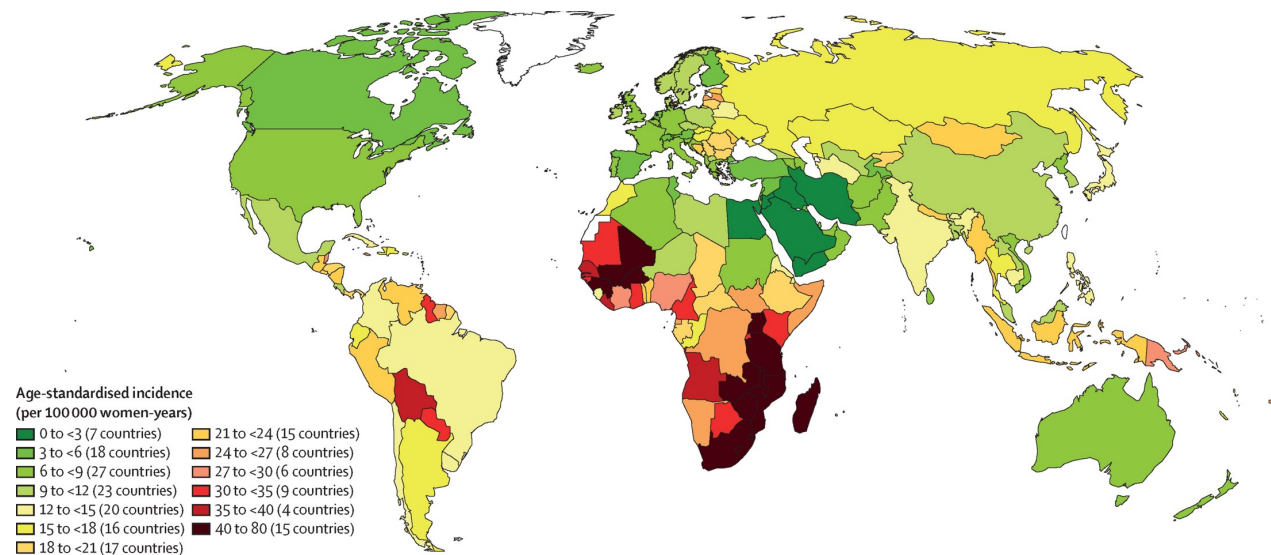# Performance and effectiveness of screening-triage strategies for cervical precancer among women living with HIV

Helen Kelly
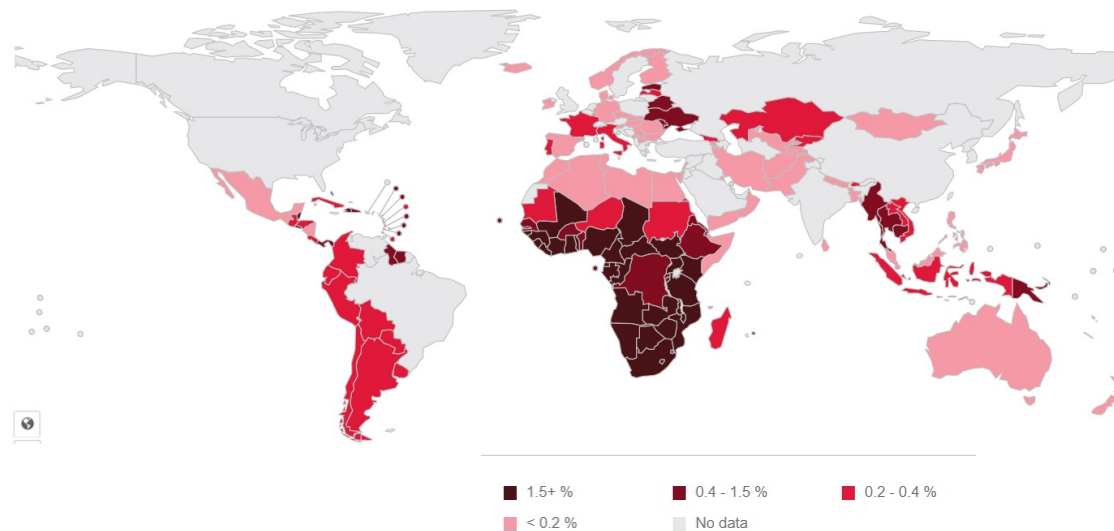
National Cancer Institute, USA &

London School of Hygiene and Tropical Medicine, United Kingdom

Invasive Cervical Cancer incidence

Age-standardised incidence
(per 100 000 women-years)

- 0 to <3 (7 countries)
- 3 to <6 (18 countries)
- 6 to <9 (27 countries)
- 9 to <12 (23 countries)
- 12 to <15 (20 countries)
- 15 to <18 (16 countries)
- 18 to <21 (17 countries)
- 21 to <24 (15 countries)
- 24 to <27 (8 countries)
- 27 to <30 (6 countries)
- 30 to <35 (9 countries)
- 35 to <40 (4 countries)
- 40 to 80 (15 countries)

HIV prevalence

ICC=AIDS defining cancer

15.6 million WLHIV globally
12.5 million WLHIV in SSA

- 1.5+ %
- 0.4 - 1.5 %
- 0.2 - 0.4 %
- < 0.2 %
- No data

GLOBOCAN 2018 ; UNAIDS 2018
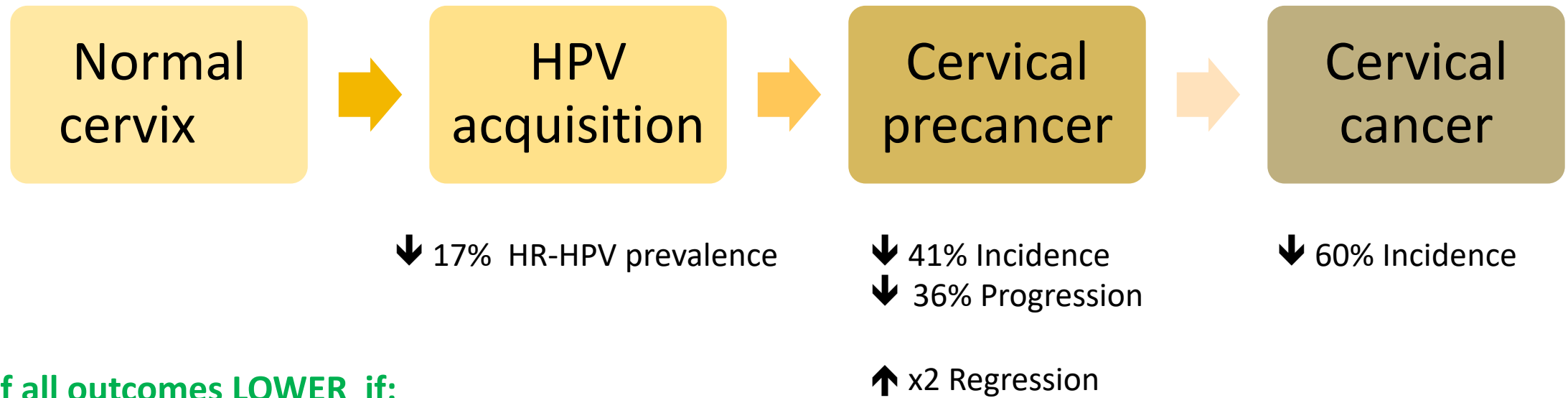
Associations HPV, HIV and Cervical Cancer

- HPV is a risk factor for **HIV acquisition** (x2) [1]

- HIV ↑ **HPV incidence** (x2) and ↓ HPV clearance [1]

- ↑ multiple HR infection & broader range [2]

- HIV ↑ **cervical cancer** (x6) [3]

- Effect ART complex
- Increasing **longevity** on ART *vs.* increasing **cumulative incidence** => **NEED**
- Population attending specialist services => **OPPORTUNITY**

[1]Looker *JIAS* 2018, 21:e25110 ; [2]Clifford, *AIDS*, 2006; [3]Stelzle, Lancet Glob Health 2021

Antiretroviral therapy and cervical HPV & ICC

| Normal cervix | → | HPV acquisition | → | Cervical precancer | → | Cervical cancer |

↓ 17% HR-HPV prevalence

↓ 41% Incidence
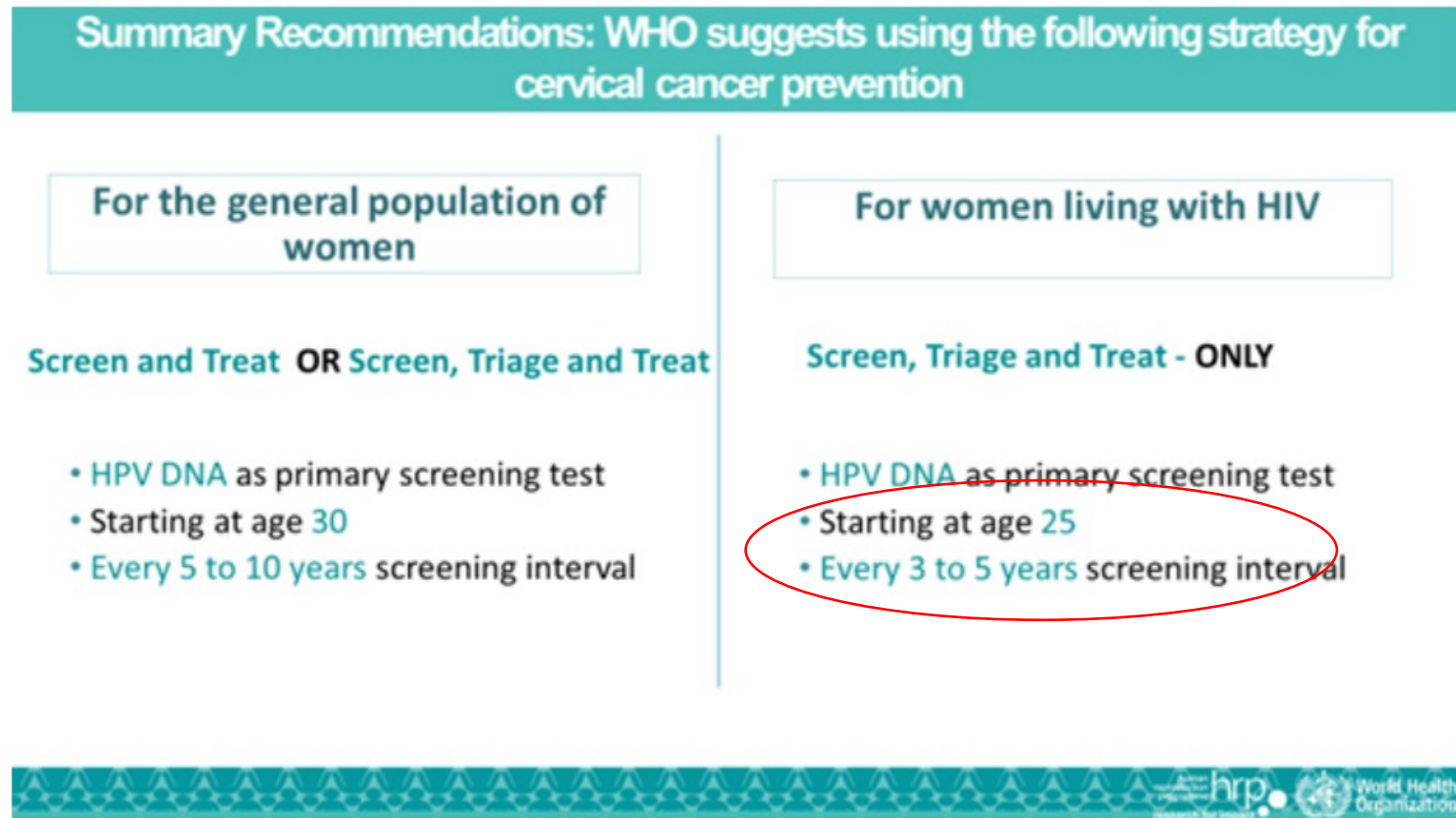↓ 36% Progression

↑ x2 Regression

↓ 60% Incidence

RISK of all outcomes LOWER if:

– **Started early (higher nadir CD4)**

– **Prolonged ART duration, good adherence & effective treatment (sustained viral suppression and increasing CD4)**

Universal ART (UNAIDS 95-95-95) era:

Is risk of cervical precancer and ICC among WLHIV = risk among HIV negative women?

WHO recommendations for screening WLHIV

Summary Recommendations: WHO suggests using the following strategy for cervical cancer prevention

For the general population of women

Screen and Treat OR Screen, Triage and Treat

- HPV DNA as primary screening test
- Starting at age 30
- Every 5 to 10 years screening interval

For women living with HIV

Screen, Triage and Treat - ONLY

- HPV DNA as primary screening test
- Starting at age 25
- Every 3 to 5 years screening interval

WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition. Geneva: World Health Organization; 2021

Diagnostic accuracy of screening-triage strategies

Primary objective

To evaluate the **diagnostic accuracy** of screening and screening-triage strategies for **CIN2+/CIN3+** among **women living with HIV (WLHIV)**

Methods

Systematic review and meta-analysis

Results

35 studies, N=**17,744 WLHIV**

VIA = 14 studies
Cytology = 20 studies
HPV-DNA = 25 studies

	N (%)
Study design	
Cross-sectional	27 (77%)
Prospective cohort	6 (17%)
Randomised controlled trial	2 (6%)
Region	
Sub-Saharan Africa	19 (54%)
Asia	8 (23%)
Latin America	2 (6%)
North America	3 (9%)
Europe	3 (9%)
Enrolment period	
Pre-combination ART (pre-1996)	3 (9%)
Early ART (1996-2008)	8 (23%)
Recent ART (2009-2015)	17 (49%)
Universal ART (post-2015)	5 (14%)
Not reported	2 (6%)

Median CD4+ count (range)	271 – 592 cells/µl
Taking ART, %	71%
Median Age (range)	30 - 46 years
HR-HPV pooled prevalence, %	47%
CIN2+ pooled prevalence, % (IQR)	14%
CIN3+ pooled prevalence, % (IQR)	9%

Diagnostic accuracy of VIA for CIN2+/CIN3+

- **14 studies** in 7,434 WLHIV

- VIA abnormal ranged from 6% to 56%

- **Variable sensitivity (44 to 78%) & specificity (47 to 97%)**

StudyId	Country	Biopsy		Sensitivity (95% CI)		Specificity (95% CI)
Chibwesha, 2016	Zambia	All women		0.632 (0.384, 0.837)		0.905 (0.852, 0.944)
Chung, 2013	Kenya	All women		0.702 (0.551, 0.827)		0.626 (0.578, 0.673)
Mabeya, 2012	Kenya	All women		0.846 (0.651, 0.956)		0.508 (0.417, 0.599)
Kelly, 2021 (SA)	South Africa	Colpo-directed + random (screen+)		0.538 (0.395, 0.678)		0.744 (0.705, 0.781)
Kelly, 2021 (BF)	Burkina Faso	Colpo-directed + random (screen+)		0.692 (0.386, 0.909)		0.804 (0.768, 0.836)
Boddu, 2021	India	Colpo-directed + random (screen+)		0.778 (0.400, 0.972)		0.723 (0.651, 0.788)
Kuhn, 2010	South Africa	Colpo-directed + ECC (all women)		0.583 (0.277, 0.848)		0.703 (0.648, 0.754)
Firnhaber, 2012	South Africa	Colpo-directed (screen+)		0.686 (0.587, 0.775)		0.623 (0.594, 0.652)
Ndizeye, 2019	Burundi	Colpo-directed (all women)		0.750 (0.428, 0.945)		0.957 (0.938, 0.971)
Joshi, 2013	India	Colpo-directed (all women)		0.821 (0.665, 0.925)		0.874 (0.853, 0.893)
Sahasrabuddhe, 2012	India	Colpo-directed (all women)		1.000 (0.735, 1.000)		0.782 (0.728, 0.829)

Sensitivity: 0 .25 .5 .75 1
Specificity: 0 .25 .5 .75 1

Diagnostic accuracy of VIA for CIN2+/CIN3+

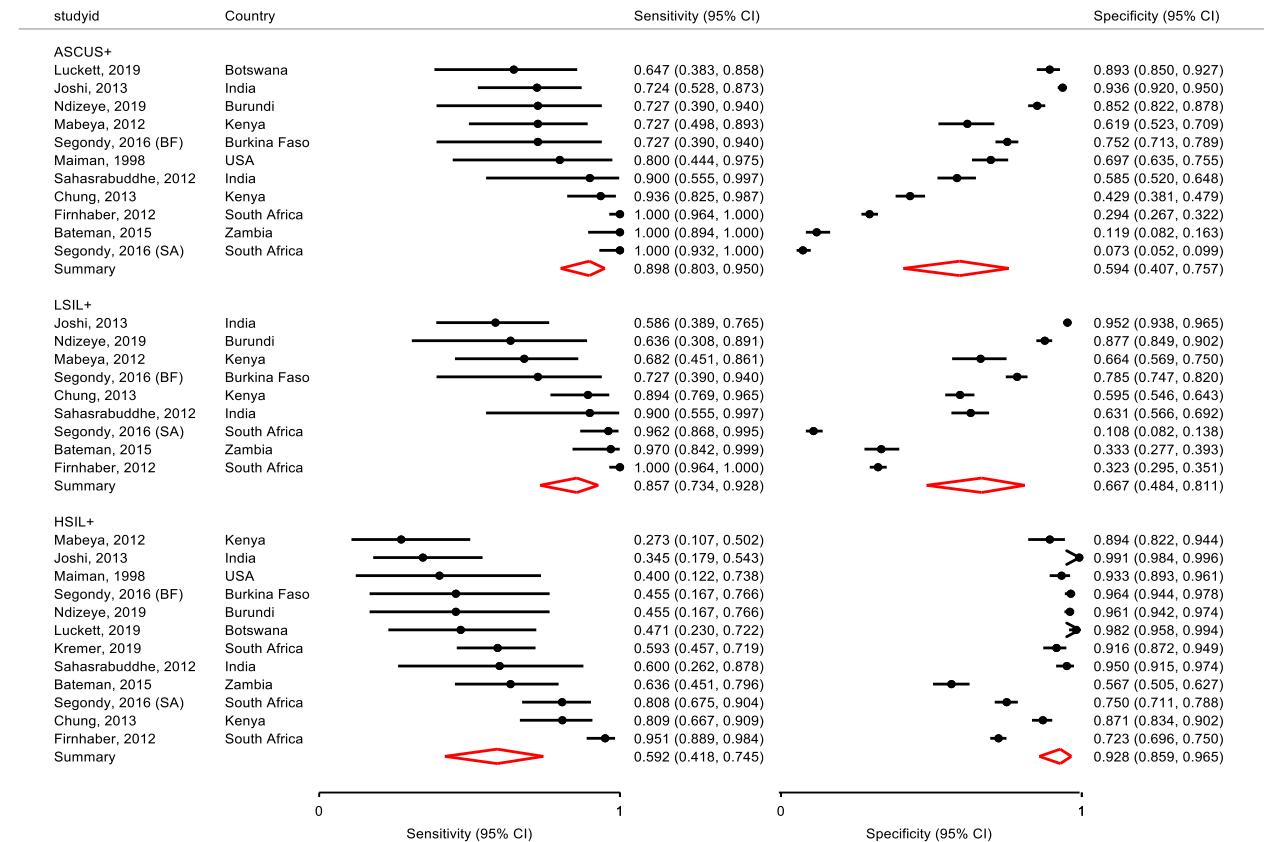Biopsy indication + histological verification of disease :

1. all women underwent colposcopy ➔ colposcopy directed biopsy and random biopsy of colposcopy normal women.
2. screen-positive women (at minimum HR-HPV) ➔ biopsy
3. VIA+ ➔ colposcopy abnormal women ➔ biopsy

Sensitivity lower in studies with low risk of disease misclassification (pooled sensitivity: 56% vs. 84%)

	Sensitivity for CIN2+ (%, 95%CI)	I^2	Specificity for <CIN2 (%, 95%CI)	I^2
Screen approach				
VIA – naked eye[a]				
Studies with ≥95% histology verification[44, 61, 62, 67, 70]	56.0 (45.4-66.1)	64.9%	73.8 (59.8-84.2)	94.4%
Studies with 50-95% histology verification[36, 44, 59, 64]	65.1 (52.1-76.1)	58.5%	68.3 (55.6-78.8)	94.7%
Studies with <50% histology verification[50, 65, 66, 68]	83.7 (77.1-88.7)	10.0%	87.8 (75.0-90.5)	97.1%

Diagnostic accuracy of cervical cytology

- **20 studies** in 9,802 WLHIV

- Sensitivity and specificity estimates variable for CIN2+/CIN3+

- In settings enrolled in External Quality Assessment **sensitivity HSIL+ for CIN3+=87.5%** (95%CI: 76.0-94.0), **specificity=78.8%** (95%CI: 70.2-85.4).
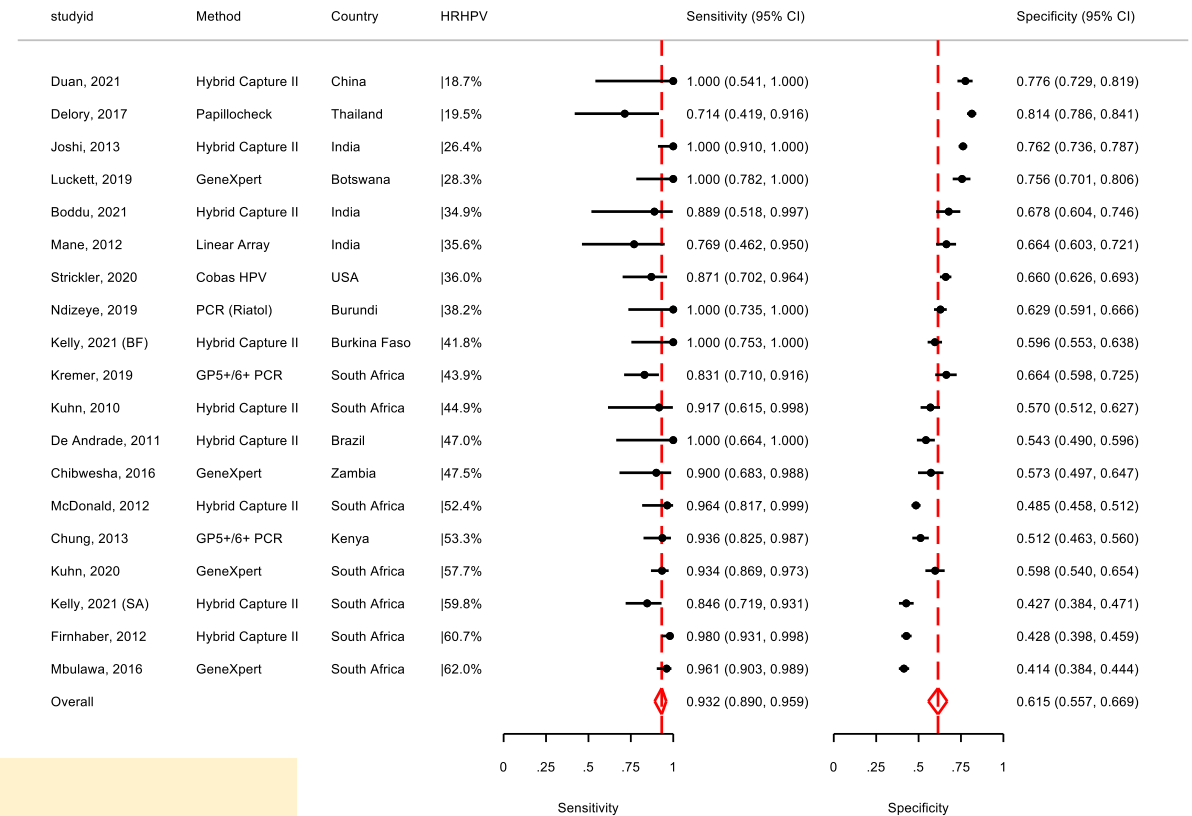

studyid	Country	Sensitivity (95% CI)	Specificity (95% CI)
ASCUS+			
Luckett, 2019	Botswana	0.647 (0.383, 0.858)	0.893 (0.850, 0.927)
Joshi, 2013	India	0.724 (0.528, 0.873)	0.936 (0.920, 0.950)
Ndizeye, 2019	Burundi	0.727 (0.390, 0.940)	0.852 (0.822, 0.878)
Mabeya, 2012	Kenya	0.727 (0.498, 0.893)	0.619 (0.523, 0.709)
Segondy, 2016 (BF)	Burkina Faso	0.727 (0.390, 0.940)	0.752 (0.713, 0.789)
Maiman, 1998	USA	0.800 (0.444, 0.975)	0.697 (0.635, 0.755)
Sahasrabuddhe, 2012	India	0.900 (0.555, 0.997)	0.585 (0.520, 0.648)
Chung, 2013	Kenya	0.936 (0.825, 0.987)	0.429 (0.381, 0.479)
Firnhaber, 2012	South Africa	1.000 (0.964, 1.000)	0.294 (0.267, 0.322)
Bateman, 2015	Zambia	1.000 (0.894, 1.000)	0.119 (0.082, 0.163)
Segondy, 2016 (SA)	South Africa	1.000 (0.932, 1.000)	0.073 (0.052, 0.099)
Summary		0.898 (0.803, 0.950)	0.594 (0.407, 0.757)
LSIL+			
Joshi, 2013	India	0.586 (0.389, 0.765)	0.952 (0.938, 0.965)
Ndizeye, 2019	Burundi	0.636 (0.308, 0.891)	0.877 (0.849, 0.902)
Mabeya, 2012	Kenya	0.682 (0.451, 0.861)	0.664 (0.569, 0.750)
Segondy, 2016 (BF)	Burkina Faso	0.727 (0.390, 0.940)	0.785 (0.747, 0.820)
Chung, 2013	Kenya	0.894 (0.769, 0.965)	0.595 (0.546, 0.643)
Sahasrabuddhe, 2012	India	0.900 (0.555, 0.997)	0.631 (0.566, 0.692)
Segondy, 2016 (SA)	South Africa	0.962 (0.868, 0.995)	0.108 (0.082, 0.138)
Bateman, 2015	Zambia	0.970 (0.842, 0.999)	0.333 (0.277, 0.393)
Firnhaber, 2012	South Africa	1.000 (0.964, 1.000)	0.323 (0.295, 0.351)
Summary		0.857 (0.734, 0.928)	0.667 (0.484, 0.811)
HSIL+			
Mabeya, 2012	Kenya	0.273 (0.107, 0.502)	0.894 (0.822, 0.944)
Joshi, 2013	India	0.345 (0.179, 0.543)	0.991 (0.984, 0.996)
Maiman, 1998	USA	0.400 (0.122, 0.738)	0.933 (0.893, 0.961)
Segondy, 2016 (BF)	Burkina Faso	0.455 (0.167, 0.766)	0.964 (0.944, 0.978)
Ndizeye, 2019	Burundi	0.455 (0.167, 0.766)	0.961 (0.942, 0.974)
Luckett, 2019	Botswana	0.471 (0.230, 0.722)	0.982 (0.958, 0.994)
Kremer, 2019	South Africa	0.593 (0.457, 0.719)	0.916 (0.872, 0.949)
Sahasrabuddhe, 2012	India	0.600 (0.262, 0.878)	0.950 (0.915, 0.974)
Bateman, 2015	Zambia	0.636 (0.451, 0.796)	0.567 (0.505, 0.627)
Segondy, 2016 (SA)	South Africa	0.808 (0.675, 0.904)	0.750 (0.711, 0.788)
Chung, 2013	Kenya	0.809 (0.667, 0.909)	0.871 (0.834, 0.902)
Firnhaber, 2012	South Africa	0.951 (0.889, 0.984)	0.723 (0.696, 0.750)
Summary		0.592 (0.418, 0.745)	0.928 (0.859, 0.965)

CIN3+ detection

Kelly et al, 2022 eClinicalMedicine (under review)

Diagnostic accuracy of HPV-DNA tests

- **25 studies** in 14,487 WLHIV

- **Screen-positive** ranged from **44%** to **51%**

- **Sensitivity** for CIN3+ = **93%** (range: 85% to 96%)

- **Low specificity for <CIN2 = 60%** (range: 55% to 66%)
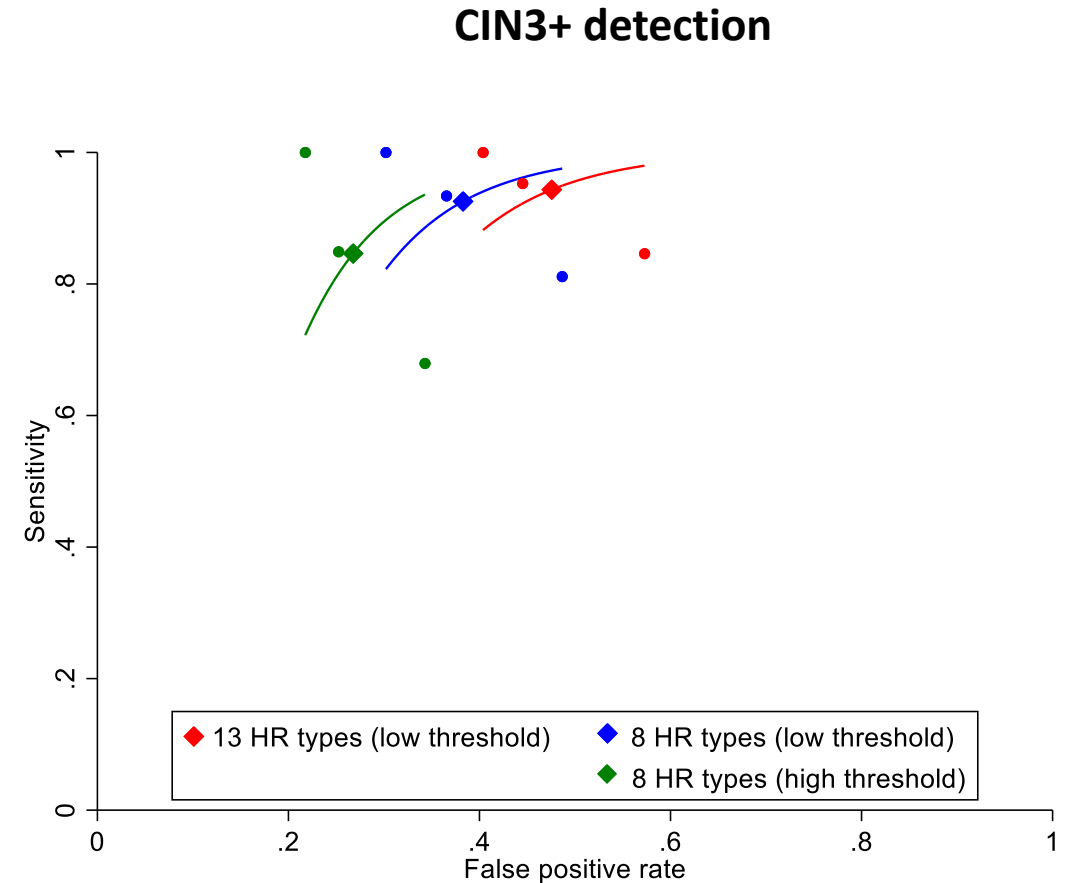
- Specificity varied by HPV prevalence

The **specificity** of HPV DNA test **higher** in:
- older vs. younger women
- Women with **higher CD4+ T-cell count** and on **prolonged ART**

CIN3+ detection

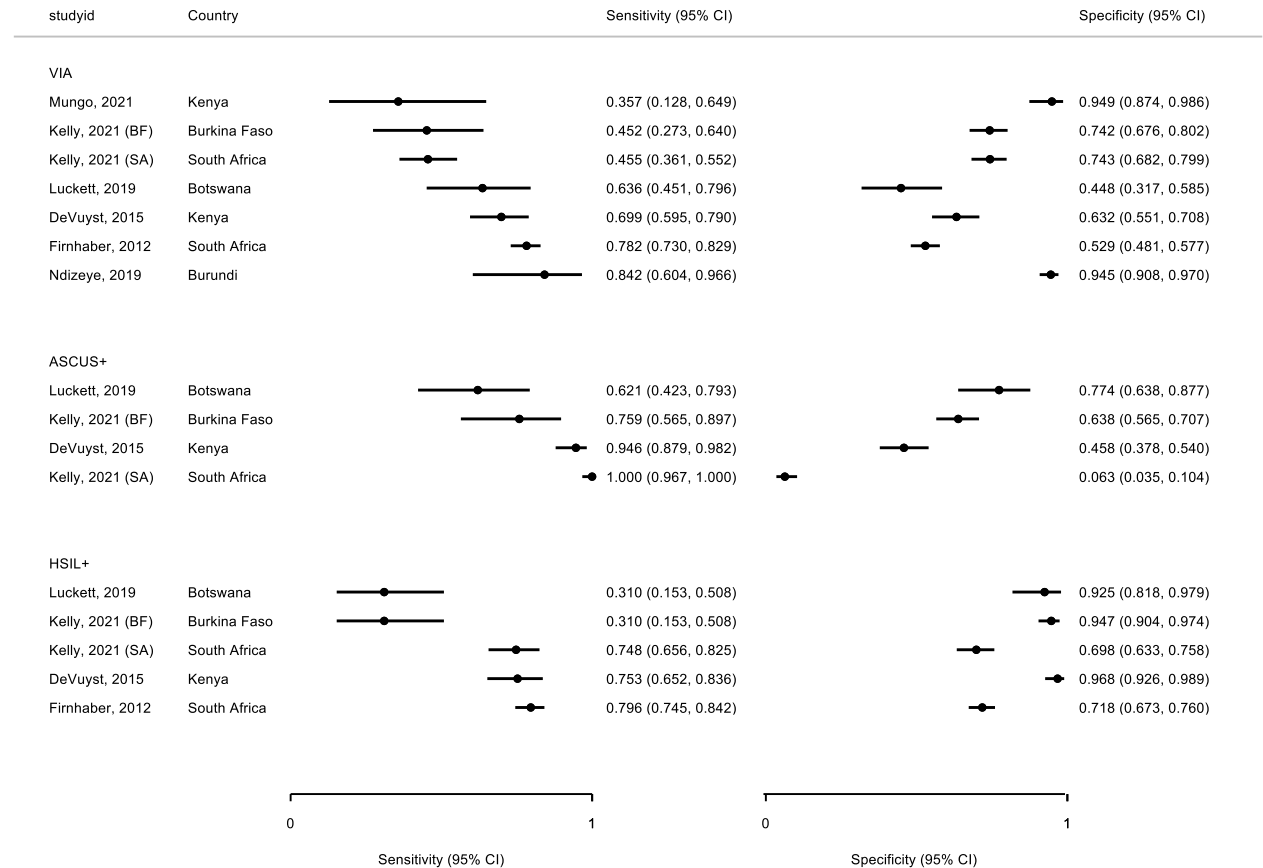| studyid	Method	Country	HRHPV	Sensitivity (95% CI)	Specificity (95% CI)
Duan, 2021	Hybrid Capture II	China	18.7%	1.000 (0.541, 1.000)	0.776 (0.729, 0.819)
Delory, 2017	Papillocheck	Thailand	19.5%	0.714 (0.419, 0.916)	0.814 (0.786, 0.841)
Joshi, 2013	Hybrid Capture II	India	26.4%	1.000 (0.910, 1.000)	0.762 (0.736, 0.787)
Luckett, 2019	GeneXpert	Botswana	28.3%	1.000 (0.782, 1.000)	0.756 (0.701, 0.806)
Boddu, 2021	Hybrid Capture II	India	34.9%	0.889 (0.518, 0.997)	0.678 (0.604, 0.746)
Mane, 2012	Linear Array	India	35.6%	0.769 (0.462, 0.950)	0.664 (0.603, 0.721)
Strickler, 2020	Cobas HPV	USA	36.0%	0.871 (0.702, 0.964)	0.660 (0.626, 0.693)
Ndizeye, 2019	PCR (Riatol)	Burundi	38.2%	1.000 (0.735, 1.000)	0.629 (0.591, 0.666)
Kelly, 2021 (BF)	Hybrid Capture II	Burkina Faso	41.8%	1.000 (0.753, 1.000)	0.596 (0.553, 0.638)
Kremer, 2019	GP5+/6+ PCR	South Africa	43.9%	0.831 (0.710, 0.916)	0.664 (0.598, 0.725)
Kuhn, 2010	Hybrid Capture II	South Africa	44.9%	0.917 (0.615, 0.998)	0.570 (0.512, 0.627)
De Andrade, 2011	Hybrid Capture II	Brazil	47.0%	1.000 (0.664, 1.000)	0.543 (0.490, 0.596)
Chibwesha, 2016	GeneXpert	Zambia	47.5%	0.900 (0.683, 0.988)	0.573 (0.497, 0.647)
McDonald, 2012	Hybrid Capture II	South Africa	52.4%	0.964 (0.817, 0.999)	0.485 (0.458, 0.512)
Chung, 2013	GP5+/6+ PCR	Kenya	53.3%	0.936 (0.825, 0.987)	0.512 (0.463, 0.560)
Kuhn, 2020	GeneXpert	South Africa	57.7%	0.934 (0.869, 0.973)	0.598 (0.540, 0.654)
Kelly, 2021 (SA)	Hybrid Capture II	South Africa	59.8%	0.846 (0.719, 0.931)	0.427 (0.384, 0.471)
Firnhaber, 2012	Hybrid Capture II	South Africa	60.7%	0.980 (0.931, 0.998)	0.428 (0.398, 0.459)
Mbulawa, 2016	GeneXpert	South Africa	62.0%	0.961 (0.903, 0.989)	0.414 (0.384, 0.444)
Overall				0.932 (0.890, 0.959)	0.615 (0.557, 0.669)

Restricted genotype approach

- Specificity of 14-HR vs. 8-HR* : **53% vs. 63%** (CIN3+) with no change in sensitivity

- **Combined with a higher cut-off** for test positivity increased specificity (**73%**) but with some loss in sensitivity (82%).

CIN3+ detection

Sensitivity

False positive rate

♦ 13 HR types (low threshold)   ♦ 8 HR types (low threshold)
♦ 8 HR types (high threshold)

*8 HR-HPV types (HPV-16, -18, -31, -33, -35, -45, -52, or 58)

Triage of HPV-positive WLHIV

- VIA operators and cytologists reported to be blinded to HPV

- Similar heterogeneity observed as in screening

- HSIL+ high sensitivity & specificity for CIN3+ (80.2/84.1%)

- Combination of restricted genotype + visual methods/cytology??

studyid	Country	Sensitivity (95% CI)	Specificity (95% CI)
VIA			
Mungo, 2021	Kenya	0.357 (0.128, 0.649)	0.949 (0.874, 0.986)
Kelly, 2021 (BF)	Burkina Faso	0.452 (0.273, 0.640)	0.742 (0.676, 0.802)
Kelly, 2021 (SA)	South Africa	0.455 (0.361, 0.552)	0.743 (0.682, 0.799)
Luckett, 2019	Botswana	0.636 (0.451, 0.796)	0.448 (0.317, 0.585)
DeVuyst, 2015	Kenya	0.699 (0.595, 0.790)	0.632 (0.551, 0.708)
Firnhaber, 2012	South Africa	0.782 (0.730, 0.829)	0.529 (0.481, 0.577)
Ndizeye, 2019	Burundi	0.842 (0.604, 0.966)	0.945 (0.908, 0.970)
ASCUS+			
Luckett, 2019	Botswana	0.621 (0.423, 0.793)	0.774 (0.638, 0.877)
Kelly, 2021 (BF)	Burkina Faso	0.759 (0.565, 0.897)	0.638 (0.565, 0.707)
DeVuyst, 2015	Kenya	0.946 (0.879, 0.982)	0.458 (0.378, 0.540)
Kelly, 2021 (SA)	South Africa	1.000 (0.967, 1.000)	0.063 (0.035, 0.104)
HSIL+			
Luckett, 2019	Botswana	0.310 (0.153, 0.508)	0.925 (0.818, 0.979)
Kelly, 2021 (BF)	Burkina Faso	0.310 (0.153, 0.508)	0.947 (0.904, 0.974)
Kelly, 2021 (SA)	South Africa	0.748 (0.656, 0.825)	0.698 (0.633, 0.758)
DeVuyst, 2015	Kenya	0.753 (0.652, 0.836)	0.968 (0.926, 0.989)
Firnhaber, 2012	South Africa	0.796 (0.745, 0.842)	0.718 (0.673, 0.760)

Sensitivity (95% CI)   Specificity (95% CI)

CIN2+ detection

Effectiveness of screening in WLHIV

Cervical precancer (CIN2+) incidence over 36 months

- ⬇ **80%** in HPV-and-treat group vs. no delayed screening (**Relative Risk=0.20, 95% CI 0.06–0.69**)

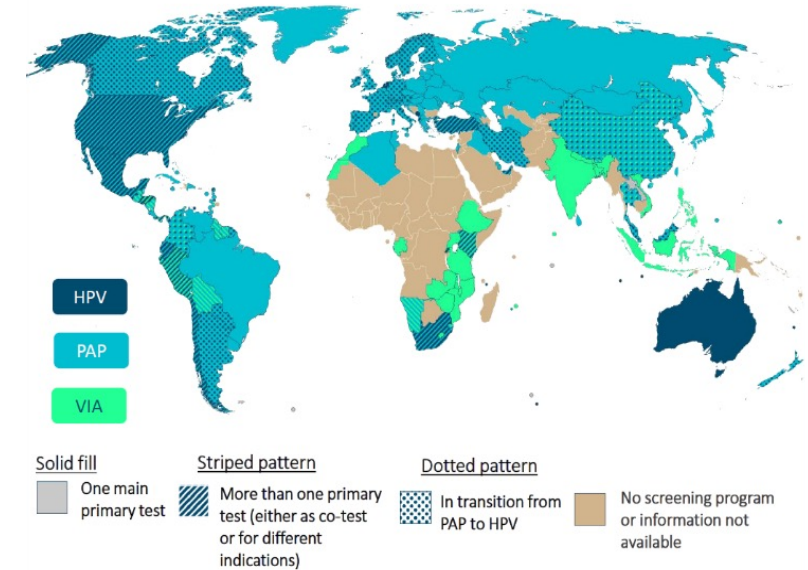- ⬇ **49%** VIA-and-treat group vs. no delayed screening (**Relative Risk=0.51, 95% CI 0.29–0.89**)
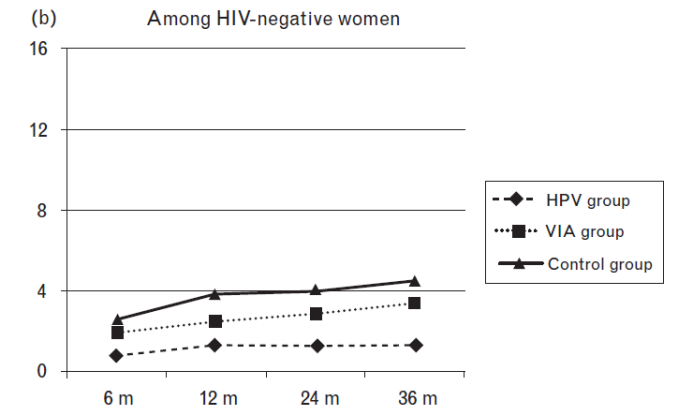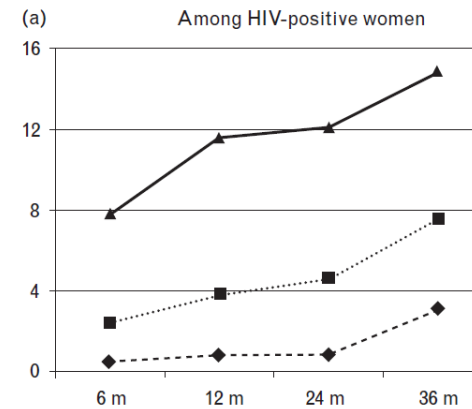
Effectiveness influenced by:
- Accuracy of screening-triage strategies
- Coverage of screening
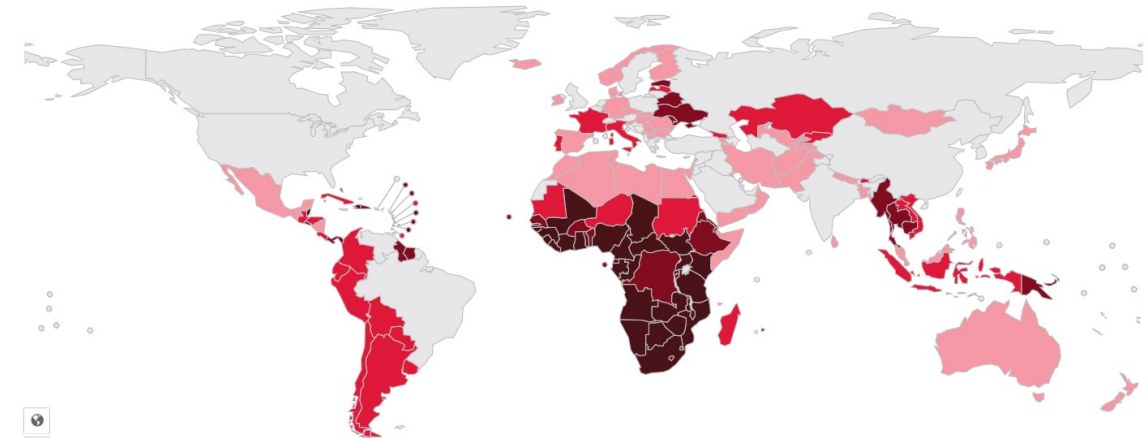- Treatment of screen positive (coverage and effectiveness)

Kuhn et al 2010, AIDS.24(16):2553-61

Screening coverage

- Estimated cervical cancer screening coverage in 2019, women **aged 30-49** years in **127 countries** worldwide

- **38%** of women aged 30-49 years have been screened at least once in their lifetime;

  88% in high-income settings

  15% in low-income countries

- => WHO target of **70% screening coverage**
- **HPV DNA test or cytology** most common in HIC
- **VIA** more common in Sub-Saharan Africa

- WLHIV????

HPV
PAP
VIA

Solid fill
One main primary test

Striped pattern
More than one primary test (either as co-test or for different indications)

Dotted pattern
In transition from PAP to HPV

No screening program or information not available

HIV prevalence

Serrano et al. National cervical cancer screening programs and coverage worldwide. 33rd International Papillomavirus Conference Barcelona, 23-27 March, 2020 2020

Questions remain

- Optimal screening-triage strategy
  - HR-HPV screen with restricted genotype/other molecular method in screening alone ?

- Optimal interval of screening??
  - More prospective data on HR-HPV infection/cervical precancer incidence at 12, 24, 36 months

- Implementation
  - Opportunity for integration in HIV care (+/- self sampling)
  - Feasible? Acceptable? Cost-effective?

- Change in access to ART and effectiveness
  - change in HPV prevalence and cervical cancer trends in future ?
  - Impact on molecular screening methods

Initiation & frequency of screening

Age-specific incidence rates of cervical cancer according to HIV-attribution status
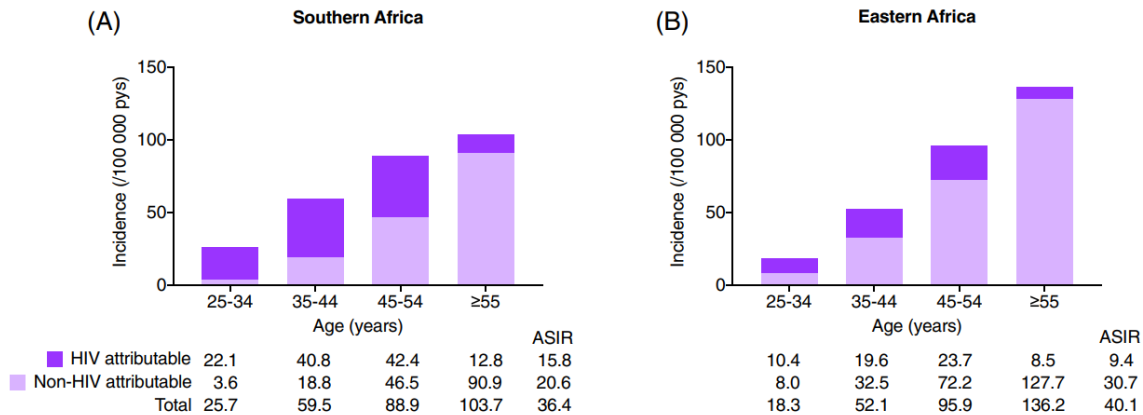
Cervical precancer incidence in screen neg WLHIV

Cyto normal WLHIV followed over 5 years (USA)

- HR-HPV - : similar risk WLHIV vs. HIV-neg

- HR-HPV+ : similar risk WLHIV CD4>500 vs. HIV neg

- WLHIV with <CIN2 followed over 16 months (SSA)
  - CIN2/3 incidence ↑ VIA neg (2-4%) vs. HPV-DNA neg (0.5-2%)

Data on cervical precancer by age?

Lacking long term prospective data to ascertain optimal interval

Khalil et al, Int. J. Cancer. 2022;150:761–772; Strickler et al; Clin Infect Dis 2021 May 4;72(9):1529-1537; Firnhaber et al; PLoS One 2016 Jan 5;11(1):e0144905; Kelly et al, PLOS Medicine. 2021;18(3):e1003528.