

Optimizing Prevention and Control of Cervical Cancer in Women Living with HIV

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on “Towards Elimination of Cervical Cancer in the Americas”

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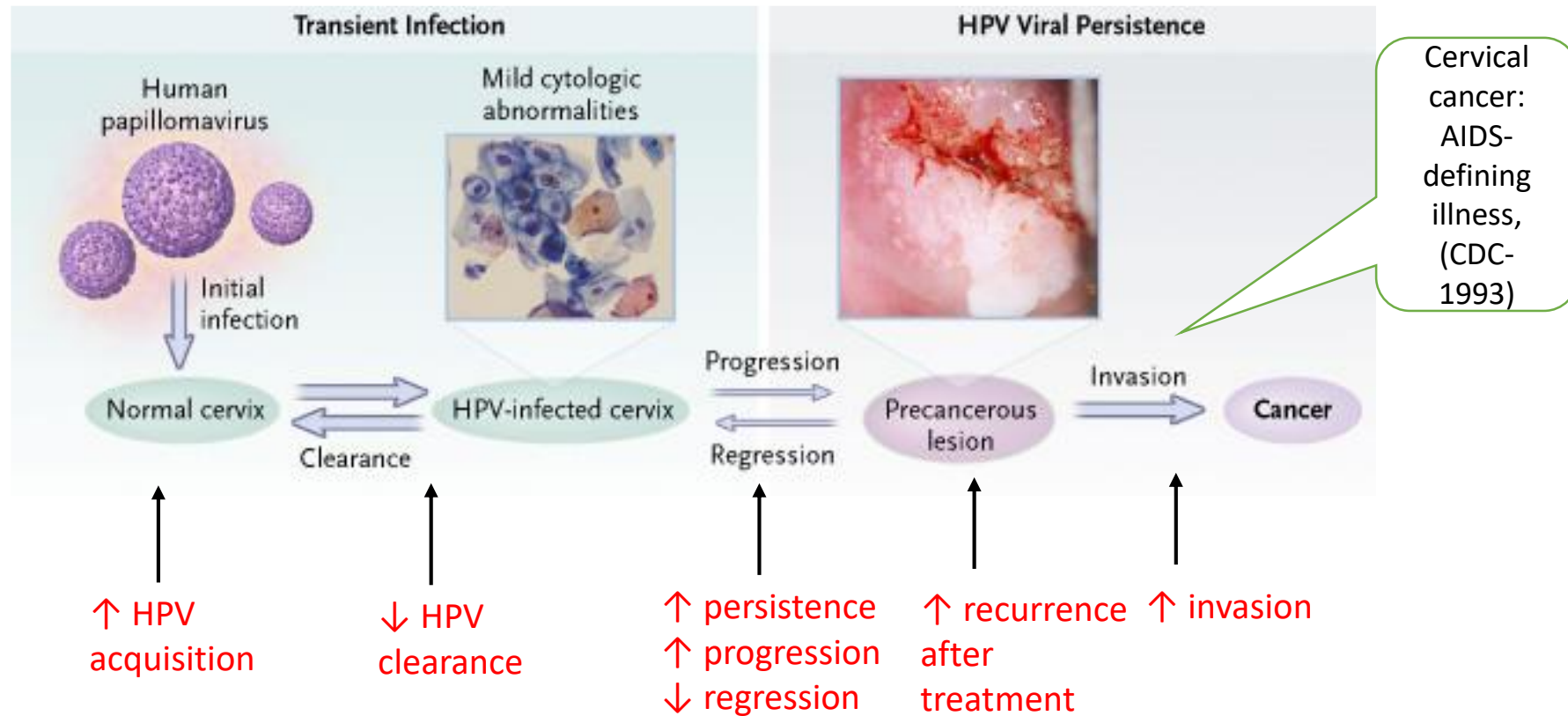
Addressing Cervical Cancer in Women Living with HIV

- **Dual disease burden** accentuated by immunosuppression
- **Unprecedented cervical cancer prevention and treatment intervention opportunities** linked to HIV prevention, care, and treatment programs
- **Models for care delivery** by integration of vertical health initiatives

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HPV-mediated Cervical Carcinogenesis in the context of HIV/AIDS



Postulated Mechanisms for High HPV-disease Burden in HIV+ Women:

- **Loss of Immune Control**
- **Latent Viral Reactivation with Immunosuppression/modulation/reconstitution**
- **Viral-Viral Interactions between HIV and HPV**
- **Correlated high-risk behaviors (low condom use, multiple partners)**

Figure ref:
Wright & Schiffman, NEJM 2003

Dual disease burden of cervical cancer and HIV

- **HIV+ women have a high HPV/cervical cancer burden that is accentuated by immunosuppression**

Prevalent detection 3 to 5 times vs. HIV-uninfected women

- 30-80% HIV+ women have prevalent carcinogenic HPV genotypes
- 10-40% HIV+ women have prevalent cervical precancerous lesions
- Cervical cancer is detected at screening in 1.3-3.7% HIV+ women

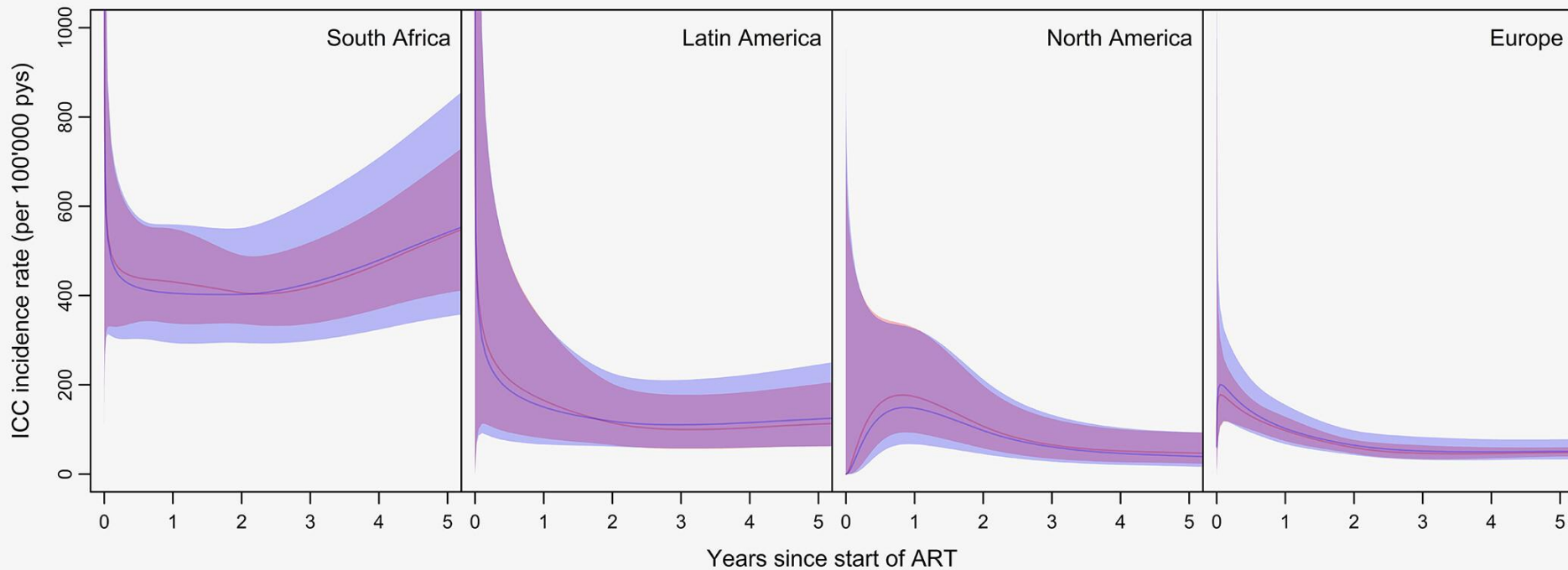
Wide ranges reflective of

- *heterogeneity in age distribution of cohorts*
- *stage of HIV disease and immunosuppression*
- *variable approaches to diagnosis of HPV infection, pre-cancerous lesions, and cervical cancer*

- **Younger age at cancer diagnosis, more aggressive clinical course, less responsiveness to chemoradiation**

Cervical Cancer Risk in HIV+ women: Multicohort Analysis across Four Continents

Rohner et al 2019



Main Findings:

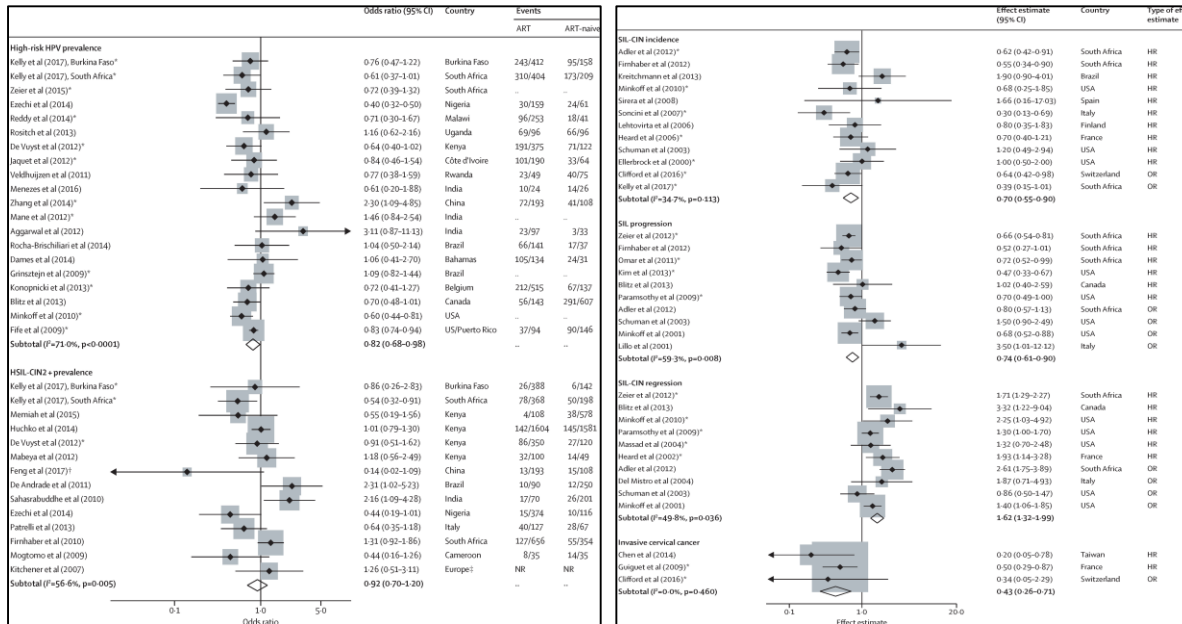
- CxCa incidence notably high among women living with HIV in South Africa and Latin America
- Five years after ART initiation, ICC incidence remained elevated
- Reduced CD4 cell count and older age at ART initiation were associated with increased CxCa risk

Challenges in Interpretation of Findings:

- Limited precision due to low incident cases (<20 in LA & NA)
- Lack of/limited information on duration of HIV infection, continuation and duration of antiretroviral therapy, HPV status/types, cervical cancer screening history, smoking status, hysterectomy status, cancer stage

Association of Antiretroviral Therapy (ART) with HPV/CIN/Cervical Cancer Risk in HIV+ women: Global Meta-Analysis

Kelly et al 2017



Main Findings:

Globally, HIV+ women on ART had

- Decreased prevalence of HPV and cervical precancerous lesions
- Decreased incidence and progression rates of cervical precancerous lesions
- Increased regression of cervical precancerous lesions
- Decreased risk of invasive cervical cancer

Key Interpretations:

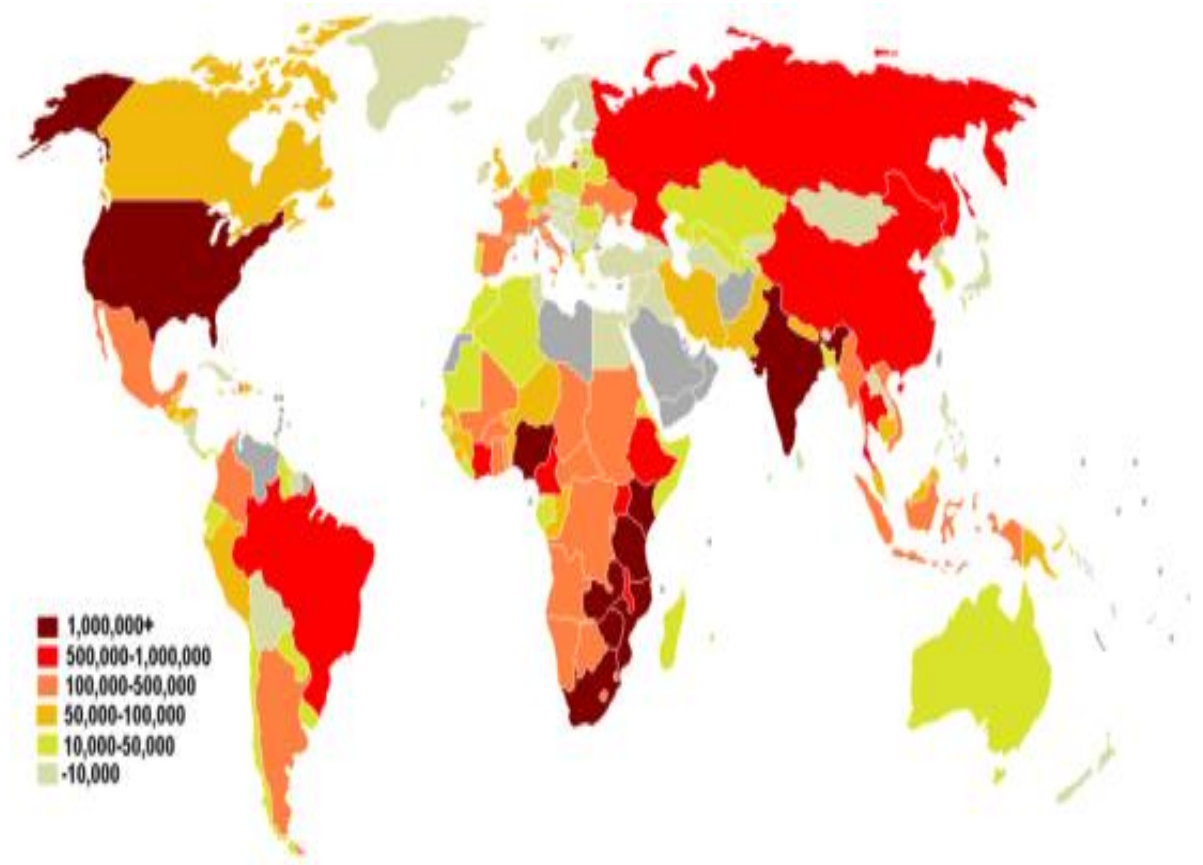
- Studies adjusting for nadir/current CD4+ and time-varying effects of ART were more likely to show a protective effect of ART
- Cross-sectional studies from Latin America and Asia (vs. other regions) did not show lower risk of precancer with ART, likely reflecting older (lower) CD4+ thresholds for ART initiation.
- Early initiation of ART, virologic control, and sustained adherence likely important for immune recovery and reducing HPV-related morbidity

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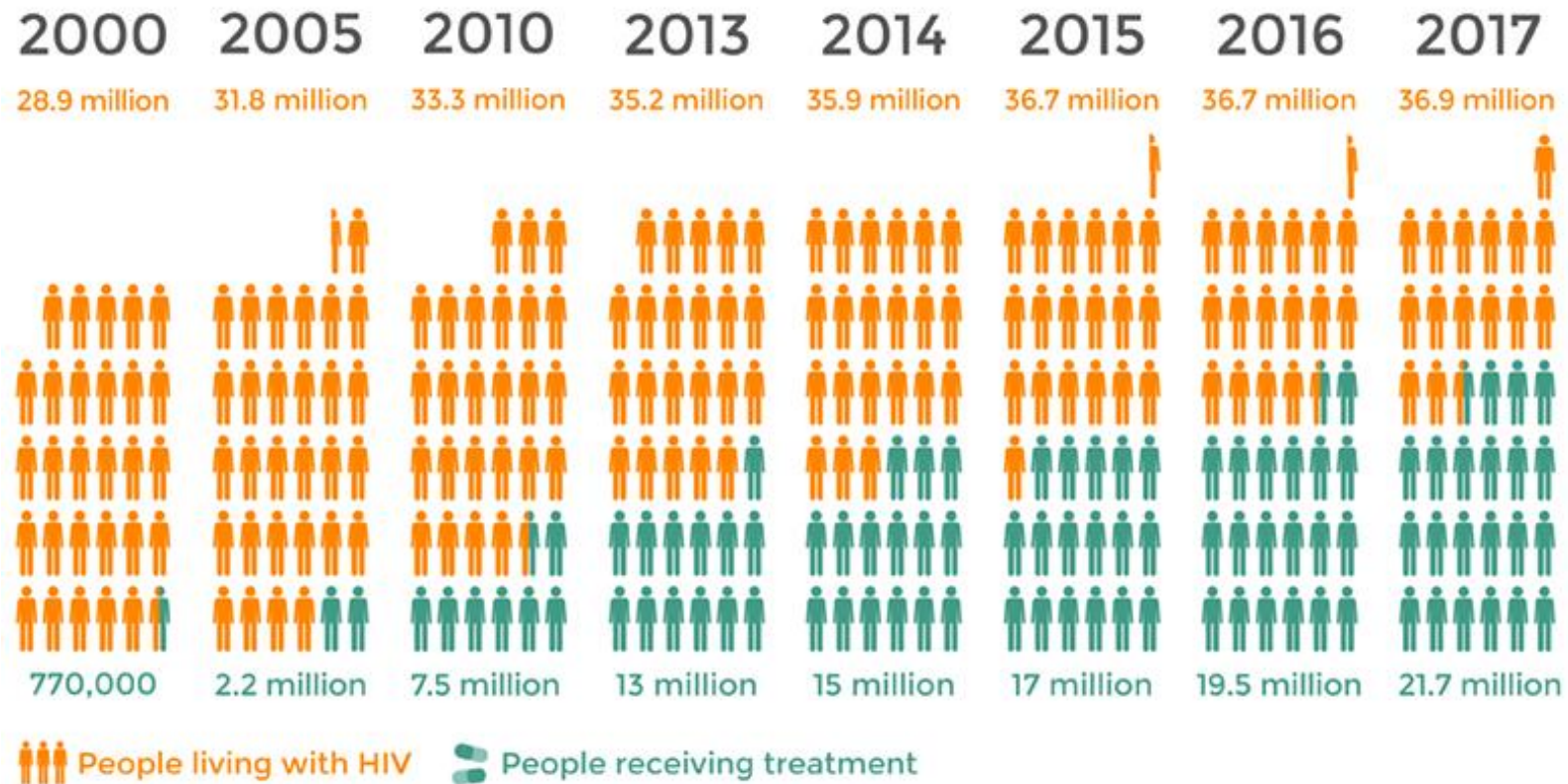
Global HIV/AIDS Burden

- >36 million HIV+ globally
- ~50% women
- >90% in low & middle-income countries



Ref: UNAIDS, 2017

Global Trends in Number of People Living with HIV and Accessing Antiretroviral Therapy



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

Why Should We Let HIV+ Women Die Due to Cervical Cancer after Extending their Lives with Antiretroviral Therapy?

Key Funded Initiatives on Cervical Cancer Prevention and Control in the past two decades

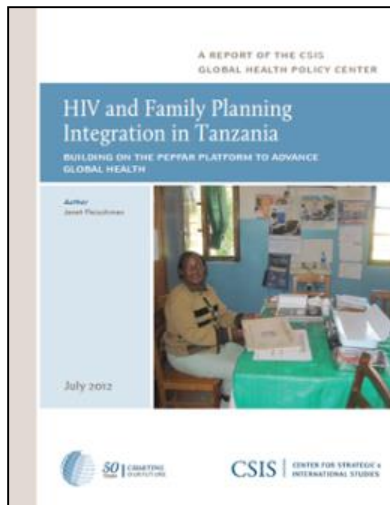
- **Gates Foundation/ACCP** (IARC, JHPIEGO, Engender Health, PAHO, PATH) – develop and evaluate low-cost cervical cancer prevention methods in Africa, Asia, Latin America (1999)
- **WHO** – VIA-cryotherapy demonstration projects in 6 African nations (2005)
- **PEPFAR** – Implementing screen-and-treat cervical cancer prevention for HIV+ women in targeted countries: PEPFAR-CxCa “1.0” (2005), Pink Ribbon Red Ribbon (2011), and PEPFAR-CxCa “2.0” (2018)
- **Global Cervical Cancer Elimination Initiative** (WHO) (2018)
- **Other Multilateral, Bilateral, & National initiatives and private philanthropy-supported initiatives**



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Horizontal Integration of other Vertical Disease Control Programs with HIV/AIDS care and prevention programs

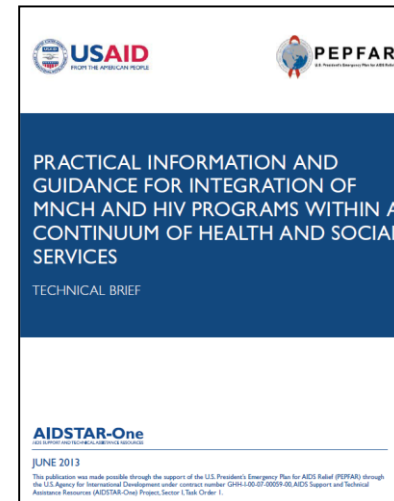
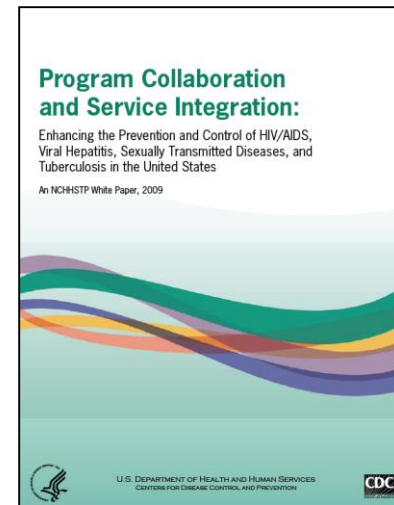


- Family Planning and Reproductive Health

- Tuberculosis

- STD/Hepatitis

- Maternal, neonatal and child health services



Type of integration of HIV/AIDS care and cervical cancer screening and treatment services

Sigfrid et al 2017

Integration model	CaCx Services	CaCx methods	Setting	Author and Country
Within clinic integration using internal staff	CaCx screening	VIA	HIV clinics	• Morgan 2014 [Guyana]
		PAP	HIV / ID clinics	• Sirivongrangsorn 2007* [Thailand]
			GUM clinic	• Ibrahim 2013 [England]
	CaCx 'screen and treat' minor lesions	VIA + Cryotherapy	HIV clinics	• Ekong 2013 [Uganda]
			Family planning clinics	• Moon 2012 [Mozambique]
			Mobile HIV clinics	• Mulenga 2012 [Zambia]
	CaCx 'screen and treat' larger lesions	VIA + Cryotherapy + LEEP	HIV clinics and RCH clinics	• Anderson 2015 [Côte d'Ivoire, Guyana, and Tanzania] • Martin 2014 [Guyana]^
			HIV clinics	• Huchko 2011 [Kenya]
Coordination between co-located clinics/specialists	CaCx screening	VIA	HIV clinic and RCH clinic	• Odafe 2013 [Nigeria]
			ART and blood giving clinics	• Horo 2012 [Côte d'Ivoire]^*
		PAP+ colposcopy	HIV/ID clinic	• Fink 2012 [Argentina]
	CaCx 'screen and treat' minor lesions	VIA + Cryotherapy	Cervical Cancer Prevention Program clinics in HIV clinics	• Mwanahamuntu 2013 [Zambia] *** • Ramogola-Masire 2012 [Botswana]
			Public health clinics	• Parham 2010 [Zambia]^***
	CaCx 'screen and treat' larger lesions			
Complex program of integration and coordination	CaCx screening	PAP	HIV / ID clinics	• McCree-Hale 2011 [Tanzania]
	CaCx 'screen and treat' minor lesions	VIA + Cryotherapy	Family planning, and child and maternal health clinics	• Khozaim 2014 (Kenya) • Plotkin 2014 [Tanzania]
	CaCx 'screen and treat' larger lesions	VIA + Cryotherapy + LEEP	HIV clinics and/or Public health clinics	• Mungo 2013 [Kenya] • Pfaendler [Zambia] • Shiferaw.2016 [Ethiopia]^

Barriers:

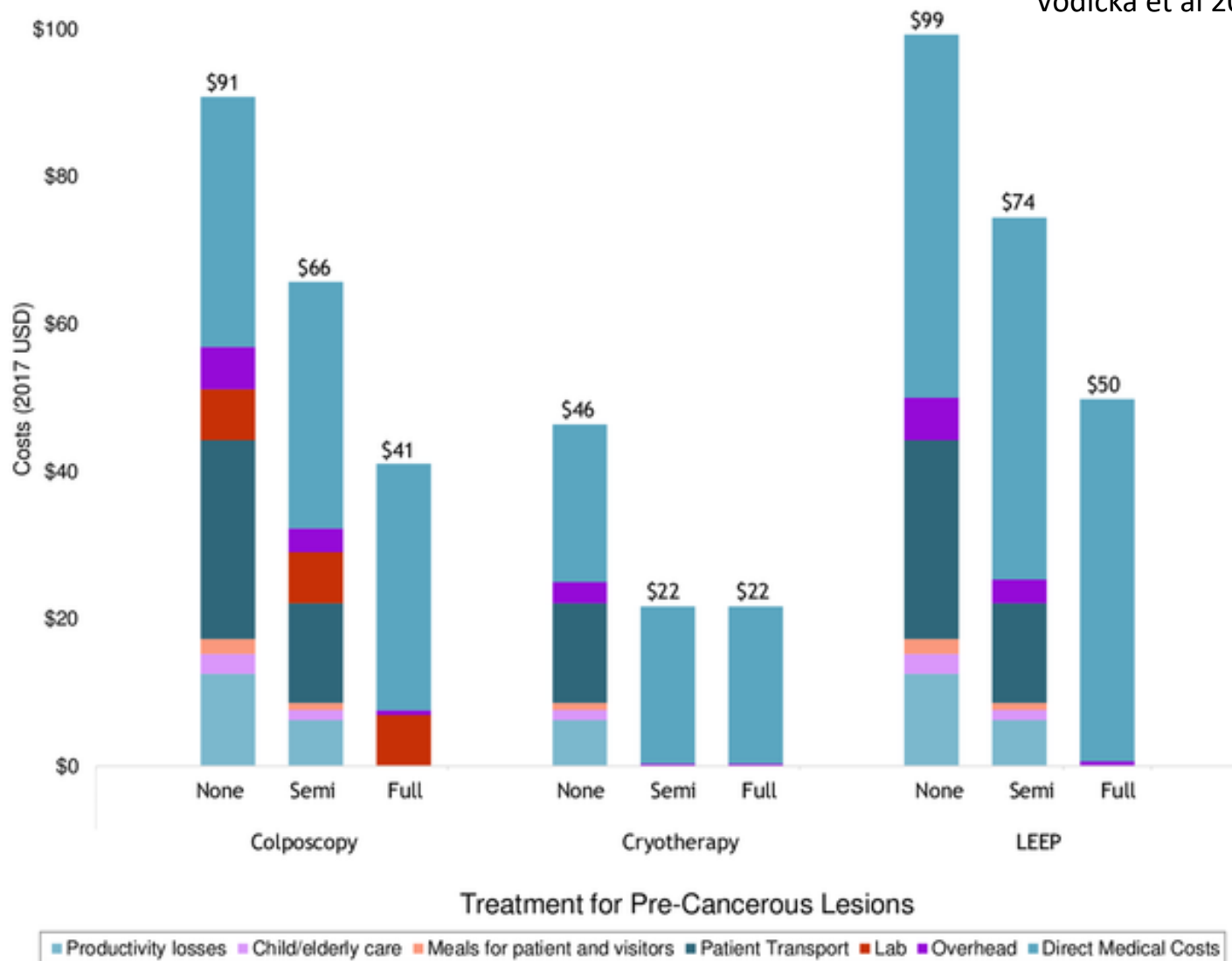
- loss to follow up for further treatment
- limited human-resources
- logistical and chain management support

Facilitators:

- Using visual screening methods, digital technology
- Community engagement
- Comprehensive staff training and supervision

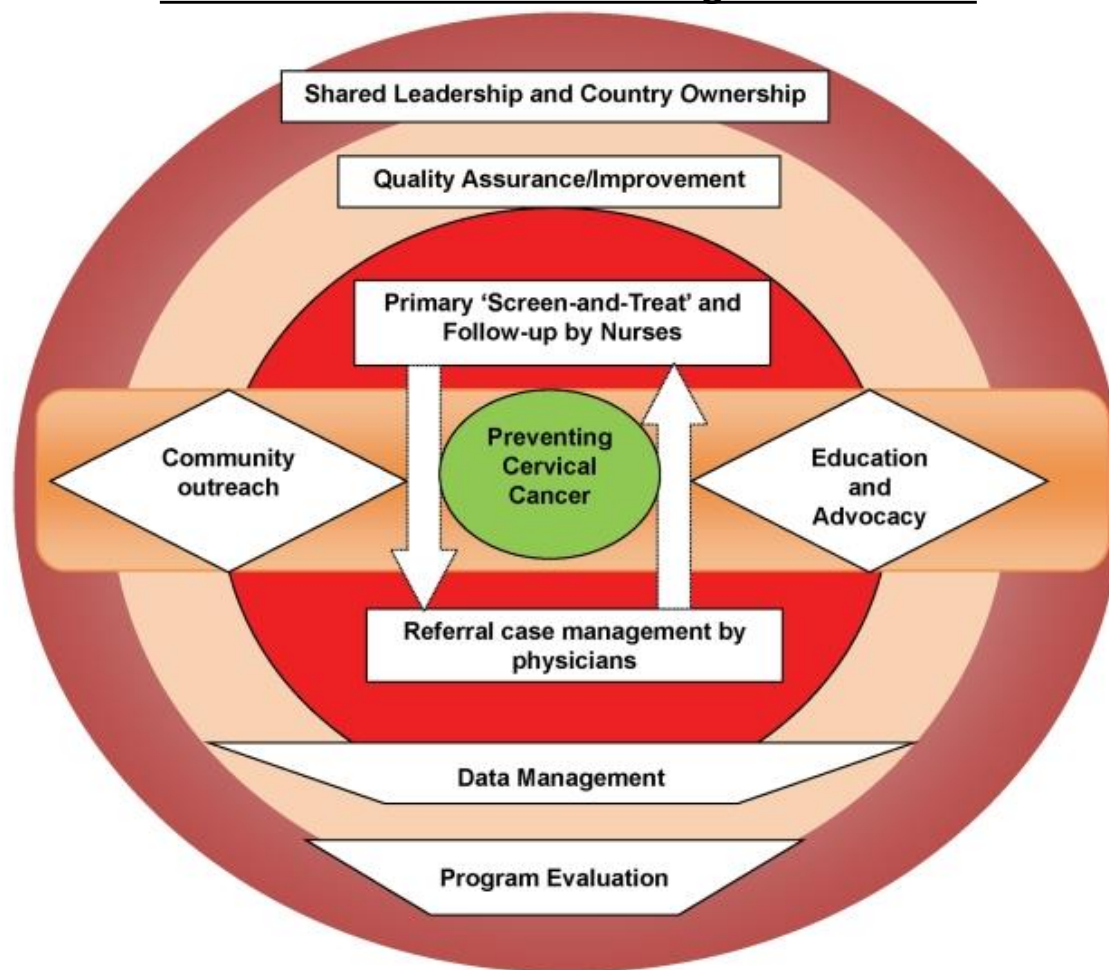
Comparison of integrated vs. non-integrated costs of treatment for pre-cancerous lesions by care component (Kenya)

Vodicka et al 2019



Zambian Model of Cervical Cancer Prevention Interventions Linked to HIV/AIDS Care Programs

Cervical Cancer Prevention Program in Zambia



Mwanahamuntu et al 2011

Critical Importance of Training and Quality Assurance in Implementing 'Screen-and-Treat' Programs linked to HIV/AIDS care



Images Courtesy: Drs. Groesbeck Parham, Mulindi Mwanahamuntu, Sharon Kapambwe
Cervical Cancer Prevention Program in Zambia

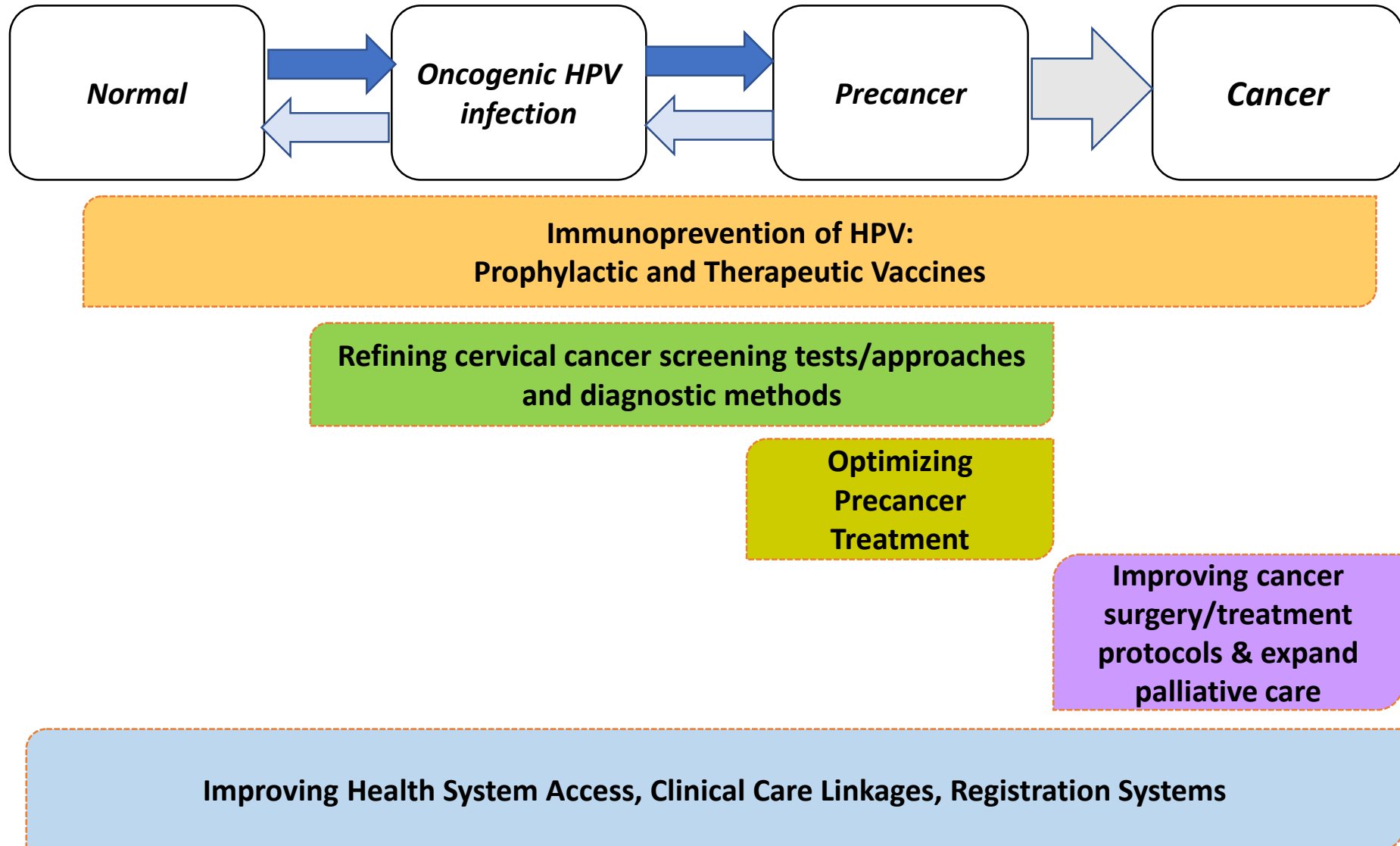
Lessons learned: Integrating Cervical Cancer Prevention and Control Services with HIV/AIDS Care in Limited Resource Settings

- To launch and sustain cervical cancer prevention programs, it is smart to piggyback on HIV/AIDS prevention and care implementation programs
- Task shifting to nurses and clinician support by telemedicine facilitates scale-up
- Community mobilization and peer-to-peer support systems vital for broader community-level acceptance
- Build and enhance capacity for precancer & cancer treatment and management (“don’t screen if you can’t treat”)
- Support early initiation and adherence to antiretroviral therapy for immune recovery and reducing HPV-related morbidity

Bottom-line

- **Lives can be saved with sustained and innovative efforts at modest cost with ‘screen-and-treat’ programs**
- **Improving access and reaching and serving the ‘last mile’ is key**
- **HPV vaccination needed to eventually “turn off the tap”**

Continuing Efforts for Improving and Optimizing Cervical Cancer Prevention & Control Interventions in HIV+ Women



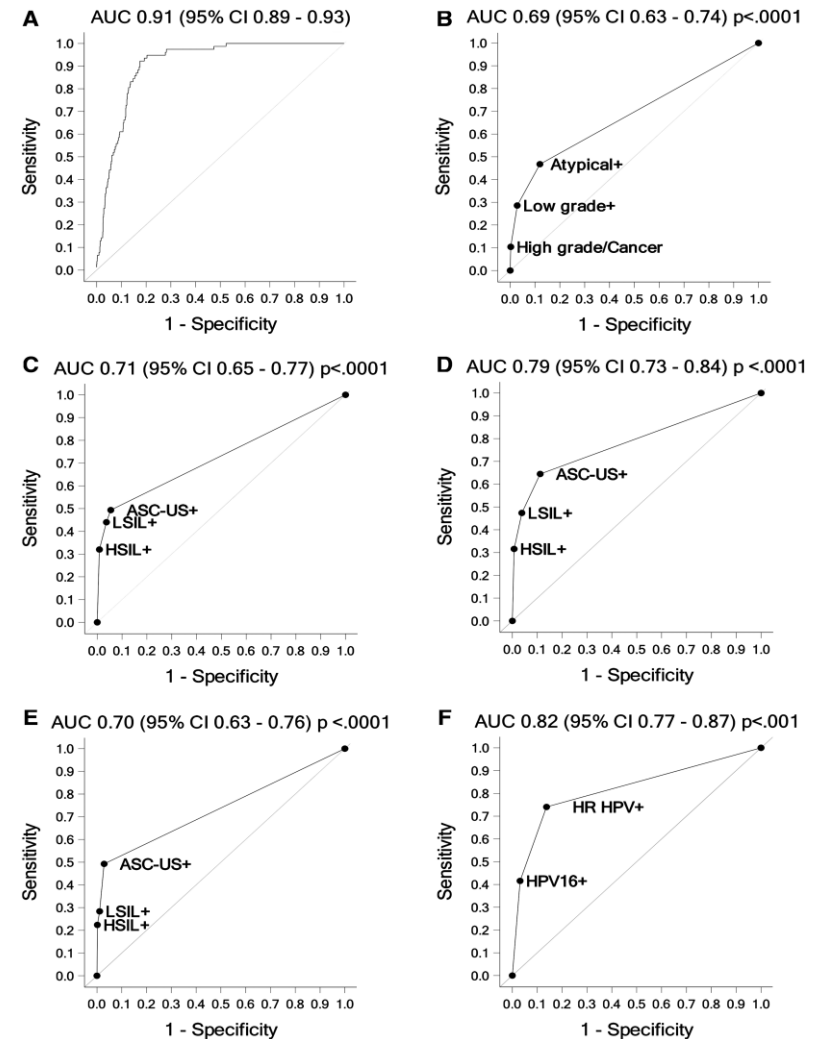
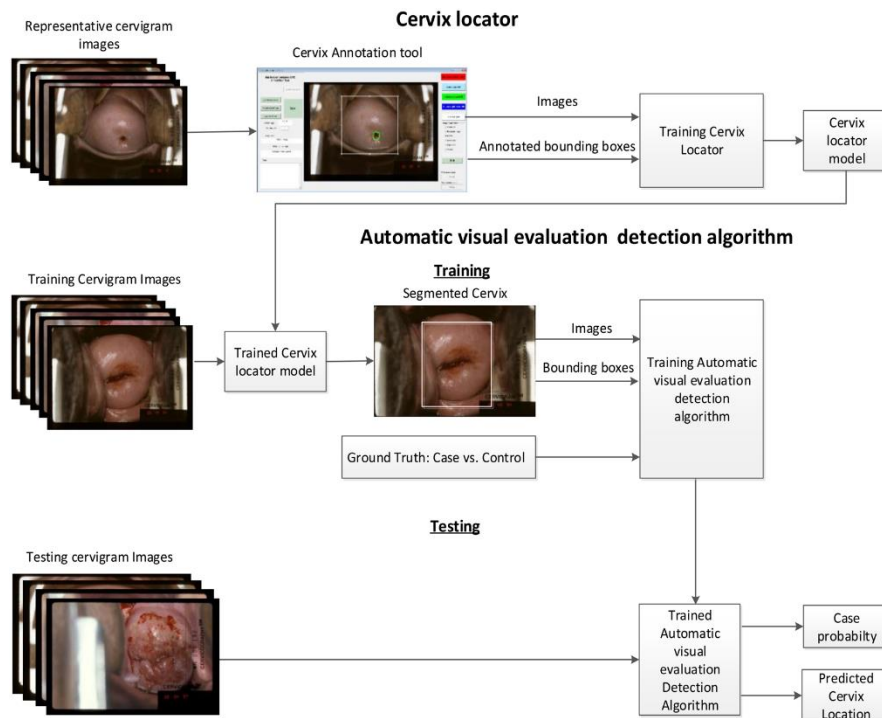
Continuing Efforts for Optimizing HPV immunoprevention for HIV+ women

- Evaluating optimal **timing, schedule, duration of protection**, and **dosing** of HPV vaccines, especially for perinatally-infected HIV+ adolescents
- Evaluating role of prophylactic HPV vaccines in
 - preventing **reactivation of latent** HPV
 - preventing **recurrence** of HPV infections in the adjunctive post-precancer treatment setting
- Understanding minimal vaccine-induced serologic titers that **predict efficacy** in the context of HIV-induced immunosuppression
- Evaluating safety and efficacy of **therapeutic HPV vaccines** in the context of reduced cellular immune response due to HIV
- Evaluating novel vaccines that seek to provide a **combined preventive and therapeutic benefit**

Continuing Efforts for Optimizing Screening and Triage approaches for HIV+ women

- Evaluating **primary HPV screening** to replace cytology/visual screening
 - **Self-collection of samples** for optimizing access
 - Balancing **sensitivity** and **specificity**, given high HPV prevalent detection in HIV+ women
- Evaluating **improved triage approaches** for HPV positive test results
 - **Visual** (e.g., automated visual evaluation, portable colposcope, high-resolution microendoscope)
 - **Microscopic** (e.g., reflex cytology, p16/Ki67 immunocytochemistry)
 - **Molecular** (e.g., HPV E6/E7 oncoprotein testing, HPV mRNA, HPV methylation)

Proof-of-Principle study of 'Automated Visual Evaluation' (AVE) via artificial intelligence/machine learning on cervical images



Hu L et al 2019

Continuing Efforts for Optimizing Approaches for Cervical Precancer Treatment in HIV+ women

- Evaluating alternatives to gas-based cryotherapy
- Non-surgical approaches as alternatives to ablative/excisional methods for treatment
 - **Locally applied agents** to induce regression of precancerous disease and clear oncogenic HPV
 - **Repurposing of drugs** for cervical precancer treatment indications
 - Evaluating optimal **topical delivery vehicles/approaches**
- Evaluating **combinations of agents**, as adjuncts/'neo-adjuvants' to ablative/excisional methods, as well as combinations of **topical agents with therapeutic HPV vaccines** to enhance efficacy

Thank you for your attention!

Questions/Comments/Feedback: vikrant.sahasrabuddhe@nih.gov



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