

Proposal for new RFA

**U.S.-Latin American-Caribbean  
HIV-HPV Prevention Clinical Trials  
Consortium**

*(U54 Specialized Center Cooperative Agreements)*

## **Partnering NCI DOCs and Program Staff**

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## Goal of the RFA

To support partnerships between investigators in the US and the Latin American and Caribbean (LAC) region for conducting collaborative clinical trials to improve preventive care and reduce the burden of HPV-associated malignancies in high-risk HIV-infected individuals

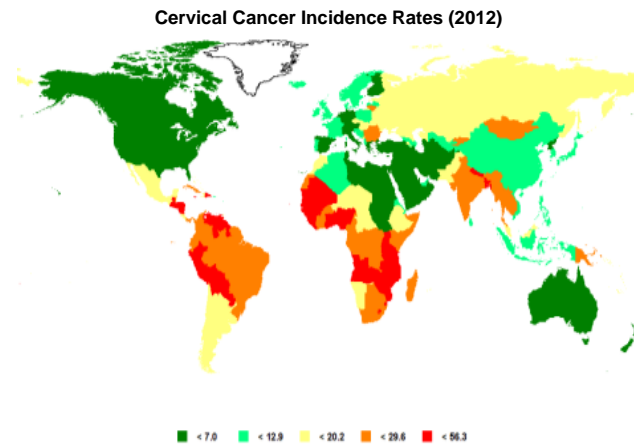
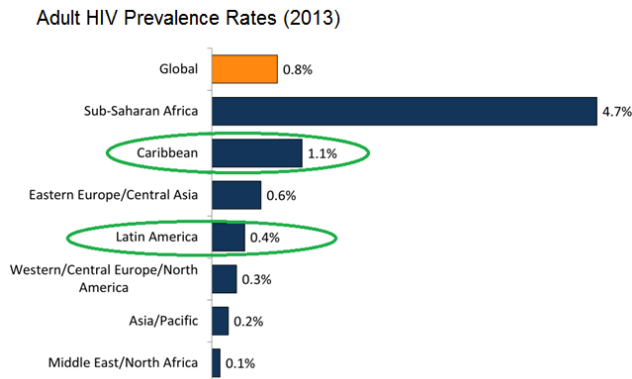
Background  
**HIV/AIDS and Cervical Cancer:**  
**Intersecting Epidemics of High Global Health Significance**

**HIV/AIDS**

- >30 million globally
- ~50% women
- ~90% in low- and middle-income countries (LMICs)
- Improving access to life-prolonging antiretroviral therapy

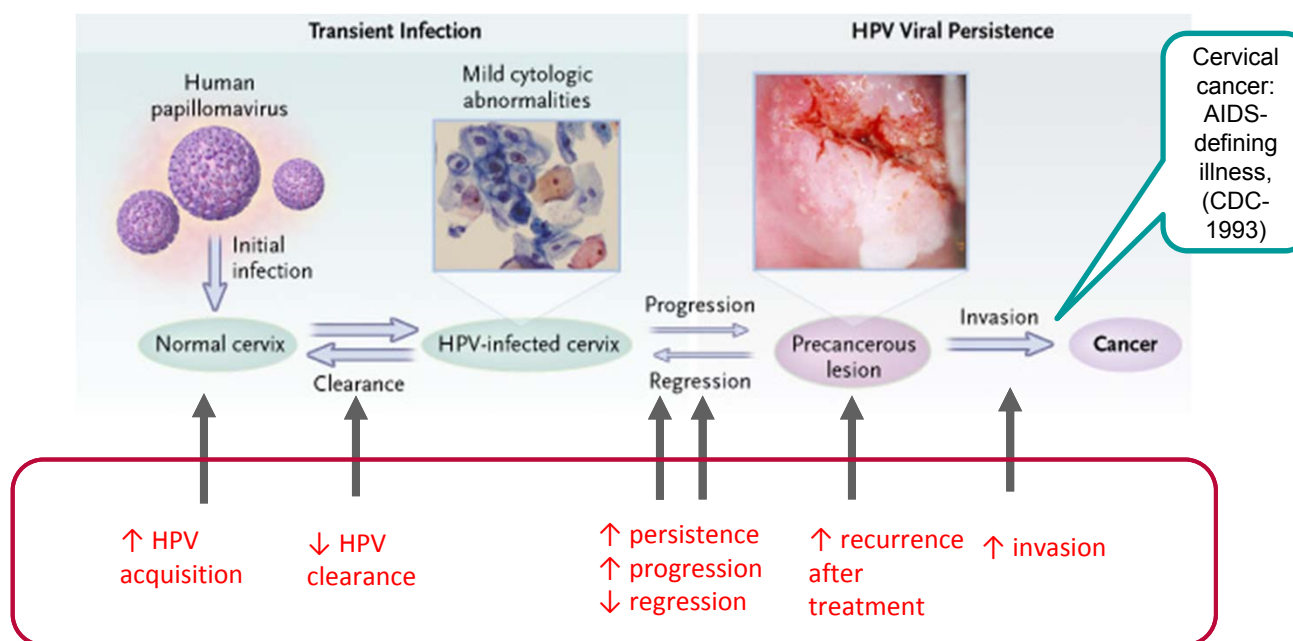
**Cervical cancer**

- >530,000 cases annually
- >275,000 deaths annually
- >85% burden in LMICs
- 1<sup>st</sup>/2<sup>nd</sup> most common cancers in women in many LMICs

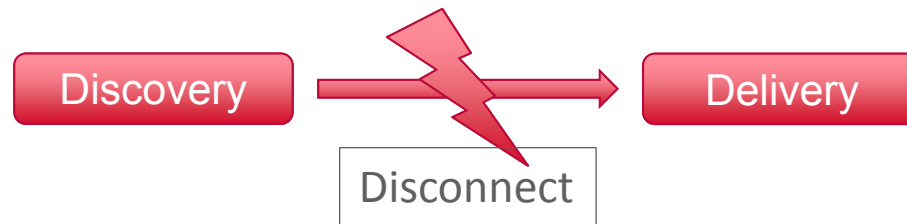


## Background

### HPV-mediated carcinogenesis in the context of HIV/AIDS



## Background and Rationale



- A wide spectrum of interventions (vaccines, screening, pre-cancer treatment) have been discovered for the prevention of HPV-related cancers, yet implementation has not been optimized, particularly for high-risk HIV+ individuals.
  - Inadequate evidence on best methods, algorithms, and follow-up protocols.
  - Unique immunosuppression-related clinical issues in context of HIV
- Clinical trials to resolve unanswered questions can inform clinical care recommendations and public health practice.

## 2013 BSA Ad-Hoc Subcommittee Recommendations on HIV-associated Cancers in LMICs

- Improve data on burden and types of HIV-associated malignancies
- Define factors that influence cancer risks in LMICs
- Define optimal methods for screening and prevention, especially for cervical cancer
- Investigate other virally-associated cancers
- Identify optimal therapies, taking into account medical infrastructure



- RFA concept developed for use of FY2018 HIV/AIDS-related research funds under the NIH Office of AIDS Research (OAR)'s ***'Trans-NIH Plan for HIV-Related Research'***
- “High Priority” topic of research for support using AIDS-designated funds → *“HIV associated comorbidities, coinfections, and complications including malignancies”*



## Rationale for focusing on the Latin American and Caribbean (LAC) region



- High HIV burden (2 million HIV+) and high cervical cancer burden
- Large public investments in HIV/AIDS care (models for HIV+ treatment for other LMICs)
- Recent strong commitments for HPV vaccination and HPV-based screening
- Strong US academic and clinical partnerships
- Long-standing NIH-funded HIV clinical trials infrastructure
  - Leading sites for landmark HIV trials (e.g., HPTN052 ‘Breakthrough of the Year 2011’)
- Middle-income settings with highly educated and capable workforce
- Minimal time-zone differences facilitating effective coordination

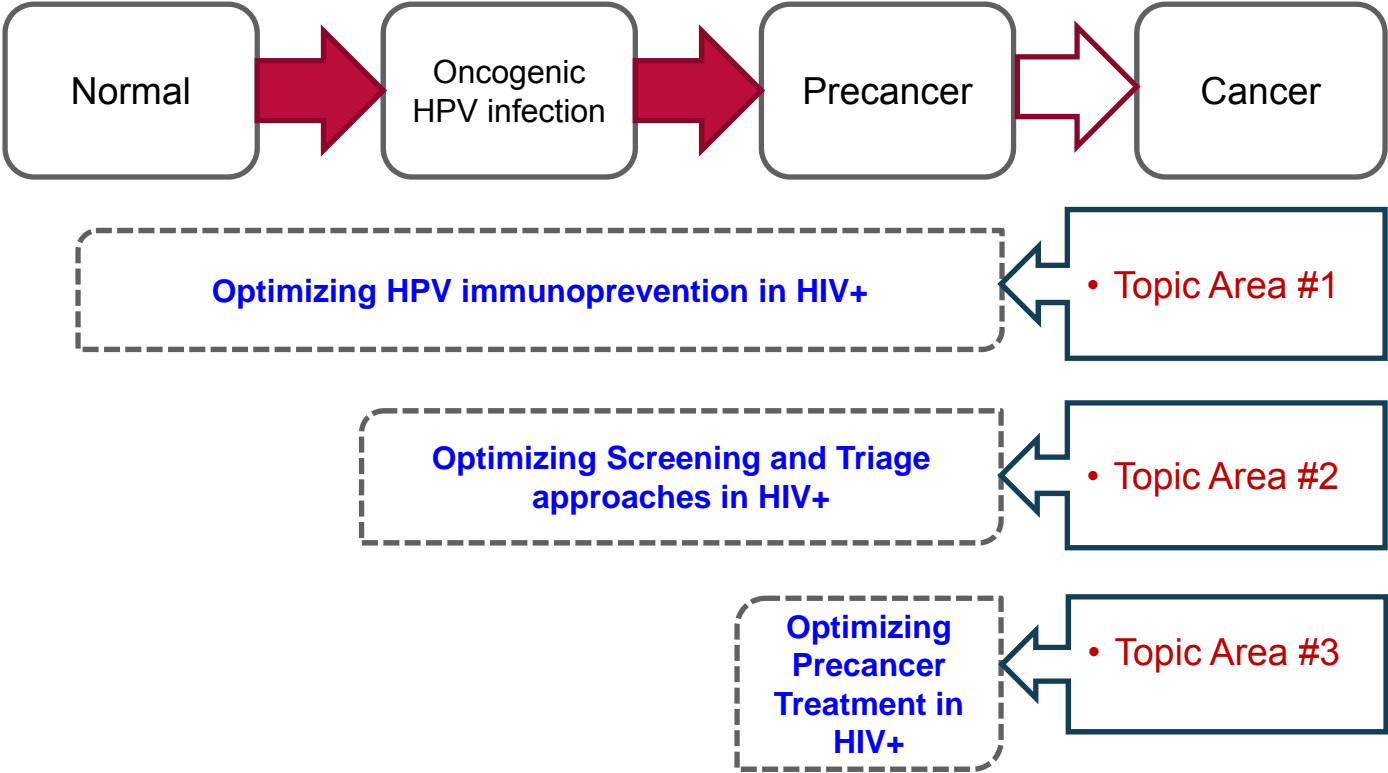
## Key Considerations

### **NCI-led Consultative Meetings to Define Research Priorities in HIV/HPV Coinfection**

- Washington, DC (May 2014): HPV diagnostics for LAC region: Workshop in partnership with PAHO
- Seattle, Washington (August 2014): HIV/HPV Research Priorities Workshop in partnership with International Papillomavirus Society
- São Paulo, Brazil (May 2015): HIV/HPV Research Investigators Meeting (9 LAC countries) in partnership with PAHO and Brazilian Ministry of Health



# Clinical Trials Research on Prevention of HPV-associated Malignancies in HIV+ individuals: Priority Topic Areas



## Topic Area #1:

# Optimizing HPV immunoprevention in HIV-infected individuals

## Outstanding Research Questions

- Optimal **timing, schedule, duration of protection, and dosing** of HPV vaccines, especially for perinatally-infected HIV+ adolescents?
- Role of prophylactic HPV vaccines in
  - preventing **reactivation of latent** HPV?
  - preventing **recurrence** of HPV infections in the adjunctive post-precancer treatment setting?
- Minimal serologic titers induced that **predict efficacy** in the context of HIV-induced immunosuppression?
- Safety and immunogenicity of **therapeutic HPV vaccines** in the context of reduced cellular immune response due to HIV?
- Role of novel candidate vaccines that seek to provide a **combined preventive and therapeutic benefit**?

## Topic Area #2:

# Optimizing Screening and Triage approaches for HIV+ women

### Outstanding Research Questions

- **Primary HPV screening** to replace cytology/visual screening?
  - **Self-collection of samples** for optimizing access?
- Ideal approaches to triage for HPV positive test results?
  - **Visual** (e.g., VIA/visual inspection after acetic acid wash)
  - **Microscopic** (e.g., reflex cytology, p16/Ki67 immunocytochemistry)
  - **Molecular** (e.g., HPV E6/E7 oncoprotein testing, HPV mRNA)
- Optimal cut-offs of HPV assay positivity to **balance sensitivity versus specificity**?
- Optimizing HPV-based '**screen-and-treat**' protocols?

### Topic Area #3:

## **Non-surgical approaches for HPV-associated precancer treatment in HIV+ individuals**

### **Outstanding Research Questions**

- Safety and efficacy of **locally applied agents** to induce regression of precancerous disease and clear oncogenic HPV?
  - **Repurposing of chemoprevention agents** (e.g., cidofovir, imiquimod, 5-fluorouracil, carrageenan)?
- Optimal **delivery vehicles** (e.g., gels/creams via intravaginal applicators, suppositories, intravaginal rings, sponges) and **delivery approaches** (clinician-applied or self-administered)?
- **Combinations of agents** delivered topically, as well as combinations of **topical agents with therapeutic HPV vaccines** to enhance efficacy?

## Portfolio Analysis

### **NCI-supported clinical research on HIV/HPV coinfection**

#### **NCI Office of HIV/AIDS Malignancy- AIDS Malignancy Consortium (AMC)**

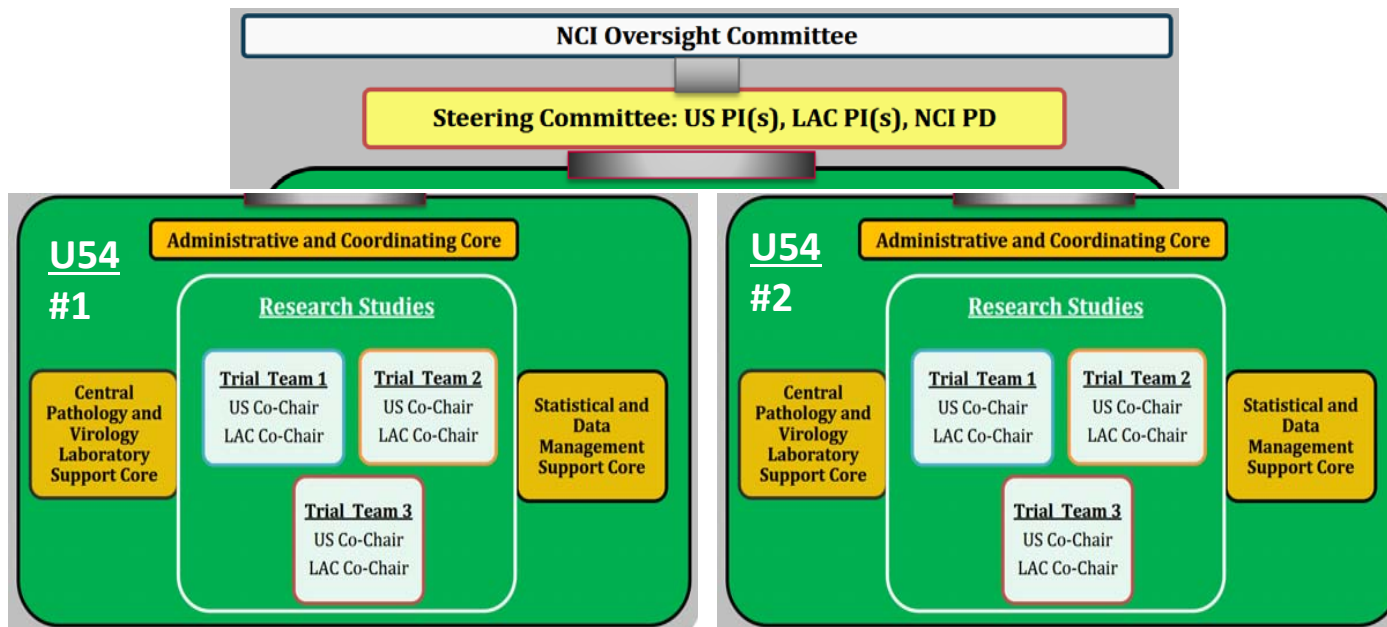
- Overlapping population (HIV+) but no directly overlapping trials/prevention trials in LAC region
- Current/past AMC portfolio:
  - Cancer treatment/management trials in HIV+ women and men (ongoing)
  - Anal precancer management trial in HIV+ men (ongoing)
  - HPV vaccination for post-cervical treatment recurrence (African sites) (new)
  - Safety/immunogenicity of HPV vaccination in HIV+ women (India) (completed)

#### **Other NCI-funded HPV/Cervical Cancer Prevention Clinical Trials, not focused on HIV+ individuals**

- DCP Early Phase Cancer Prevention Clinical Trials Consortia Program
- DCEG HPV vaccine trials in Costa Rica
- CGH Cancer Detection, Diagnosis, Treatment Technologies for Global Health (UH2/UH3)

## US-LAC HIV/HPV Prevention Clinical Trials Consortium

- Two **U54 Specialized Center Cooperative Agreement** awards in FY2018
- 4-6 clinical trials to be supported over a five-year project period (2-3 trials per award)





## Composition of Consortium and Roles of Collaborators

### ▪ Administrative/Coordinating Core

#### U.S. Institution:

- Overall oversight
- Training and study monitoring
- Liaison with NCI Staff
- Convene and liaison with DSMBs
- Regulatory support
- Study analysis, reporting, and publications

#### LAC In-country institution

- Site infrastructure and clinical care
- Laboratory testing and monitoring
- Study analysis, reporting, and publications

### ▪ Statistical and Data Management Core

- Study design and protocol development
- Study analysis, reporting, and publications

### ▪ Central Pathology and Virology Laboratory Core

- Conduct central cyto/histopathology and HPV/HIV virology/immunologic testing
- Provide external quality assurance to local study laboratories
- Liaison with external labs for specialized testing

### ▪ US-LAC Trial Teams

- US & LAC Protocol Co-Chairs
- Study design and protocol development
- Study conduct and monitoring
- Study analysis, reporting, and publications

## Budget projections by funding timeline

Each Award	Year 1	Year 2	Year 3	Year 4	Year 5	Total
<b>Cores</b>	<b>\$500K</b>	<b>\$500K</b>	<b>\$500K</b>	<b>\$500K</b>	<b>\$500K</b>	<b>\$2.5M</b>
Admin Core	\$300K	\$300K	\$300K	\$300K	\$300K	\$1.5M
Stat/Data Core	\$100K	\$100K	\$100K	\$100K	\$100K	\$0.5M
Labs Core	\$100K	\$100K	\$100K	\$100K	\$100K	\$0.5M
<b>Trials</b>	<b>\$1.0M</b>	<b>\$1.0M</b>	<b>\$1.0M</b>	<b>\$1.0M</b>	<b>\$1.0M</b>	<b>\$5.0M</b>
Trial 1	\$800K	\$500K	\$500K	\$200K	\$200K	\$2.2M
Trial 2	\$100K	\$300K	\$300K	\$400K	\$400K	\$1.5M
Trial 3	\$100K	\$200K	\$200K	\$400K	\$400K	\$1.3M
<b>Direct Costs</b>	<b>\$1.5M</b>	<b>\$1.5M</b>	<b>\$1.5M</b>	<b>\$1.5M</b>	<b>\$1.5M</b>	<b>\$7.5M</b>
<b>F&amp;A Costs</b>	<b>\$725K</b>	<b>\$725K</b>	<b>\$725K</b>	<b>\$725K</b>	<b>\$725K</b>	<b>\$3.6M</b>
<b>Total Costs</b>	<b>\$2.225M</b>	<b>\$2.225M</b>	<b>\$2.225M</b>	<b>\$2.225M</b>	<b>\$2.225M</b>	<b>\$11.125M</b>
<b>Two Awards</b>	<b>\$4.45M</b>	<b>\$4.45M</b>	<b>\$4.45M</b>	<b>\$4.45M</b>	<b>\$4.45M</b>	<b>\$22.25M</b>

## Application Review Criteria for the RFA

- **Overall Impact:** Likelihood of high-impact, policy-translatable research via effective collaborative partnerships?
- **Significance:** Improvements in scientific knowledge, technical capabilities, clinical practice? Change in concepts, interventions, technologies, services?
- **Investigators:** Ongoing successful record of US-LAC partnerships? Appropriate governance and organizational structures? Appropriate leadership balance?
- **Approach:** Appropriate strategy/methodology/analyses for aims of specific trials? 'Shovel-ready' concepts presented for timely launch of trials? Presentation of alternative strategies, and benchmarks for success?
- **Innovation:** Use of novel concepts/designs/methodologies/interventions?
- **Environment:** Access to subject populations? Institutional support, equipment and other physical resources available?

## Evaluation Criteria for Program Success of the RFA

- **Conduct high-impact, policy-translatable research on HIV/HPV coinfection**
  - Identify key unanswered questions that merit clinical trials evaluation
  - Conduct 4-6 high quality clinical trials to inform practice and guidelines
- **Formation of effective collaborative partnerships**
  - Strengthen NIH-funded US-LAC collaborations focused on HIV and cancer
  - Develop/fill-gaps in management of international clinical trials (e.g., drug acquisition and distribution, material transfer agreements)
- **Timely development of protocols and launch of clinical trials**
  - Development and launch of  $\geq 1$  trial by Year 2
  - Development and launch of  $\geq 2$  trials by Year 3
- **Scientific/publications output**
  - Presentation of  $\geq 2$  abstracts yearly in scientific conferences/meetings
  - Submission of  $\geq 4$  manuscripts from primary study end-points and  $\geq 10$  manuscripts overall

## Clarifications in response to feedback from BSA Subcommittee reviewing this RFA

- **Rationale for focusing research on the LAC HIV/AIDS population:**
  - Unique opportunity to study and intervene in a population at high-risk for cancer, as well as gain biologic insights into viral-host interactions and immunologic contributions to cancer development
  - Highly screened/treated cohorts of HIV+ individuals in the US/other high-income settings limit ability to study improvements in implementation of screening and treatment interventions
  - Researching cost-effective and innovative cancer prevention interventions in the LAC HIV+ population will inform improvements in implementation delivery systems for HIV+ individuals in the US and other settings
- **Spectrum of research invited under this RFA**
  - Will include dissemination and implementation clinical trials that seek to improve preventive clinical care delivery

Questions?

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## Key Considerations

### Why U54 Specialized Center Cooperative Agreement mechanism?

- i. Studies developed in response to ***high-priority programmatic needs*** (e.g., HIV/HPV prevention trials, HPV vaccination, global health, health disparities)
  - ii. ***Flexibility in support of ancillary activities*** vital for the success of the primary research effort (e.g., laboratory quality assurance, data management, regulatory approvals, agent acquisition)
  - iii. Allows ***oversight from NCI staff*** (NCI Oversight Committee, Consortia Steering Committee)
  - iv. Awardees serve as ***regional/national resource centers*** for special research purposes (HIV/HPV prevention clinical research), in-country staff help identify appropriate priorities
- 
- Assistance-mechanism (Cooperative agreement) preferred over procurement-mechanism (R&D contract) since data would primarily benefit research and clinical communities, rather than NIH specifically.
  - Cooperative agreement preferred since experience with NIH-supported clinical trials has shown that they require close ongoing cooperation on the project between the sponsor and the performer.