Concept for a new RFA

'CASCADE': Global Clinical Trials Network to Improve Screening and Preventive Therapy Outcomes for Cervical Cancer among Women Living with HIV

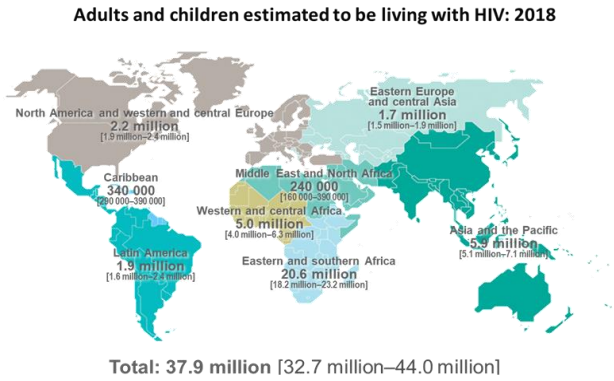
Vikrant Sahasrabuddhe
Division of Cancer Prevention

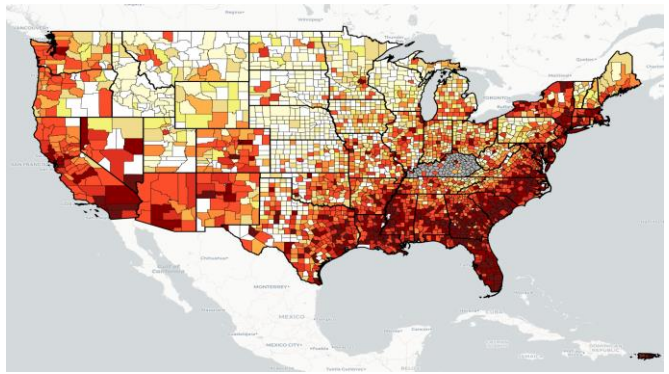
NIH NATIONAL CANCER INSTITUTE

HIV/AIDS and Cervical Cancer: Intersecting Epidemics of High Public Health Significance

HIV/AIDS

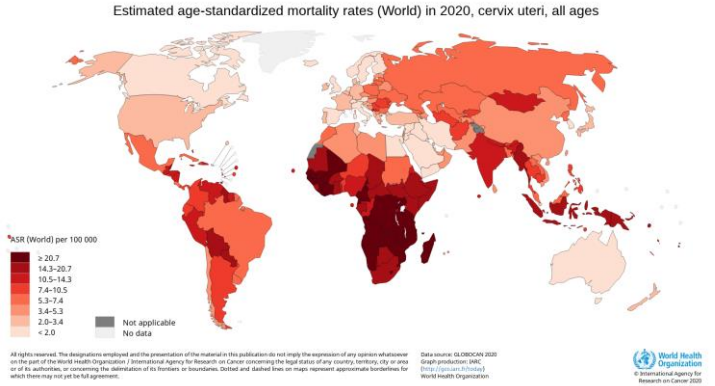
- Globally: >37 mill. persons, >18.8 mill. women with HIV
- US: >1.2 mill. persons, >250,000 women with HIV

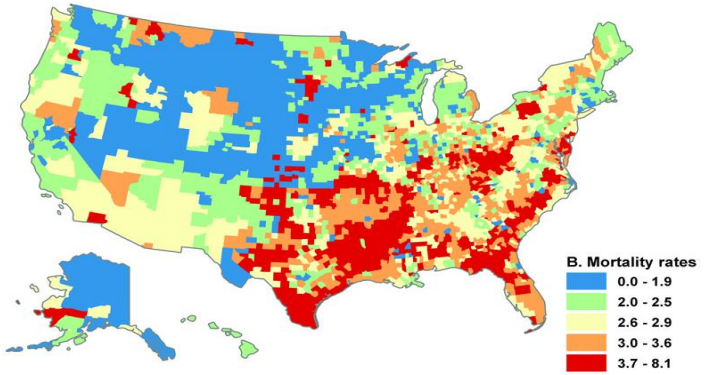




Cervical cancer

- Globally: >604,000 cases and >340,000 deaths *annually*
- US: >13,000 cases and >5,700 deaths *annually*





Refs: UNAIDS, 2018; AIDSVu 2020; IARC-WHO 2020; Horner et al 2011

HPV-mediated Cervical Carcinogenesis in the Context of HIV

Higher burden of HPV and cervical cancer among women with HIV

- accentuated by immunosuppression
- refractory to antiretroviral therapy

Cervical cancer among women living with HIV

- younger age at cancer diagnosis
- more aggressive clinical course
- less responsiveness to treatment

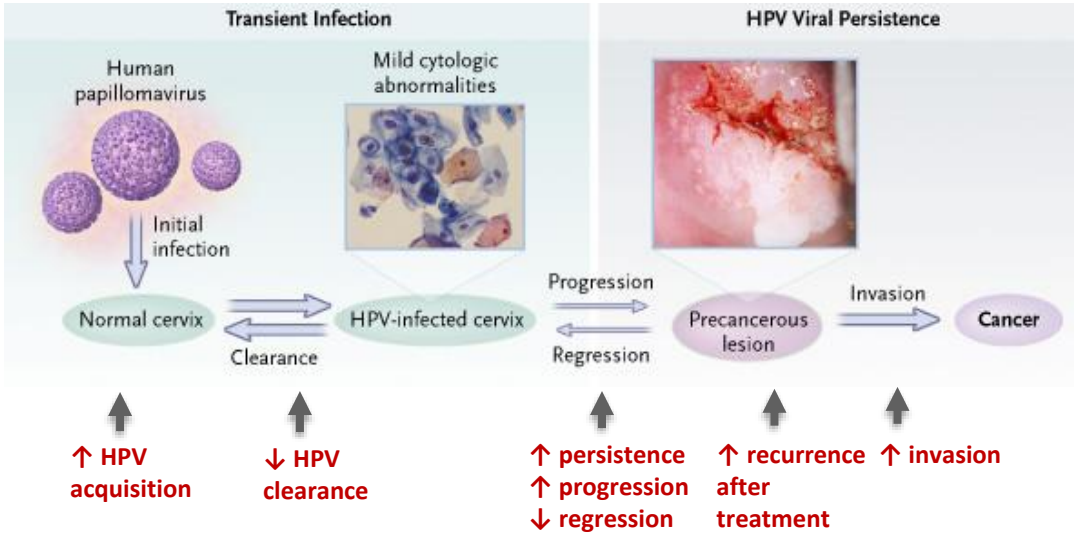
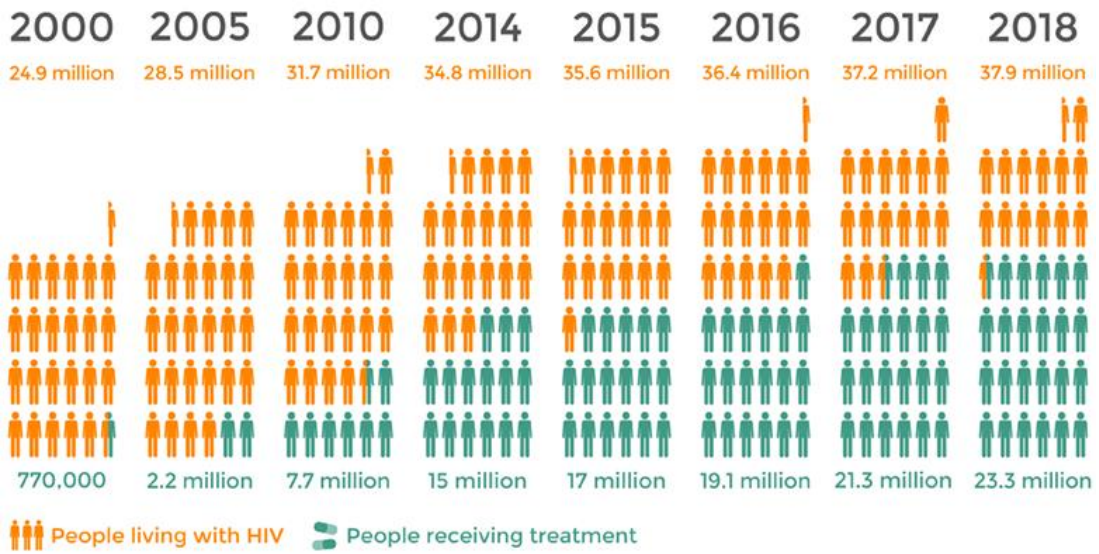


Figure ref: Wright & Schiffman, NEJM 2003

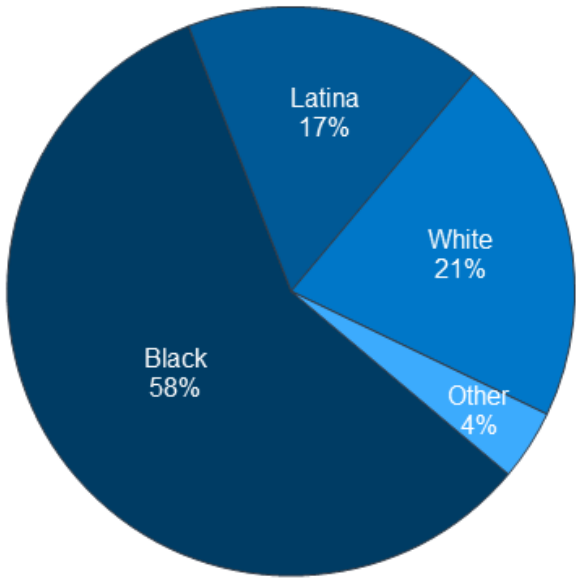


Ref: https://www.avert.org/global-hiv-and-aids-statistics

Why Should---and How Could---We Let Women With HIV Die Due to Lack of Effective Cervical Cancer Prevention Services after Extending their Lives with Antiretroviral Therapy?

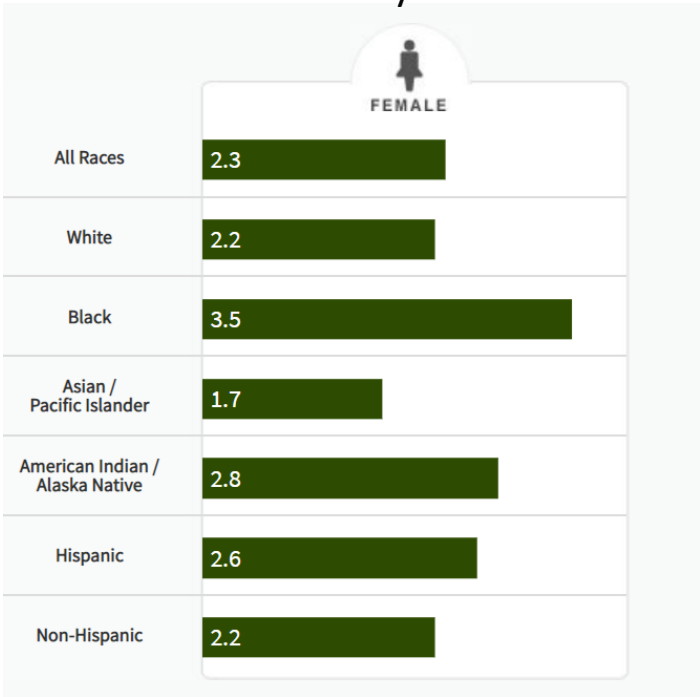
Racial and Ethnic Disparities are a prominent feature influencing the burden of both HIV/AIDS and Cervical Cancer in the United States

HIV/AIDS Diagnoses among Women in the US



Source: Kaiser Family Foundation 2018
https://www.kff.org/hivaids/fact-sheet/women-and-hivaids-in-the-united-states

Cervical Cancer Mortality Rates in the US



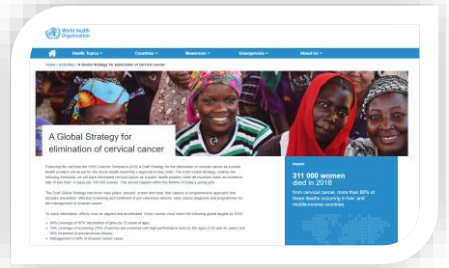
Source: NCI SEER Cancer Fact Sheets
https://seer.cancer.gov/statfacts/html/cervix.html

Rationale for the ‘CASCADE’ Clinical Trials Network

- **Acceleration in key catalytic technologies and regulatory pathways**:
  - HPV self-sampling approvals (‘Last Mile’ Initiative)
  - Development of point-of-care visual/diagnostic approaches
  - Multiple portable ablative/excisional devices in late-trials




- **Renewed impetus on bilateral and multilateral initiatives for cervical cancer screening and treatment**:
  - PEPFAR ‘Go Further’ HIV-Cervical Cancer Partnership expansion
  - World Health Organization’s Global Cervical Cancer Elimination Initiative



The proposed ‘**CASCADE**’ Network will seek to conduct **pragmatic clinical trials evaluating the effectiveness of clinically-proven interventions in intended-use settings** with a goal to optimize the cervical cancer screening and treatment cascade for women living with HIV

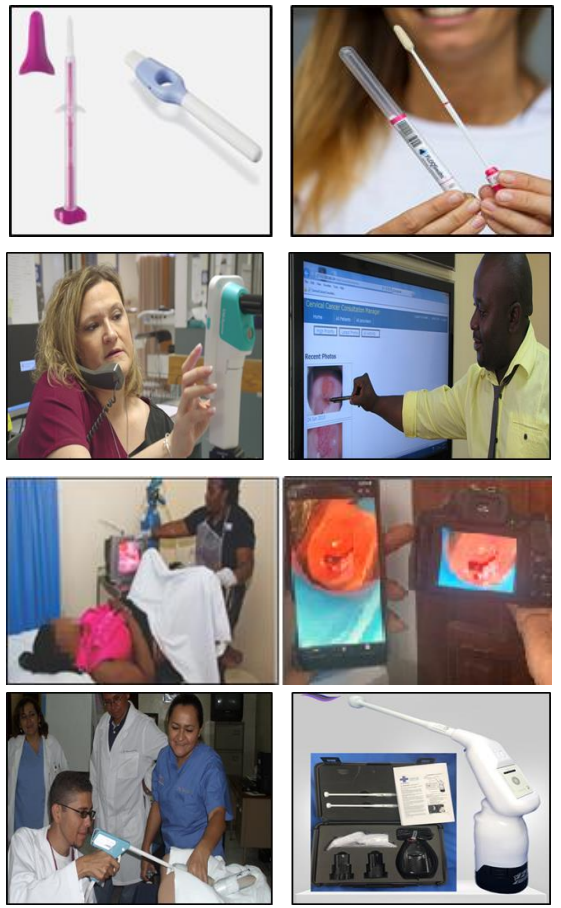
‘CASCADE’ Clinical Trials Network: Focus Areas and Study Designs

Clinical Trial Focus Areas

- **Screening Uptake** (e.g., HPV self-sampling strategies vs. standard of care)
- **Management of Screen Positives** (e.g., immediate ablation vs. molecular/visual triage)
- **Precancer Treatment Access** (e.g., task-shifting: independent decision-making vs. telemedicine consults)
- **Optimization of Precancer Treatment** (e.g., comparison of portable devices, comparison of treatability thresholds)

Sites of Clinical Trials

- Resource constrained settings in **Low- and Middle-Income Countries (LMICs)**
- Settings with high disease-burden and health disparities within the **United States**



Pragmatic Phase 3/Phase 4 Clinical Trials with ‘Hybrid’ Effectiveness-Implementation Designs

- ***Clinical effectiveness outcomes***
  - Rates of HPV detection/precancer detection
  - Rates of post-treatment HPV/precancer recurrence
  - Rates of appropriate referrals
- ***Information to inform future implementation and scale-up***
  - Rates of uptake of intervention and reductions in attrition rates
  - Costs, acceptability, and implementation fidelity

‘CASCADE’ Clinical Trials Network: design outline of a potential clinical trial

Clinics offering cervical cancer screening and treatment services to women with HIV

Clinic-level Cluster Randomization

Same-visit ablation of HPV positives (except visible cancers) without intermediate biopsy

Same-visit or deferred-visit ablation after triage with molecular biomarkers or visual approaches

Follow-up after 12 and 24-months

Follow-up after 12 and 24-months

Outcomes

- Post-treatment HPV/ precancer recurrence rates
- Reduction in attrition through cascade
- Harms/risks of treatment
- Costs and acceptability

The 'CASCADE' Clinical Trials Network will seek to fill a gap in the spectrum of NCI-supported clinical and translational research on cervical cancer prevention

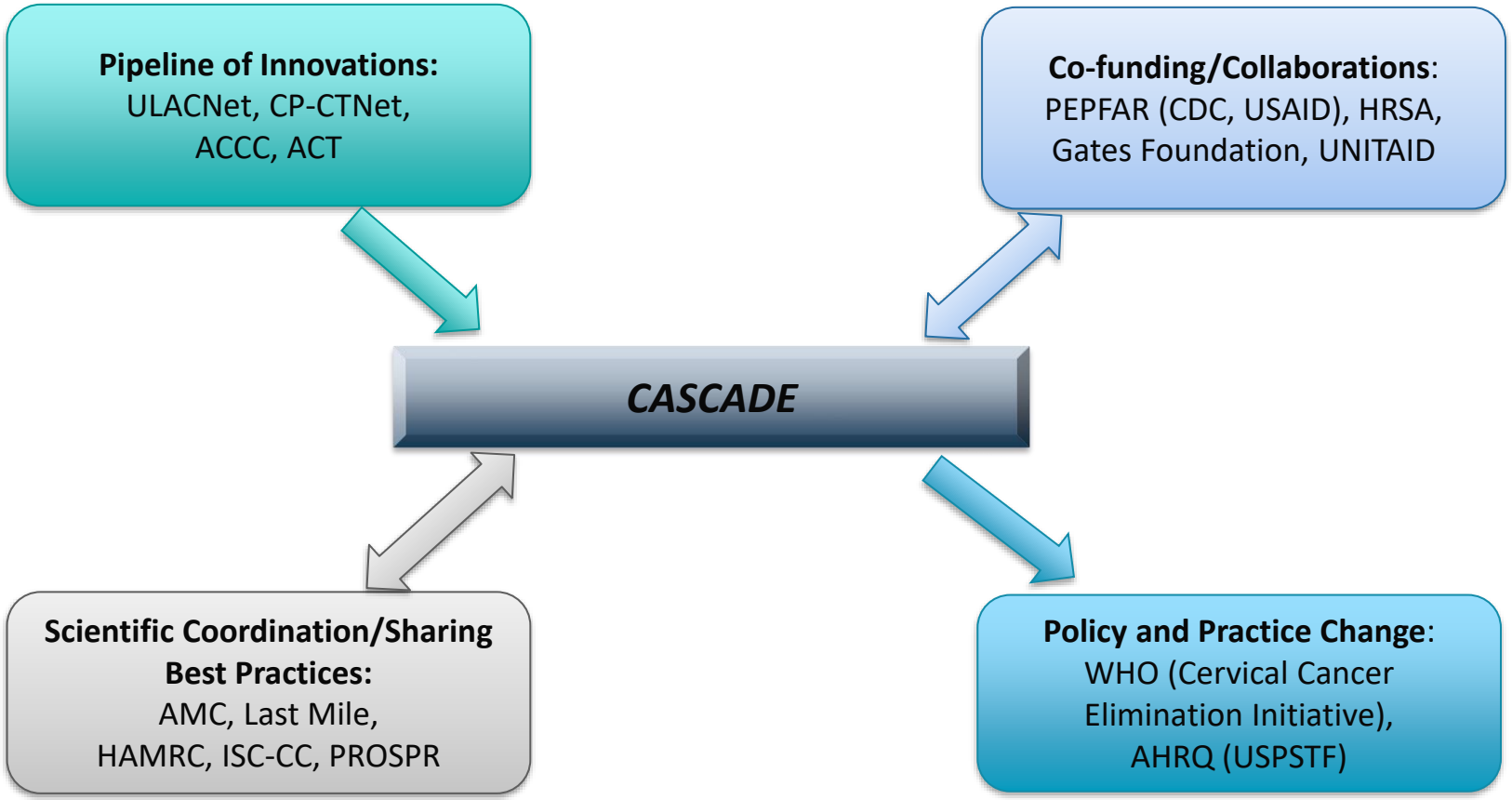
Blue: not exclusively HIV focused
Red: primarily HIV-focused

	T0 & T1	T2	T2	T3 & T4
	Pre-Clinical Development	Phase 1/2/3 Clinical Trials	Phase 3/Phase 4 Clinical Trials	Dissemination & Implementation
	Translation to Humans	Translation to Patients		Translation to Practice
Licensed HPV vaccines: dosing/uptake		CP-CTNet, ULACNet	HPV-1DT	ISC3
Novel HPV vaccines	PREVENT	CP-CTNet		
Licensed HPV tests: self-sampling			Last Mile, ***CASCADE***	PROSPR
Novel HPV molecular biomarkers	EDRN, ACT	ACCC, ACT, ULACNet	***CASCADE***	
Novel precancer diagnostic & imaging	EDRN, ACT	ACCC, ACT	***CASCADE***	
Novel ablative/excisional treatments		ACT	***CASCADE***	
HPV therapeutic vaccines	PREVENT	CP-CTNet, ULACNet, AMC		
Topical precancer therapeutics	PREVENT	CP-CTNet, ULACNet, AMC		
Management of invasive cancers		NCTN, NCORP, AMC	NCTN, NCORP, AMC	

ACCC: Cancer Moonshot 'Accelerating Cervical Cancer Control' initiative
ACT: Affordable Cancer Technologies Program
AMC: AIDS Malignancy Consortium
CP-CTNet: Cancer Prevention Clinical Trials Network
EDRN: Early Detection Research Network
HPV-1DT: NCI HPV vaccine One vs. Two dose trial in Costa Rica
ISC3: Implementation Science Centers for Cancer Control
Last Mile: NCI Cervical Cancer 'Last Mile' Initiative
NCORP: NCI Community Oncology Research Program
NCTN: NCI National Clinical Trials Network
PREVENT: Chemoprevention Agent Preclinical Development Program
PROSPR: Population-based Research to Optimize the Screening Process
ULACNet: US Latin American Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network

(Note: above listing is for illustrative purposes only, and is not an exhaustive compilation of all NCI programs)

‘CASCADE’ Clinical Trials Network: External Organizational Linkages



AHRQ: Agency for Healthcare Research and Quality
CDC: Centers for Disease Control and Prevention
HRSA: Health Resources and Services Administration
PEPFAR: President’s Emergency Plan for AIDS Relief
USAID: US Agency for International Development
USPSTF: United States Preventive Services Task Force
WHO: World Health Organization

ACCC: Cancer Moonshot ‘*Accelerating Cervical Cancer Control*’ initiative
ACT: Affordable Cancer Technologies Program
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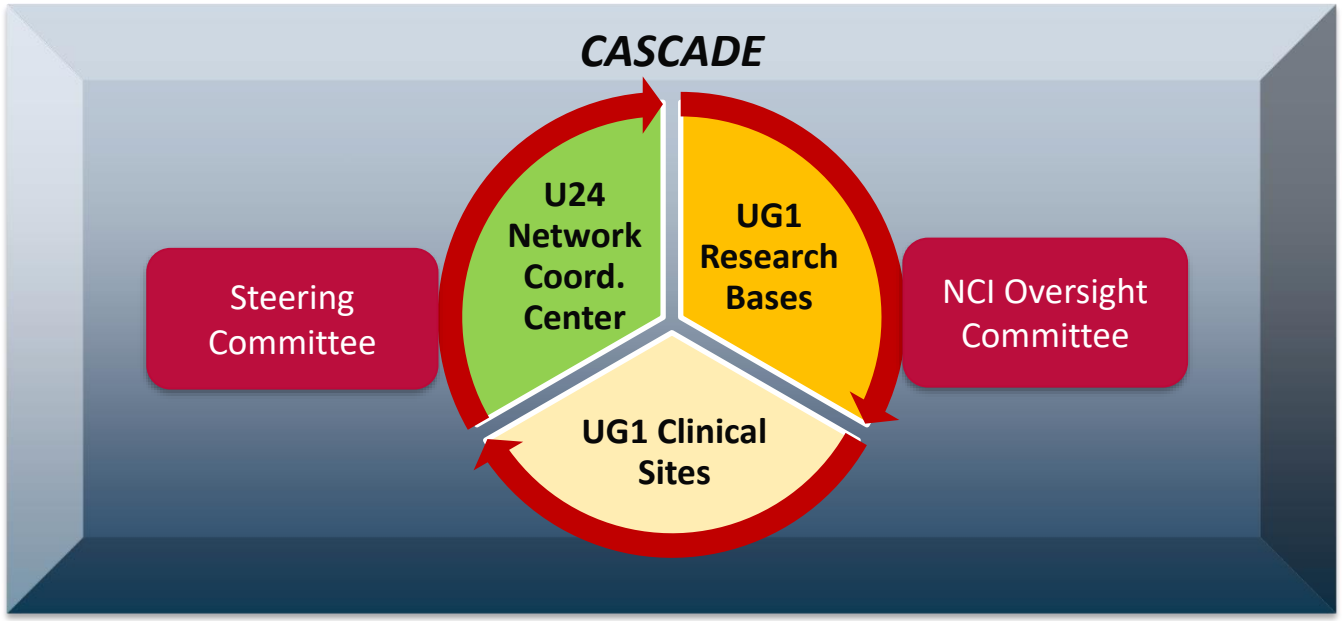
CP-CTNet: Cancer Prevention Clinical Trials Network
ISC-CC: Implementation Science Centers for Cancer Control
Last Mile: NCI Cervical Cancer ‘Last Mile’ Initiative

NCTN: NCI National Clinical Trials Network
NCORP: NCI Community Oncology Research Program
HAMRC: HIV-Associated Malignancy Research Centers
PROSPR: Population-based Research to Optimize the Screening Process
ULACNet: US Latin American Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network

‘CASCADE’ Clinical Trials Network: Proposed Program Organizational Structure



	UG1 Research Bases	*UG1 Clinical Sites*	*U24 Network Coord. Center*
Scientific and statistical leadership for concepts & protocols	***X***		
Ensuring compliance and reporting	***X***		
Training emerging investigators	***X***		
Clinical infrastructures for protocol implementation		*X*	
insights and input on clinical significance and study feasibility		*X*	
Coordinate network activities and concept/protocol review			*X*
Centralized data management			*X*
Independent clinical trial auditing			*X*

‘CASCADE’ Clinical Trials Network: Budget Requested

- Congressionally-mandated NCI HIV/AIDS Funds
- Reviewed and Approved by the NIH Office of AIDS Research (OAR) for Alignment with NIH’s HIV/AIDS Research Priorities

Type of award	Total costs per award/ per yr	No. of awards	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
U24 Network Coord. Center	$1.0 M	1	$1.0 M	$1.0 M	$1.0 M	$1.0 M	$1.0 M	$5M
UG1 Research Bases	$750,000	2-3	$1.5 M	$1.5 M	$1.5 M	$1.5 M	$1.5 M	$7.5M
UG1 Clinical Sites	$300,000	6-8	$2.5 M	$2.5 M	$2.5 M	$2.5 M	$2.5 M	$12.5M
Requested Total Budget per year			**$5 M**	**$5 M**	**$5 M**	**$5 M**	**$5 M**	**$25 M**

‘CASCADE’ Clinical Trials Network: Review by BSA Subcommittee

- ***Eligibility for participation? Existing networks or new partnerships?***
  - Applications will be open to ongoing partnerships but also encourage new/organically-developed partnerships across the range of healthcare delivery settings.
- ***Geographic areas of focus for UG1 sites?***
  - Review criteria will emphasize importance of leveraging existing US investments in clinical care delivery for cervical cancer prevention linked to HIV care, such as PEPFAR-funded programs globally and HRSA and CDC-funded healthcare delivery programs within the US.
  - Review criteria will include emphasis on settings with dual burden of HIV and cervical cancer, and on settings with persistent health disparities.
- ***Programmatic timelines and scope for new and innovative concepts?***
  - Listing of focus areas/topics for potential clinical trials is for illustrative purposes and is not prescriptive or exhaustive.
  - Once network is formed, the organizational structure and concept/protocol development pathways will be flexible to adapt and respond to opportunities and challenges.

‘CASCADE’ Clinical Trials Network: Review by BSA Subcommittee

- ***Approaches for ensuring high-quality data collection in care delivery settings in low-resource areas?***
  - Studies will be nested in ongoing standard-of-clinical care delivery efforts already funded at the clinical sites.
  - Focus will be on ensuring efficiencies in pragmatic trial conduct in clinical care delivery settings (e.g., supporting additional research staff, efforts for targeted outreach/retention, efforts for data quality and data integrity, and clinical quality assurance and monitoring).
- ***Composition of the network and applicability of research findings beyond well-organized healthcare delivery settings to ‘real world’ settings catering to underserved women with HIV?***
  - Application review criteria and funding selections decisions will place special emphasis on clinical sites in fragmented and less-organized care delivery settings to complement settings with established health care programs/delivery systems.
  - At least two of the eight UG1 Clinical Sites will be US sites catering to underserved populations such as those covered by Medicaid, CDC National Breast and Cervical Cancer Early Detection Program (NBCCEDP), HRSA-Ryan White HIV/AIDS Care Program funding, or seen at HRSA-funded Federally-Qualified Health Centers (FQHCs) including Community Health Centers, Migrant Health Centers, Health Care for the Homeless, and Health Centers for Residents of Public Housing.

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