into well-designed clinical trials. Therapeutic interventions need to be aligned with the supportive care capabilities of the medical community, which in many instances are often limited for the cancer patient. The need for effective non-myelosuppressive therapy for AIDS-related malignancies in resource poor settings cannot be overstated, where transfusion support is limited and the risk of neutropenic infections high, which carries a high mortality. These issues have been reviewed elsewhere [2]. Lastly, the best ways to provide symptom-control and palliative care programs, including hospice services to cancer patients and their families must be studied. Neoplastic complications of HIV disease in this setting are often rapidly fatal and the patient's comfort and dignity are major priorities.

6.2. Challenges

The ethics of biomedical research, especially in the developing world is the subject of ongoing discourse, a detailed review of which is beyond the scope of this report [69–73]. Ethical principles of healthcare including respect for persons, beneficence, and justice are the same around the world, but access to care is not [69,70,74–76]. Therein lies one of the greatest challenges in conducting biomedical research in developing countries. Our collaborative studies have been developed jointly by American and East African physicians in alignment with evolving international guidelines for biomedical research [70,74–76].

Our collaborative activities represent more than 6 years of a sustained endeavor dedicated to neoplastic complications of AIDS in East Africa (see Table 1). The group has carefully selected and developed the research projects discussed further below. Our work in AIDS-related malignancies has evolved in the context of a mature international collaboration now spanning 18 years at our institutions discussed at the outset. Other tangible ''value-added'' attributes of this effort are the linkages to our CFAR and Cancer Center research programs in the pursuit of fundamental clinical knowledge in AIDS and viral malignancies in the resource poor setting.

Furthermore, linkage to our Fogarty program with demonstrable success in training clinical investigators, healthcare and research personnel, provides an opportunity to enhance the standards of clinical practice and care conducted within academic health science/national referral centers in both Uganda and Kenya.

Meaningful technology transfer is another fundamental principle of our collaboration. Therapeutic strategies that can be subsequently used in clinical practice in East Africa are vital. In some instances, this benefit may not be immediate. Nonetheless, efforts to translate the results of a given trial into practice and/or a provision for access must be given priority. If this is not realistic at the outset, a plan for access must be dealt with in an even handed manner up front as part of the initial ethical review of a given study with an understanding that a successful trial may in fact lead to successor studies of the same agent. In instances where this is not possible, there must be some clear benefit added to the community in general. Tangible benefits may include demonstrable success in training clinical investigators, healthcare and research personnel providing an opportunity to enhance the standards of clinical practice and care conducted within academic and referral centers in the partner country; the pursuit of fundamental clinical knowledge in a given disease in the resource poor setting, all of which are embraced by our East African collaborators and their respective institutions. These added benefits, although not direct benefits to the study participants, ensure that communities in the partner country are not any worse than before the research commenced.

As world opinion regarding the feasibility of providing AIDS care in Africa and other resource poor settings in the world evolves, it is ethically imperative to devise clinical strategies that are pragmatic and suitable for implementation in these areas to address both underlying HIV infection and its related opportunistic illnesses. Of prime consideration to both launch and sustain international research endeavors of this kind, is to be certain that peer review can be configured to both critically and objectively review research proposals on the basis of scientific merit constantly keeping in mind, the context and the community in which it is pursued. It is clear, that careful and respectful peer review by knowledgeable reviewers of the realities of healthcare in these regions of the world is vitally important. In addition, concept development (hypothesis generation) and review of research proposals in close collaboration with international collaborators and partner nations must occur. Questions must be addressed that are of practical importance in the communities in which they are investigated, there must be a genuine respect for cultural differences in conducting international research, and research efforts by all investigators must be recognized.

7. Elements of capacity building

7.1. National Cancer Institute

In 1996, the NCI issued a solicitation for P30 Cancer Center Support Grant competitive supplemental applications dedicated to the research of AIDS-associated malignancies. This solicitation and successful award at our center paved the way for highly interactive and multidisciplinary research initiatives and collaborations amongst investigators based at the Cancer Center and CFAR. These interactions were further abetted by keen interest of the Uganda-Case Research Collaboration and Drs. Jerrold Ellner and Stuart LeGrice (respective directors of the Tuberculosis Research Unit and

CFAR at the time) to develop collaborative activities in AIDS malignancy. Two projects were completed. One project confirmed the presence of Kasposi's sarcoma-associated herpesvirus/human herpesvirus-8 (KSHV/HHV8) in Ugandans following the initial discovery of this viral pathogen [77–79]. The other project looked at the clonality of tumor-infiltrating lymphocytes in patients with Kaposi's sarcoma, given the putative lymphomagenic potential of HHV-8 and EBV and their coexistence in African Kaposi's sarcoma lesions [80]. Subsequently, other NCI and NIH initiatives have been developed to support the national research agenda in AIDS malignancy, many of which have also evolved at the Cancer Center (see Table 1).

7.2. AIDS Malignancy Consortium (AMC)

This multi-center research initiative was launched by the NCI in 1995, just prior to the dynamic decline in the incidence of AIDS-related neoplasms attributable to the emergence of the HAART era as previously alluded to. The group is comprised of clinicians and basic laboratory scientists with expertise in oncology, infectious diseases, dermatology, radiation oncology, gynecology, pathology and molecular biology working cooperatively. The initial focus of the consortium was to develop pathogenesis-based treatment for AIDS-related malignancies [Kaposi's sarcoma and non-Hodgkin's lymphoma; more recently HPV-mediated anal dysplasia and other immune deficiency tumors, such as post-transplant lymphoma and acute T-cell (HTLV-1) leukemia] capitalizing on the successful performance of timely early phases I and II clinical trials. As the burden of AIDS and malignant complications of HIV disease is greatly expanding in other portions of the world, the NCI is reappraising its research agenda for AIDS malignancies. There are reasonable prospects, as discussed herein, for suitable clinical studies to be developed in partnership with international investigators [35–41,81–83]. The Consortium will likely be re-competed during 2005, and it is anticipated that inclusion of international sites most affected by the pandemic will be considered.

7.3. AIDS and Cancer Specimen Resource (ACSR)

The national ACSR was established by the NCI in 1994 to promote research into the pathogenesis and treatment of AIDS-related malignancies, and to provide HIV-associated malignant tissue and clinical outcome data to approved researchers through a letter-of-intent (LOI) mechanism. Presently, the bank contains more than 60,000 individual specimens and associated clinical information serving investigators working in the fields of HIV/AIDS and related cancer virology, immunology, pathology, epidemiology, tumor biology, assay development as well as other fields [84]. A recent linkage and expansion of sample procurement has been undertaken in Thailand and an emerging international network, including East Africa, is also being developed.

7.4. Developmental Therapeutics program

The early phase drug development program at the Cancer Center is supported by a platform U01-cooperative agreement with CTEP supporting phase I trials of novel anticancer agents. The focus of the program is on mechanism-based drug development. The team incorporates pharmacokinetic and pharmacodynamic studies, employing sequential tumor biopsies and other laboratory correlates for ''proof-of-principle'' concept testing and to confirm drug action [85–87]. Two recently completed phase I trials of bryostatin 1 (a protein kinase C antagonist) and combretastatin A4 phosphate (a tubulin-binding and vascular targeting agent) are suitable for further evaluation in AIDS-related non-Hodgkin's lymphoma and Kaposi's sarcoma, respectively [88,89]. The AIDS Malignancy Consortium actually launched a confirmatory phase I trial (protocol AMC 029) of bryostatin in AIDS-related B-cell tumors, which was closed in March 2003 because of poor accrual. Mechanistic preclinical studies have been reported in several B-cell tumors in which the sequence of 24-h infusion of bryostatin followed by bolus vincristine yielded the greatest antitumor response [90–93]. Preclinical models have also been developed for combretastatin establishing activity in Kaposi's sarcoma [94,95]. These trials, taken together, attest that a robust strategy has been to link drug development efforts in the Cancer Center to the potential management of AIDS-related neoplasms.

7.5. Center for AIDS Research (CFAR)

Access to the Ugandan Core Laboratory, established in 1997 amongst other CFAR and institutional initiatives, and the Joint Clinical Research Centre in Kampala greatly expanded the ability to make important contributions to the clinical investigation of African AIDS-related lymphoma [96]. The stated objectives of the laboratory core include: (1) provision of comprehensive laboratory services (including state-of-the-art immunology and virology laboratories) to facilitate HIV/AIDS-related research projects of CFAR investigators; (2) to advertise these services, process requests and coordinate research-based assays; (3) to provide a mechanism for training of Ugandan scientists in collaboration with our Fogarty training program. The laboratory core also seeks to develop new assays to meet investigator needs and improve the quality of HIV/AIDS research in Uganda and to continue to engage Ugandan scientists/clinicians in research collaboration with CFAR members by promoting training scholarships, sponsoring workshops and meetings. The CFAR also supports dedicated working groups in international health and AIDS malignancies to further develop and support highly collaborative and interactive international HIV/AIDS research projects. The CFAR provided pilot funding (Developmental Core) to support the launch of the dose-modified oral chemotherapy protocol as discussed further below.

7.6. Fogarty AIDS International Training and Research Program (AITRP)

In 2000, the Case Fogarty Program successfully competed for a supplemental award dedicated to the training of healthcare researchers and personnel specifically in AIDS malignancies in both Uganda and Kenya. The specific objectives of this proposal are: (1) to train and educate Ugandan and Kenyan scientists and healthcare providers in the area of HIV-associated malignancies; (2) develop and promote scientific leadership and clinical expertise in this discipline; (3) advance knowledge in epidemiology, molecular pathogenesis and treatment of HIV-associated malignancies; (4) stimulate scientific collaboration between investigators in Africa and the United States; (5) enhance links with other NIH-sponsored programs at Case, such as the CFAR, AIDS Clinical Trials Unit, and the AIDS Malignancy Consortium. The success of this effort, as discussed below, has led to the incorporation of this aspect of the Case AITRP training initiative as part of its recent competitive renewal. What is of paramount importance, is the recognition that not only is the training of research personnel and investigators successful, but the retention rate of trained personnel to return to their native countries to support and further sustain this highly interactive collaborative international research enterprise is outstanding. Since the inception of the Case AITRP, 32 trainees have received advanced degrees in epidemiology, biostatistics, health services research, immunology, anthropology, and microbiology. All have returned to Uganda or Kenya after completion of their training.

8. Overview of accomplishments to date

8.1. Training

The linkage of the Fogarty training program dedicated to AIDS malignancy has been of paramount importance (Table 3). This has enabled the international team to launch and equally sustain this collaborative effort. All the clinical investigators trained to date have made tangible contributions to this effort substantiated by leading the clinical trial(s) and overseeing their respective research teams; presenting and publishing their observations and developing new concept proposals. Most recently, Dr. Jackson Orem from the Uganda Cancer Institute completed a 16-month *Clinical Research Scholar* training initiative in the Division of Hematology/Oncology under Fogarty sponsorship; the first of its kind in the 16-year history of the program. The focus of this scholarship was to gain an appreciation of the mechanics of the NIH extramural research program linked to numerous NIH-centers of research excellence at Case, specifically the Comprehensive Cancer Center and CFAR become familiar with Good Clinical Practice (GCP) guidelines, clinical trial design and research methodology, and biomedical ethics in the performance of clinical research endeavors; develop pilot concepts to enhance clinical skills especially in AIDS malignancies and solid tumor oncology.

8.2. Oral chemotherapy feasibility trial

An oral combination chemotherapy regimen (comprised of lomustine, etoposide, cyclophosphamide, and procarbazine) has been developed for the management of AIDS-related non-Hodgkin's lymphoma [2,97–99]. It was readily apparent to our international colleagues that oral chemotherapy, if successful, would have numerous practical advantages in the resource poor setting (reviewed in detail in reference [2]). Furthermore, published observations from two of the largest trials ever conducted in AIDS lymphoma confirmed that dose modification was much less toxic (significantly less myelosuppression) and did not compromise efficacy [2,100,101]. Taken together, a departure point for our international team was to pursue a clinical trial of dose-modified oral combination chemotherapy in the management of AIDS-related non-Hodgkin's lymphoma (see Table 4). It is also notable, that with the exception of etoposide, each of the drugs in the oral regimen is listed on the World Health Organization antineoplastic drug formulary. This first of its kind study on the African continent was subsequently sustained in 2001 by an R01 award from NCI. Linkage to the NCI-sponsored ACSR at the Ohio State University followed as discussed below. The study is now

Table 3
Case AIDS International Training and Research Program (TW00011, Dr. C. Whalen, P.I.) trainees dedicated to AIDS malignancy collaboration

Year	Trainee	Country	Training endeavor	Current position
1992	Cecily Banura, MB,ChB	Uganda	Epidemiology and biostatistics	Ugandan Ministry of Health and UCI co-inv
2000	Mwanda W. Otieno, MB,ChB	Kenya	Epidemiology and biostatistics, Doctor of Medicine (degree-thesis on Burkitt's lymphoma)	Senior Lecturer, Department of Haematology and Blood Transfusion and site-PI KNH
2003	Beatrice K. Amooti, BBLT	Uganda	Laboratory technician-OSU-ACSR project (tissue microassays)	Medical Biotechnologist, UCI
2003	Onyango J.I. Obila, BS	Kenya	Laboratory technician-OSU-ACSR project (tissue microassays)	Senior Medical Laboratory Technologist, University of Nairobi and KNH
2004	Jackson Orem, MB, ChB	Uganda	Clinical Research Scholar and clinical investigations	Senior Registrar, UCI and co-inv/co-PI

Notes: OSU-ACSR: Ohio State University-AIDS Cancer and Specimen Resource; UCI: Uganda Cancer Institute; KNH: Kenyatta National Hospital; co-inv/PI: co-investigator/principal investigator.

Table 4
Summary of clinical trials developed by the East Africa-Case AIDS malignancy research collaboration

Protocol	Regimen	Disease	Clinical research questions
CWRU 2498 (CA83528)	Dose-modified oral chemotherapy (lomustine, VP-16, cyclophosphamide and procarbazine)	1st line therapy AR-NHL	Feasibility: conduct AIDS cancer trial in resource poor setting Pragmatic design: oral therapy Assess impact of therapy on CD4+ counts and HIV-1 plasma RNA levels Tissue procurement
CASE 1403 (CTEPLOI#6441)	Bryostatin-1 (NSC 339555) + vincristine	2nd line therapy AR-NHL (includes no prior therapy cohort)	Test non-myelosuppressive regimen for efficacy in AIDS lymphoma Assess impact of therapy on CD4+ counts and HIV-1 plasma RNA levels Tissue procurement
CASE 1704 CFAR pilot project	Indinavir (Crixivan™)	Endemic (HIV-negative) KS without visceral crisis in Uganda	Test putative anti-angiogenic effects Assess impact of therapy on VEGF and HHV-8 cell-associated DNA levels Tissue procurement
CASE 2704 Physician investigator-initiated study (protocol in develooment)	Imatinib mesylate (Glivec™)	Endemic and epidemic (AIDS) KS in East Africa	Test putative anti-proliferative effects via tyrosine kinase inhibition Assess impact of therapy on HIV-1 plasma RNA and HHV-8 cell-associated DNA levels Tissue procurement

Notes: CFAR: Center for AIDS Research; AR-NHL: AIDS-related non-Hodgkin's lymphoma; KS: Kaposi's sarcoma.

testing a practical approach toward the management of this prevalent life-threatening disease [2]. The project clearly integrates training initiatives sponsored by the Case Fogarty training program as well (see Table 3). Preliminary observations from this pilot and feasibility trial have been presented at the NCI international AIDS malignancy conference and at the Ghana international conference by East African team members [38–40].

8.3. Linkage to Ohio State University tumor bank

At the outset, pilot studies conducted by the international team were successful and linked to sample procurement [79,80]. As this collaboration has matured it was realized that for sample procurement to be sustained it must be linked to well conceived clinical trials and that laboratory correlative studies that are incorporated into a given study, ideally should be performed on site. As the CFAR Ugandan Laboratory Core has taken shape, Ugandan laboratory scientists and technologists have been trained and retained to support the laboratory components so vital to the conduct of clinical trials. Similarly, a NCI supplement grant was awarded to support linkage and retrieval of clinical specimens to the NCI-sponsored ACSR at the Ohio State University. Most recently, the Fogarty program provided support for a 3-week training initiative on-site in Columbus, Ohio to train laboratory technologists from Uganda and Kenya in tumor banking procedures and tissue microarray techniques for specimen procurement linked to clinical trials conducted in East Africa (see Table 3). It is also anticipated that fresh tumor tissue collection can be pursued at the time of diagnostic biopsy. These sample collections are subjected to ethical committee and peer review and must require informed consent of study participants. To date, scores of clinical samples (e.g., peripheral blood, bone marrow and cerebrospinal fluid) have been collected as part of the oral chemotherapy trial.

8.4. Clinical research leads

A robust strategy seized upon by the international research team has been to link therapeutic leads building on observations and early phase clinical studies conducted by the Developmental Therapeutics Program in the Comprehensive Cancer Center (Table 4). An example is the recently completed phase I bryostatin trial, which is discussed below [88]. Other novel agents that may be suitable for evaluation in African Kaposi's sarcoma, include combretastatin A4 phosphate and imatinib mesylate, two agents that have been developed in the Developmental Therapeutics Program as well [89,102]. Combretastatin and imatinib mesylate are not myelosuppressive, the later drug is also orally dosed, and preclinical models and clinical rationale have been developed for both agents [94,95,103,104]. These clinical attributes are advantageous for evaluation in the resource poor setting.

8.5. Bryostatin trial

Several phase I studies with this agent have identified myalgia as the dose-limiting toxicity, lack of myelosuppression, and activity in B-cell tumors [88,105–109]. Bryostatin

is also known to have potent immunomodulatory effects increasing IL-2 levels and IL-2 receptor expression [110]. It is hypothesized that these effects on IL-2 will have salutary effects on levels of circulating CD4+ lymphocytes in HIV-infected patients [111]. Based on these clinical observations, the identical bryostatin regimen and schedule tested by our phase I program and carefully aligned with preclincal models has been approved in concept by the NCI to evaluate further in AIDS-related non-Hodgkin's lymphoma in East Africa. This regimen was found to be active in a highly refractory group of patients with B-cell malignancies, where 40% of patients had meaningful clinical outcomes with either objective response (including both complete and partial responses) and/or long-term freedom from progression exceeding 5 years [88]. Furthermore, the safety profile of the regimen is ideally suited to the resource poor setting.

8.6. Indinavir trial

Large epidemiologic studies have clearly identified a sharp decline in the incidence of AIDS-related Kaposi's sarcoma with the evolution of the HAART era [8–10]. Survival of patients with AIDS malignancies has no doubt improved coincident with improvements of antiretroviral therapy as well [5,6,112]. Following these clinical observations, preclinical animal models have been reported in which the protease inhibitors have been found to have potent anti-tumor and anti-angiogenic effects on KS-like spindle cell tumors [65,66]. With this backdrop, Dr. Orem, upon completion of his Fogarty training clinical research scholarship, submitted a physician-investigator initiated pilot concept proposal that has been awarded by the Center for AIDS Research. The international team has carefully considered the design of this study and has chosen to investigate a single-agent protease inhibitor regimen initially in endemic (HIV-seronegative) disease. Rationale for this decision is based on the logistical and ethical constraints often placed on primary treatment trials of HIV-infected patients, and patients with AIDS malignancies as well in the resource poor setting. The economic realities of healthcare in these regions remain an obstacle, and the simple fact is that for the majority of HIV-infected individuals potent antiretroviral therapies are beyond reach. The international team hypothesizes that protease inhibitor-based therapy will be efficacious in endemic Kaposi's sarcoma, and the safety profile of single-agent protease inhibitor therapy will be markedly better than systemic chemotherapy, primarily in patients without visceral disease or crisis. Furthermore, published observations have suggested that the beneficial effects of potent antiretroviral therapies on Kaposi's sarcoma may be restricted to protease inhibitors and not to the non-nucleoside reverse transcriptase inhibitor-based regimens [113]. The international team thought it would be prudent to test this hypothesis initially in endemic disease. This tumor is commonly encountered in clinical practice and novel therapies with an improved therapeutic index are clearly needed. It is anticipated that the international team will gain clinical experience with a primary antiretroviral approach in the management of endemic disease prior to embarking on an AIDS Kaposi's sarcoma trial. In this manner, the design of successor AIDS Kaposi's sarcoma trials employing different antiretroviral regimens will be better guided. Indinavir was selected as the protease inhibitor of choice, simply because this is the most commonly used agent of this class in clinical practice in Uganda [114]. It is anticipated that this pilot study will be launched over the coming year.

9. Recommendations and conclusion

This dedicated international research collaboration in AIDS malignancy will continue to evolve. The success of this effort is realized by the long-term international commitment of the collaborating investigators and institutions to sustain an investigative effort of this kind in keeping with NIH and ethical standards for the conduct of research; the provision of formal training of investigators and research personnel on clinical problems our East African partners are faced with in practice; the development of pragmatic clinical trials and therapeutic intervention to facilitate technology transfer and enhance clinical practice. The realities of being able to train (coupled with an outstanding retention rate) investigators and research partners aligned with ethical and sound research methodologies and developing pragmatic clinical trials cannot be overstated. We believe these two ingredients in our pursuit of developing a dedicated international collaboration in AIDS malignancy have greatly contributed to the success of these efforts. These principles have recently been echoed as well as part of a global response to cancer in the developing world [115]. Genuine respect for cultural differences, prioritization of concept development focusing on problems of importance and interest to East African collaborators, and recognition of this effort are also of paramount importance and must be reflected in scientific publications. Other investigators are encouraged to publish similar or related highly collaborative international research partnerships and progress focusing on specialized areas of the AIDS epidemic in resource-constrained settings.

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