

# RFA Reissuance Request

## **AIDS Malignancy Consortium**

*Office of HIV and AIDS Malignancy (OHAM)*

Cooperative Agreement  
5 Years Funding  
\$24,000,000 year 1  
\$113,730,523 total over 5 years

# Background - HIV Epidemic

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Approximately **36.7 million** people live with HIV world wide, and there are **~1.8 million** new infections per year:

- United States
  - **~1.1 million** people live with HIV
  - ~40,000 new infections per year
- Sub Saharan Africa (SSA)
  - **~19 million** People live with HIV
  - ~960,000 new infections per year
- Latin America
  - **~2.3 million** people live with HIV
  - ~100,000 new infections per year

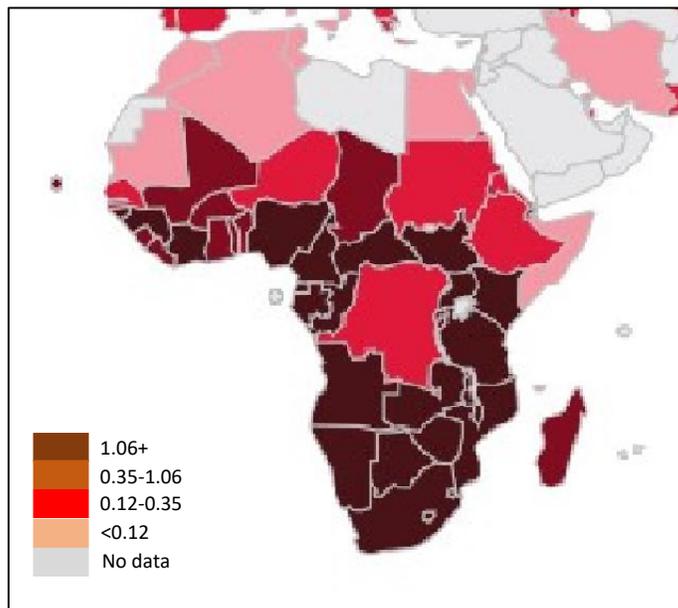
*Cancer has been a prominent manifestation of HIV/AIDS since the beginning of the epidemic and is a leading cause of morbidity and mortality in HIV-infected people*

# Estimates of the Incidence and Burden of Selected AIDS-Related Cancers in USA

Cancer type	Incidence per 100,000 person years	Number of cases/year in USA
<b>AIDS Defining</b>		
NHL	194	1650
Kaposi sarcoma	110	910
Cervix	47	80
<b>Non-AIDS Defining</b>		
Lung	78	840
Anus	59	760
Liver	32	390
Hodgkin lymphoma	22	320
Oral cavity/pharynx	13	290

# Burden of HIV/AIDS, Cervical Cancer and Kaposi Sarcoma in Sub Saharan Africa (SSA)

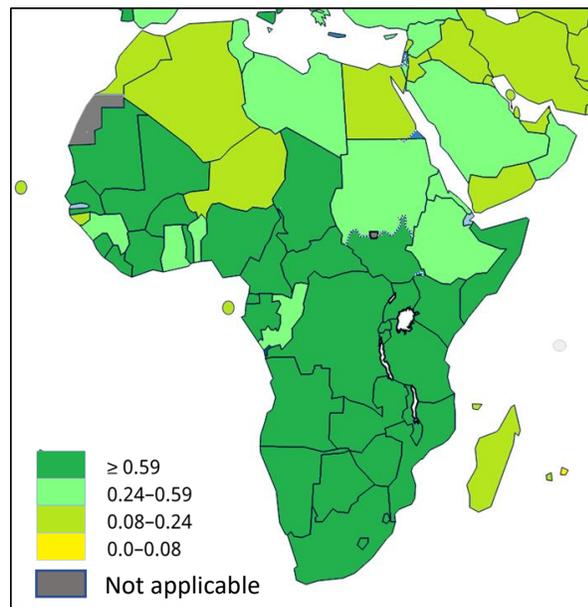
## HIV Incidence



### UNAIDS 2017

- Incidence per 1000 persons
- ~90% in low- and middle-income countries (LMICs)

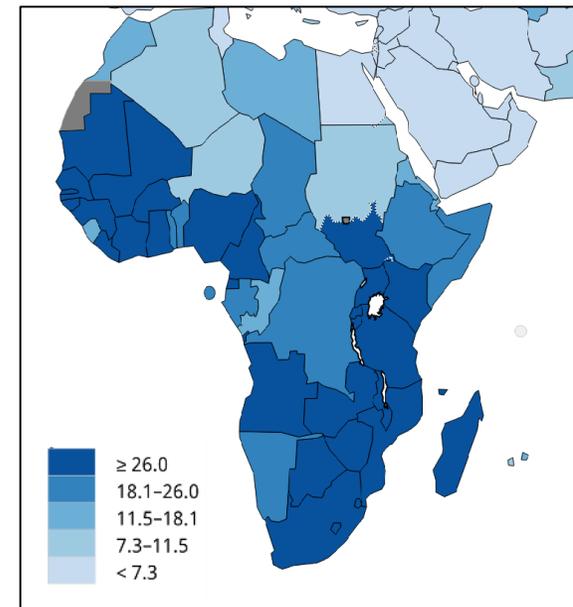
## Kaposi Sarcoma Incidence



### Globocan 2018

- Incidence per 100,000 persons
- 41,800 new cases/year worldwide
- 20,000 deaths/year
- > 90 % of cases in LMICs
- Most common cancer in men **overall** in some countries in SSA

## Cervical Cancer Incidence



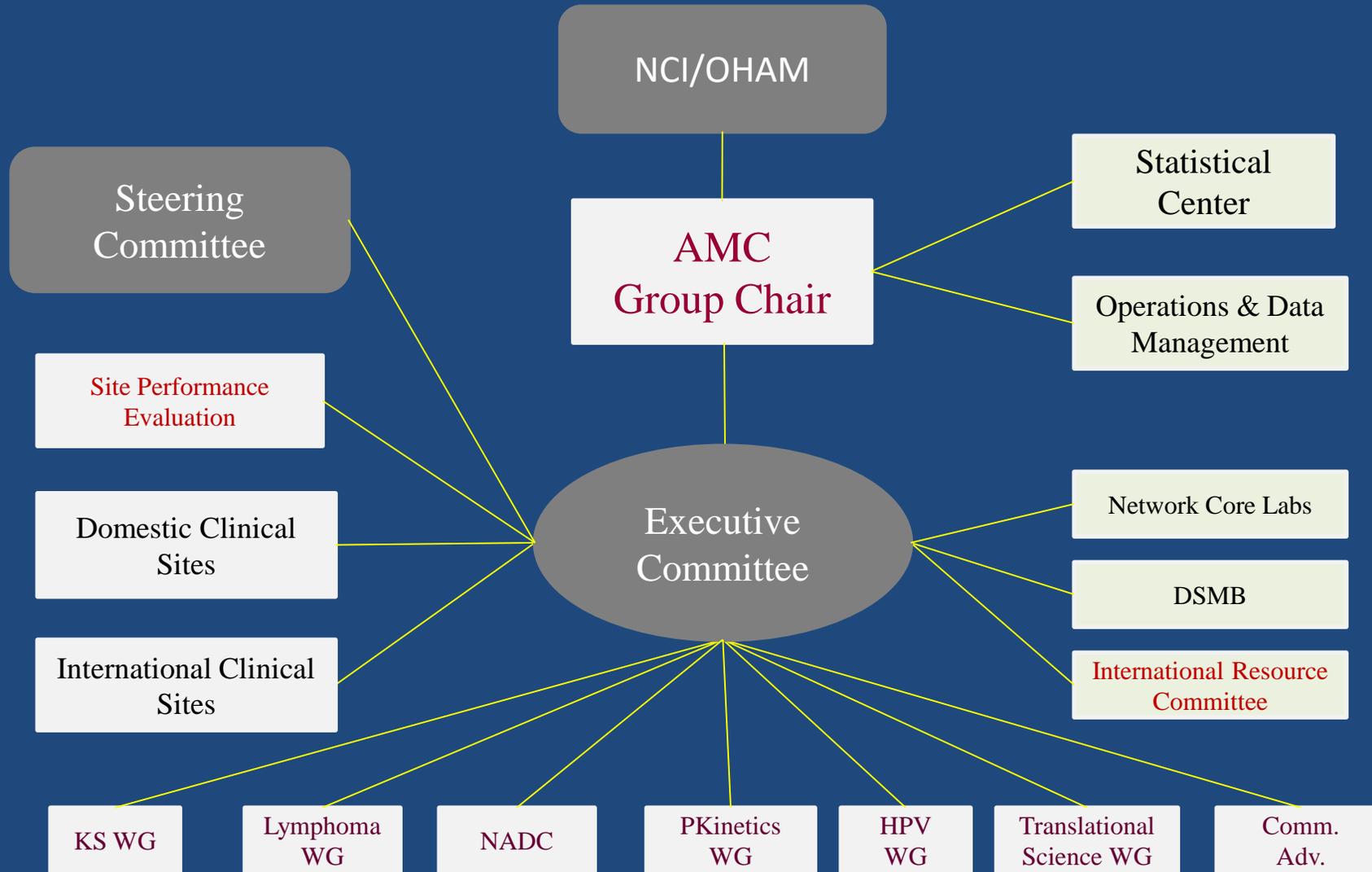
### Globocan 2018

- Incidence per 100,000 women
- 1<sup>st</sup>/2<sup>nd</sup> most common cancers in women in many LMICs

# AMC Mission

- Develop and evaluate clinical interventions for the treatment and prevention of malignancies in people with HIV
- Conduct Phase I, II and III clinical trials of HIV-related malignancies
- Investigate the biology of these malignancies in the context of clinical trials
- Contribute specimens and clinical data to the AIDS and Cancer Specimen Resource (ACSR)

# AIDS Malignancy Consortium



# AMC Sites



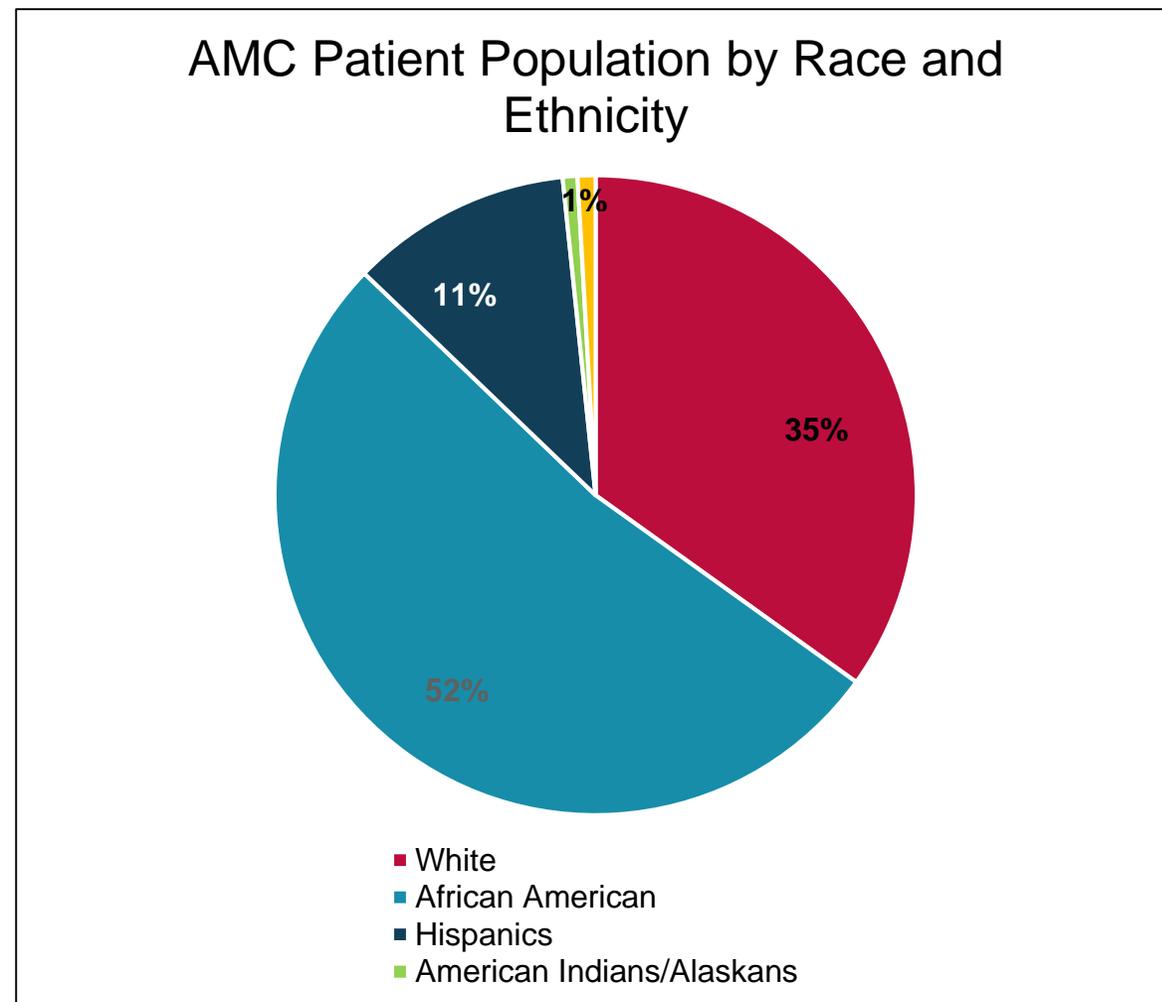
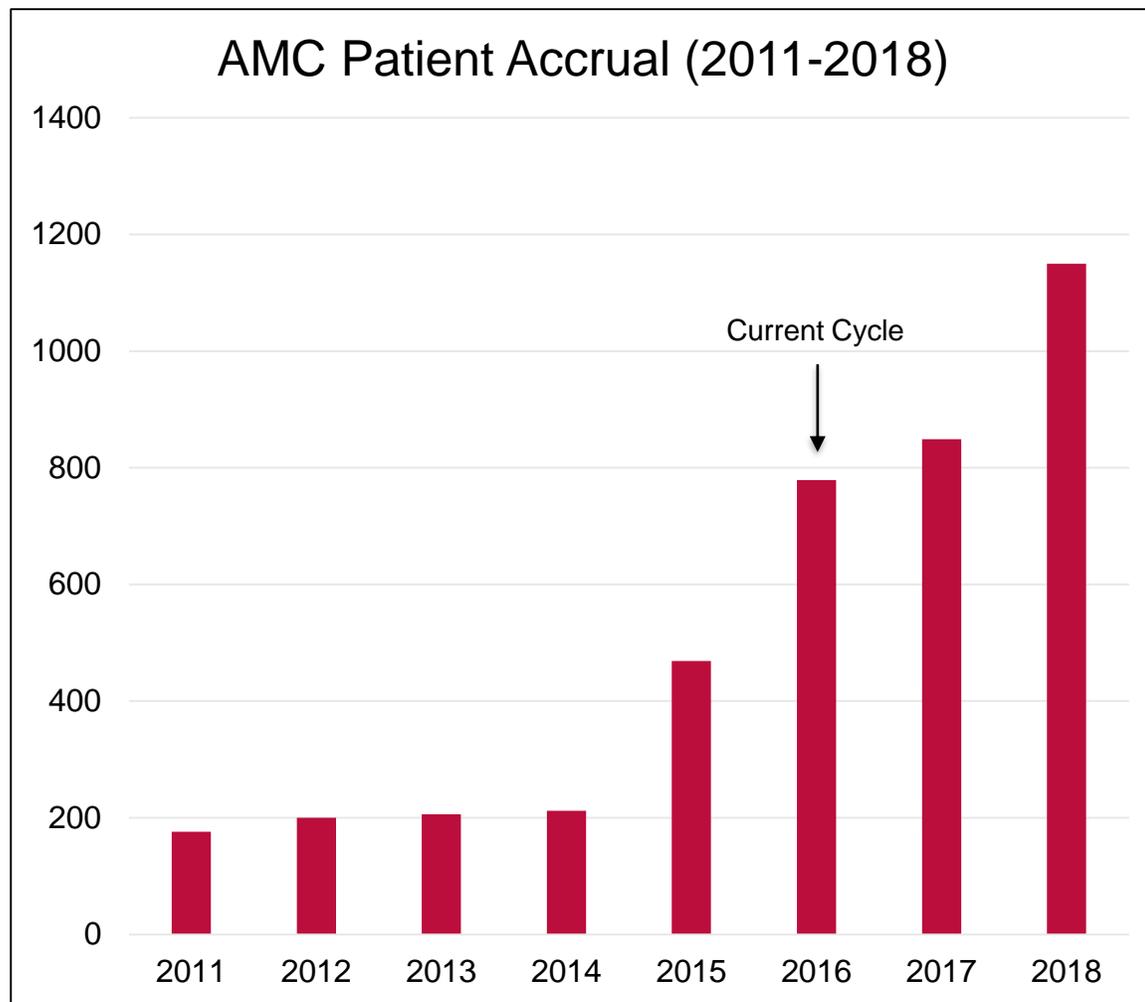
# Some Performance Parameters

- Developed 15 protocols so far in this grant cycle (the past 36 months).
- 14 protocols completed enrollment.
- 2887 patients accrued (2350 ANCHOR + 537 non-ANCHOR). (Excluding survey, laboratory and quality of life studies)
- 14 protocols actively accruing patients.
- Approximately 63% of accrued US participants are of African-American or Hispanic origin.
- In the last 3 years, published approximately 39 papers in peer-reviewed journals.

# Anal Cancer HSIL Outcomes Research (ANCHOR) Study

- A randomized controlled trial to establish whether treatment of anal high grade squamous intraepithelial lesions (HSIL) is an effective strategy to prevent anal cancer.
- It will thus evaluate whether screening for HSIL is warranted.
- 5058 patients with HSIL will be randomized to treatment vs. active monitoring.
- To date, >7000 screened and >2804 randomized.
- The study will establish a bank of blood, anal swab and tissue specimens to study molecular pathogenesis of progression from HSIL to cancer.

# AMC Overall Accrual and Demographics



## AMC Accomplishments this Grant Cycle

- Evaluated **immunotherapy approaches** to solid tumors in HIV patients: e.g. use of ipilimumab and nivolumab in advanced solid tumors, and brentuximab vedotin, or nivolumab for Hodgkin lymphoma.
- Development and assessment **of new approaches for the front-line treatment of AIDS lymphoma: e.g. ibrutinib and R-DA-EPOCH; vorinostat and R-DA-EPOCH.**
- Investigated treatments with novel mechanisms of action for KS (**e.g. bortezomib, lenalidomide, sEphB4-HAS**).
- Conducted KS international trials that defined standard of care in limited resource settings.

# AMC Accomplishments (Cont.)

- Provided evidence for efficacy of the HPV vaccine in preventing HSIL among HIV-infected individuals naïve to the vaccine type.
- Assessment of a **therapeutic vaccine** directed to E6 and E7 HPV 16/18 genes using electroporation.
- Established a network of clinicians trained in high resolution anoscopy and treating anal HSIL. These treatments and platform are being used for the conduct of the **ANCHOR** Study.
- Completed a feasibility study in **Africa** of the safety, toxicity, and compliance of concomitant chemotherapy and radiotherapy for HIV-associated locally-advanced **cervical cancer**.
- Examined **pharmacokinetic interactions** of antiretroviral agents and novel anti-cancer agents (**e.g. sunitinib, cabozentnib**) in HIV subjects with solid tumors.

# AMC Practice-Changing Accomplishments

- Established the standards for chemotherapy in aggressive CD20+ AIDS-related lymphomas, including use of combination anti-retroviral therapy (cART) with rituximab-CHOP;
- Helped establish treatment standard for drug-resistant severe Kaposi Sarcoma (paclitaxel) and assessed the relative merits of the 2 most efficacious drugs (paclitaxel vs. liposomal doxorubicin);
- Established infrared coagulation as the leading method of treatment of anal high grade squamous intraepithelial lesions (HSIL);
- Established the superiority of paclitaxel over etoposide or bleomycin/vincristine (**the previous standard of care**) for treating KS in Africa;
- Demonstrated that HIV-associated aggressive lymphoma patients who meet standard eligibility criteria for autologous or allogeneic stem cell transplant respond well to transplantation – as a result, this is **now standard of care**;
- Development and initiation of the ANCHOR trial (N=5058), which will likely define standard for anal cancer screening. The study is more than half accrued.

# Current Scientific Needs

- Cancer continues to be among the leading causes of death among HIV-infected patients in the U.S., and in some studies is the leading cause.
- The standards of care for progressive KS and NHL have not been optimized.
- Non-AIDS-defining cancers (especially lung, liver, head & neck, anal) are increasing in areas where cART is widely available.
- The impact of AIDS and cART on anti-cancer chemotherapy, on toxicity profiles, and on response to treatment are not sufficiently studied.
- Need to optimize treatment in resource-limited countries.

# AMC Mid-Cycle Evaluation

- Uniquely positioned to carry forward the NCI clinical agenda in HIV-associated malignancies;
- Well-elaborated succession plan;
- Expanded their international agenda and had effected the development and capacity building of their international sites;
- Promoted young investigators in leadership roles in AMC activities;
- Increased engagement of community representatives in AMC activities;
- Outstanding record of the disease Working Groups to complete ongoing trials and to develop new trials, and the renewed focus in cutting-edge immunotherapy-based clinical trials.

# Review - Recommendations

- To give more attention to increase accrual;
- To consider development of cancer prevention intervention trials and strategies, other than ANCHOR trial;
- To expand to areas of cancer survivorship;
- To expand genomic studies in domestic and international trials; and
- To develop a structured strategic plan relative to prioritization of research-related areas of emphasis.

# AMC Plans for Increasing Domestic Enrollment

- Open new sites in geographical areas with high HIV disease burden (including ANCHOR Sites).
- Streamline the protocol development process and make the protocols more “user friendly”.
- Plan to restructure the current domestic Clinical Sites compensation model to be more incentive-dependent.
- Recruitment of an Executive Officer to oversee the protocol development. Work closely with the protocol chairs and operations to facilitate the process.

# Proposed AMC Budget Year One

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**Two components:** AMC base \$9,975,000  
ANCHOR \$14,025,000

**Total: \$24,000,000**

**Current Year 5 Budget:** AMC base \$ 9,175,000  
ANCHOR \$14,025,000

**Total: \$23,200,000**

**Difference: \$ 800,000**

*Rationale:*

- *Increased costs related to foreign trials*
  - *Costs for drug sourcing, storage, distribution*
  - *Operations center, site monitoring, clinical trials insurance*
- *Increased costs related to moving to central IRB*

# Total AMC Budget

	Year 1	Year 2	Year 3	Year 4	Year 5
AMC Base	9,975,000	10,274,250	10,582,478	10,899,952	11,226,952
ANCHOR	14,025,000	14,025,000	11,375,000	10,643,210	10,703,681
Total	24,000,000	24,299,250	21,957,478	21,543,162	21,930,633

Total cost for 5 years: **\$113,730,523**

*Source of Funds: NCI AIDS funds, including a \$5.6 million yearly increase to AIDS base from the OAR for ANCHOR*

# AMC Patient Costs

Core structure + patient care \$16,655,000

Cost per patient \$12,000

Minimum 1400 patients

25 domestic sites + 7-9 non-AMC ANCHOR Sites

11 International sites in SSA & Latin America

# New AMC Group Chair

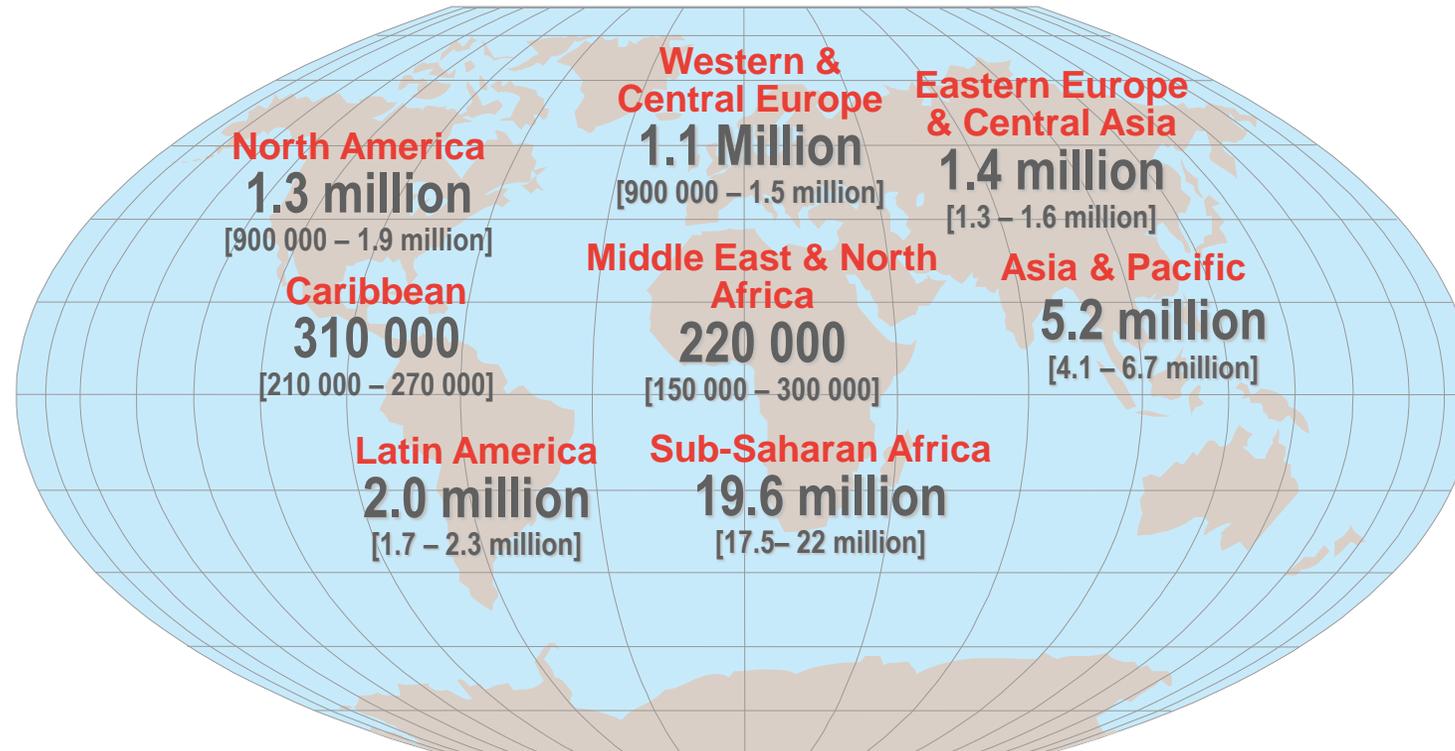
- Dr. Joseph Sparano, is the next AMC Group Chair, from Montefiore Medical Center, Bronx, NY.
- Vice Chair of the AMC since 2009
- Vice Chair, ECOG-ACRIN Research Group, May, 2013-present
- Served as the Group Chair of the New York Cancer Consortium (2005-2011)
- Well recognized nationally and internationally

# Some Areas Where the AMC Can Make Unique Contributions

- Only group with expertise and focus on HIV/AIDS-associated cancers.
- Poised to evaluate **immunotherapy** approaches for malignancies in HIV-infected patients
- Conducts preventive and therapeutic trials for **Kaposi sarcoma and HPV-related precancers and cancers** in HIV patients.
- Only NCI-supported clinical trial network to conduct interventional trials for HIV malignancies in LMIC.
- Investigation of pharmacokinetic interactions between novel anticancer drugs and antiretroviral drugs - will facilitate the inclusion of HIV patients on larger **CTEP studies**.
- Has established a network of clinicians trained in high resolution anoscopy and treating anal HSIL. In addition to **ANCHOR**, this resource can be used for other key studies in this area.

# Questions

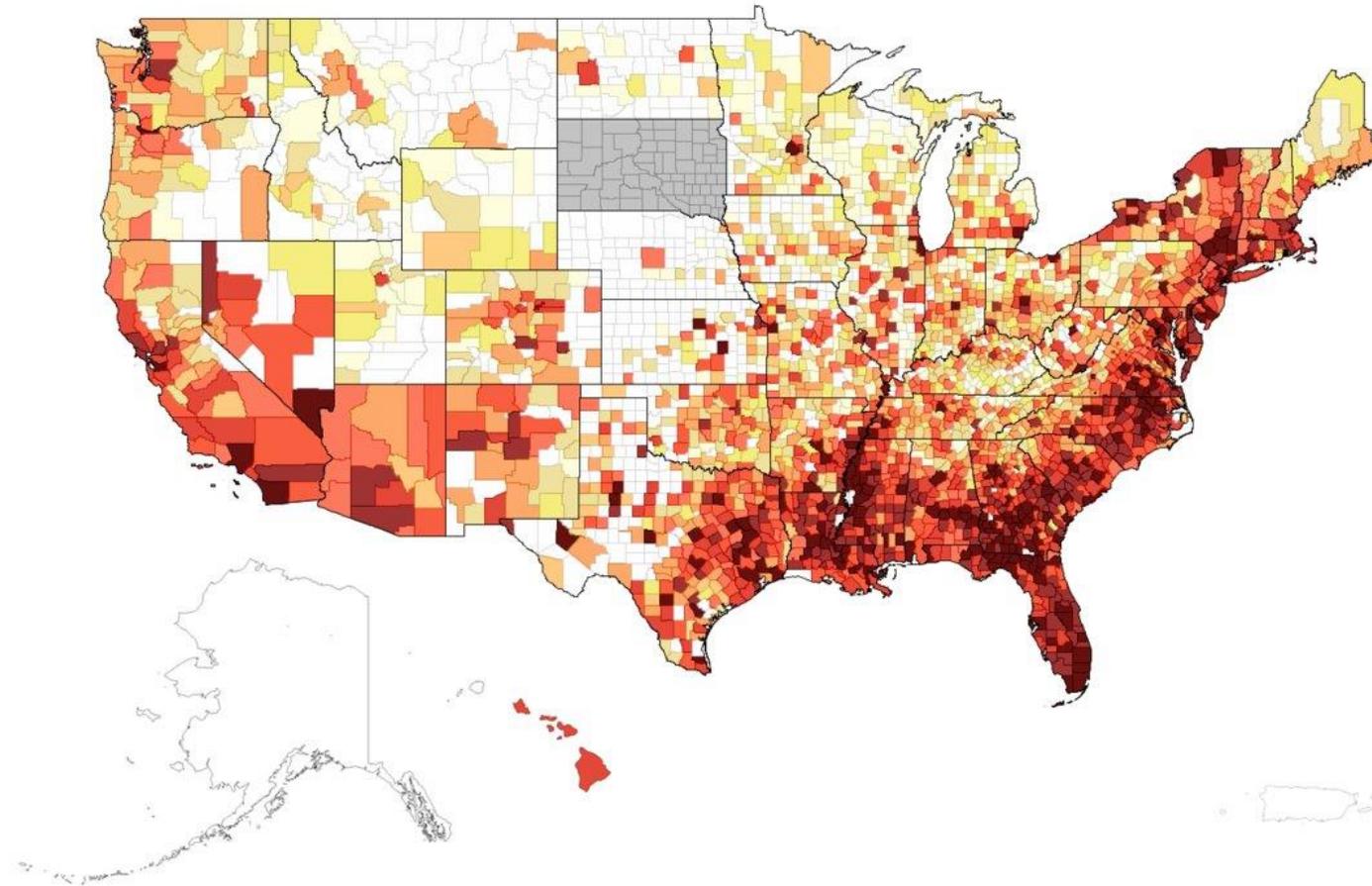
## Adults and children estimated to be living with HIV, 2017



- 2.1 million new cases/year
- ~50% women
- ~90% in low- and middle-income countries (LMICs)
- 1.1 Million deaths/year

**Total: 36.9 (31.1 – 43.9) million**

# Incidence of HIV Infection in the US



AIDS*Vu* 

Rates of Persons Living with Diagnosed HIV, by County, 2014 per 100,000 person-years

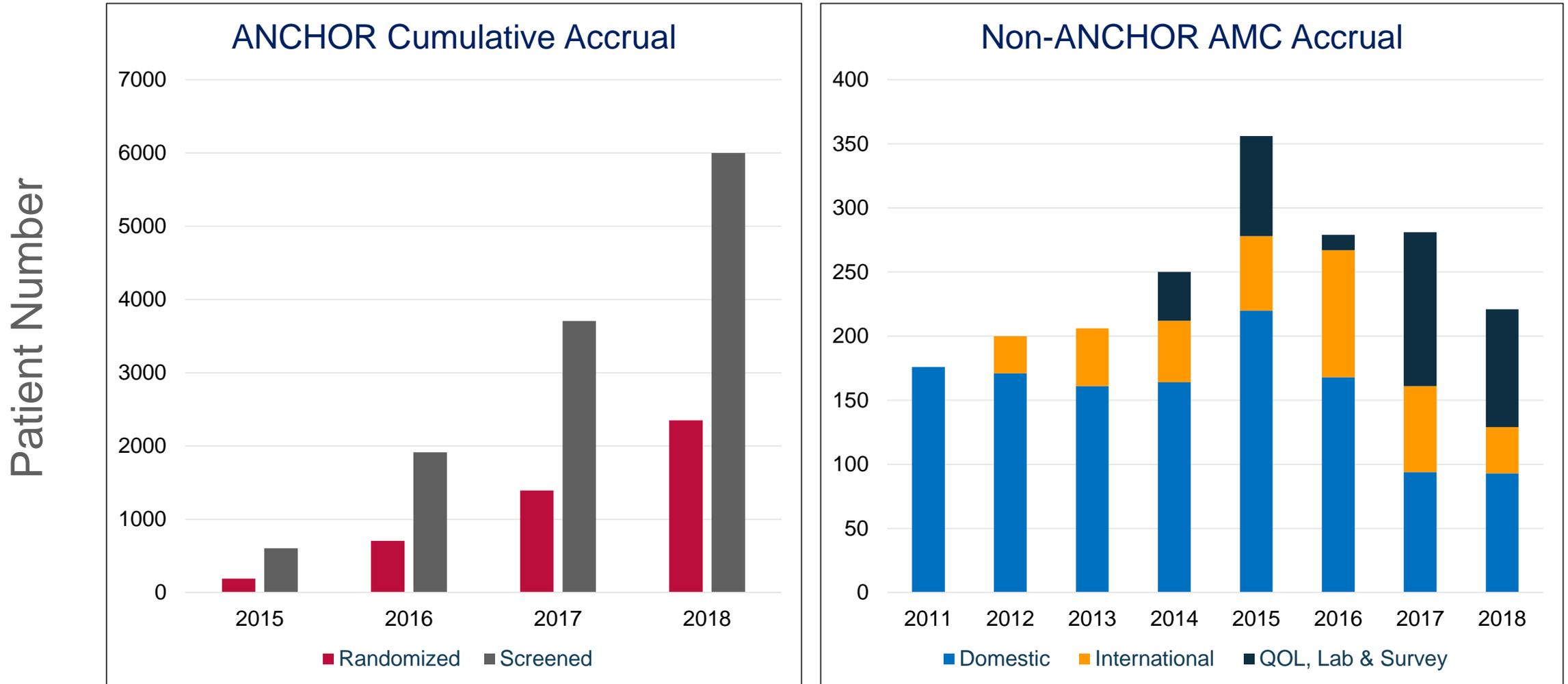
0 - 50   51 - 60   61 - 80   71 - 90   91 - 120   121 - 150   151 - 190   191 - 250   251 - 380   381+

Data not shown \* 

# A Brief History of the AMC

- Prior to 1995 AIDS-related cancer trials were the charge of the Oncology Committee of the NIAID-sponsored AIDS Clinical Trials Group (ACTG).
- In 1994-5, AIDS-related cancer trials were transferred to the NCI. The AMC was created as a group of 15 semi-autonomous clinical trial sites with multiple PIs and three scientific working groups - KS, NHL, HPV.
- In 2006, the AMC was restructured to a cooperative group structure with a single PI.
- AMC is now comprised of 25 domestic clinical sites and 11 international sites and a network laboratory.

# AMC Patient Accrual



# Some Aspects of the AMC that Affect Cost and Enrollment

- Simultaneous treatment of two life threatening diseases
- Majority of patients are indigent, lack insurance and are from socioeconomically disadvantaged areas both domestically and internationally
- Rarity of events requires a wider network of U.S. sites to enroll meaningful numbers
- Patient numbers prevent economy of scale
- Diversity of cancers require wider expertise
- Due to the rarity of the events, there is no vested interest from Pharma, and the Government is just about the only viable source of support.

# Aspects of AMC that Affect Cost (cont.)

- International studies are critical but require capacity building as the regions with heavy disease burden have never been traditional NCI partners.
- Dedicated full time personnel are needed for international sites.
- The AMC pays for costs of drug procurement, storage and distribution for international studies.
- Monitoring and site inspection for international sites.
- The grant pays for standard of care costs for international studies including pathology and imaging.
- The AMC conducts its own study monitoring, auditing, and performance evaluation through a subcontract paid by the grant.

# Cancer is the Most Frequent Cause of Death in HIV-Infected Patients in the HAART Era

Cause of Death	2000	2005	2010
Cancer (all)	29%	33%	36%
Cancer – AIDS Defining	16%	13%	9%
Cancer – non-AIDS defining	13%	21%	27%

Mortalité 2000, 2005, and 2010 Studies:

C. Lewden et al., *Cancer* 2014; *CID* 2009, and M.

Phillippe et al., *AIDS* 2014.

# Collaborations with other Groups

- **ACTG:** AIDS KS protocols; HPV vaccine studies.
- **BMT-CTN:** Development of autologous and allogeneic stem cell transplant protocols.
- **CCR/Cooperative Groups:** Dose adjusted EPOCH+/- Rituximab in adults with Burkitt lymphoma, plasmablastic lymphoma and c-Myc positive DLBCL.
- **ACSR:** Contributing tumor and other specimens and working with development of international pathology capability in resource limited countries.
- **ATN (Adolescent HIV-positive Treatment Network):** Protective effects of the HPV quadrivalent vaccine in young HIV-positive Males who have sex with males.