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
**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
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

HPV-mediated Cervical Carcinogenesis in the Context of HIV

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?

Figure ref: Wright & Schiffman, NEJM 2003
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

Cervical Cancer Mortality Rates in the US

Source: Kaiser Family Foundation 2018

Source: NCI SEER Cancer Fact Sheets
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
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

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.

<table>
<thead>
<tr>
<th>T0 &amp; T1</th>
<th>T2</th>
<th>T3 &amp; T4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Clinical Development</strong></td>
<td><strong>Phase 1/2/3 Clinical Trials</strong></td>
<td><strong>Phase 3/Phase 4 Clinical Trials</strong></td>
</tr>
<tr>
<td>Translation to Humans</td>
<td>Translation to Patients</td>
<td>Translation to Practice</td>
</tr>
</tbody>
</table>

**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

**Additional Programs**
- 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: Proposed Program Organizational Structure

#### U24 Network Coord. Center
- NCI Oversight Committee
- Steering Committee

#### UG1 Research Bases
- UG1 Clinical Sites

<table>
<thead>
<tr>
<th>Task</th>
<th>UG1 Research Bases</th>
<th>UG1 Clinical Sites</th>
<th>U24 Network Coord. Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific and statistical leadership for concepts &amp; protocols</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ensuring compliance and reporting</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training emerging investigators</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical infrastructures for protocol implementation</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Insights and input on clinical significance and study feasibility</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Coordinate network activities and concept/protocol review</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Centralized data management</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Independent clinical trial auditing</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
**‘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

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