Elimination of cervical cancer: Screen & Treat step by step

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Khayelitsha Cervical Cancer Screening Project

Study team

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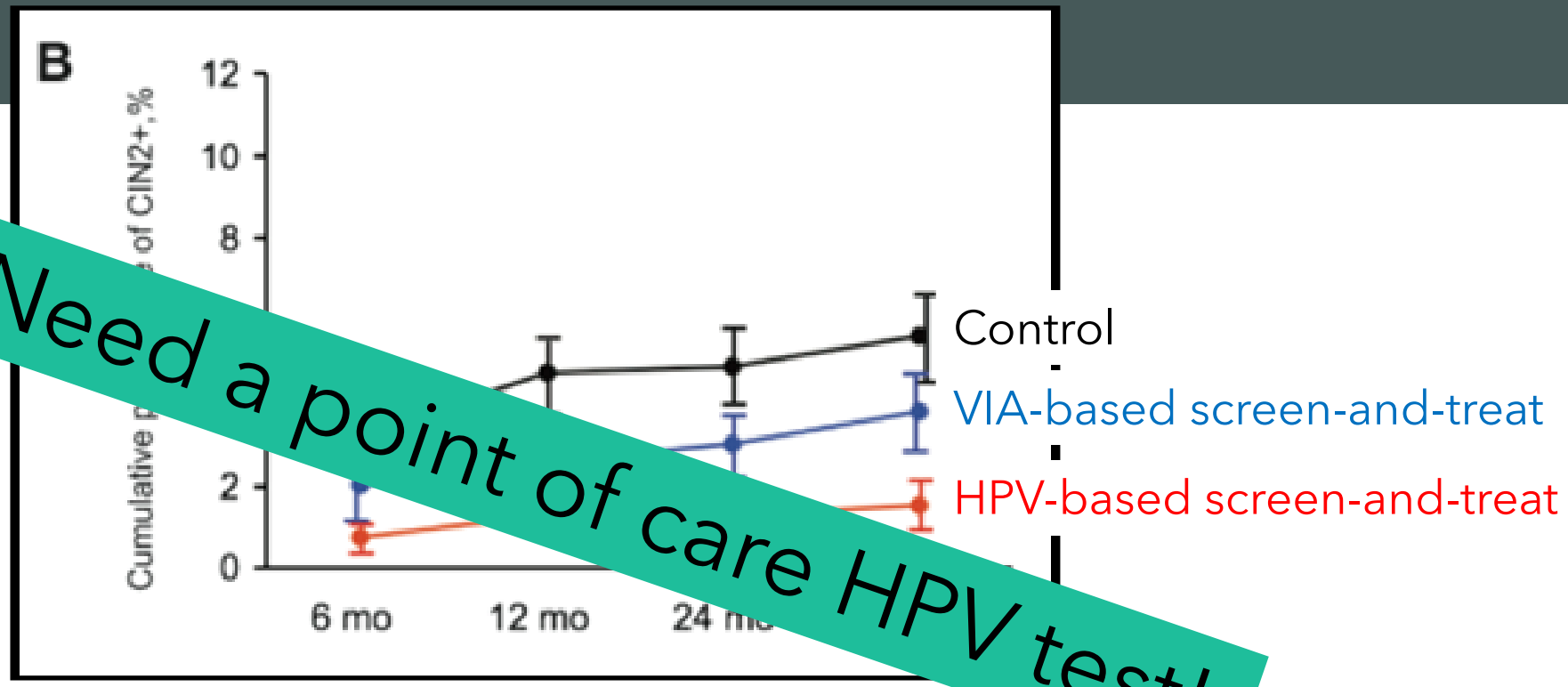
Rationale

- Screening needs to be strengthened to meet elimination goals
- Vaccination is essential but is not enough on its own
- Fundamental weakness of conventional screening is ATTRITION between screening test and treatment procedure
- Screen-and-treat bridges the screening test to treatment procedure gap
- Screen-and-treat reduces attrition leading to more effective and more efficient programs

Randomized trial of screen-and-treat

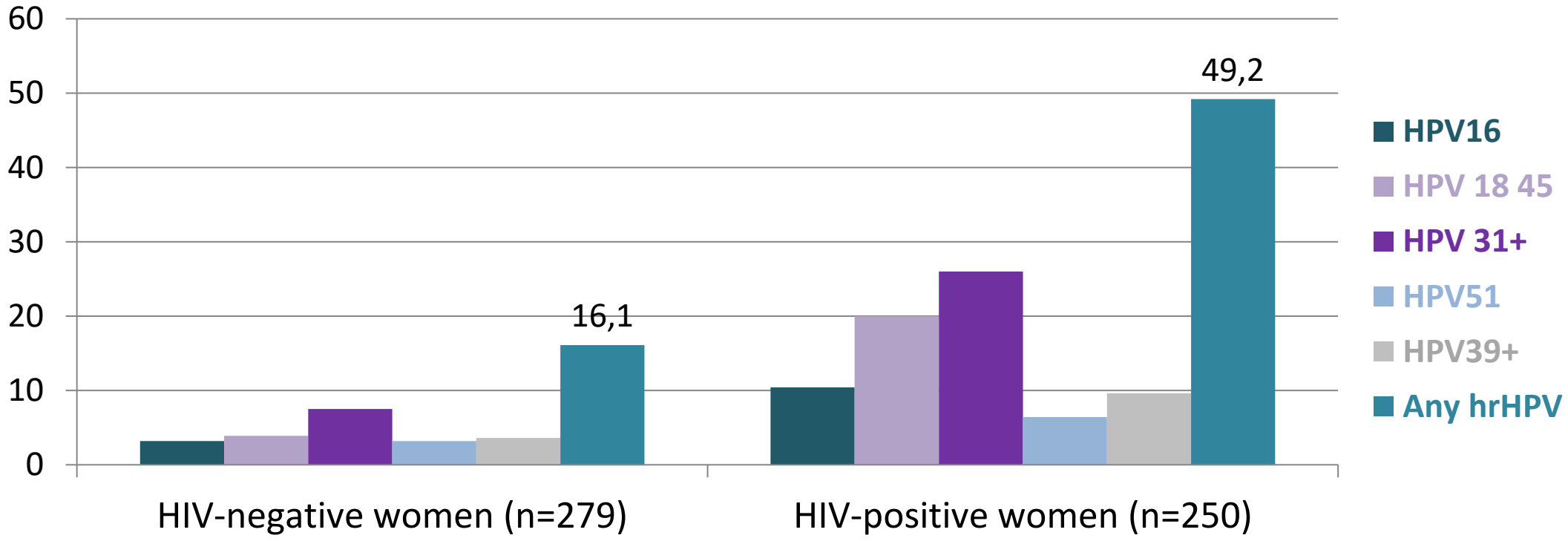


Need a point of care HPV test!

Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC, Jr. Screen-and- approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial**. JAMA** 2005;294:2173-81.

Denny L, Kuhn L, Hu CC, Tsai WY, Wright TC, Jr. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. **J Natl Cancer Inst** 2010;102:1557-67.

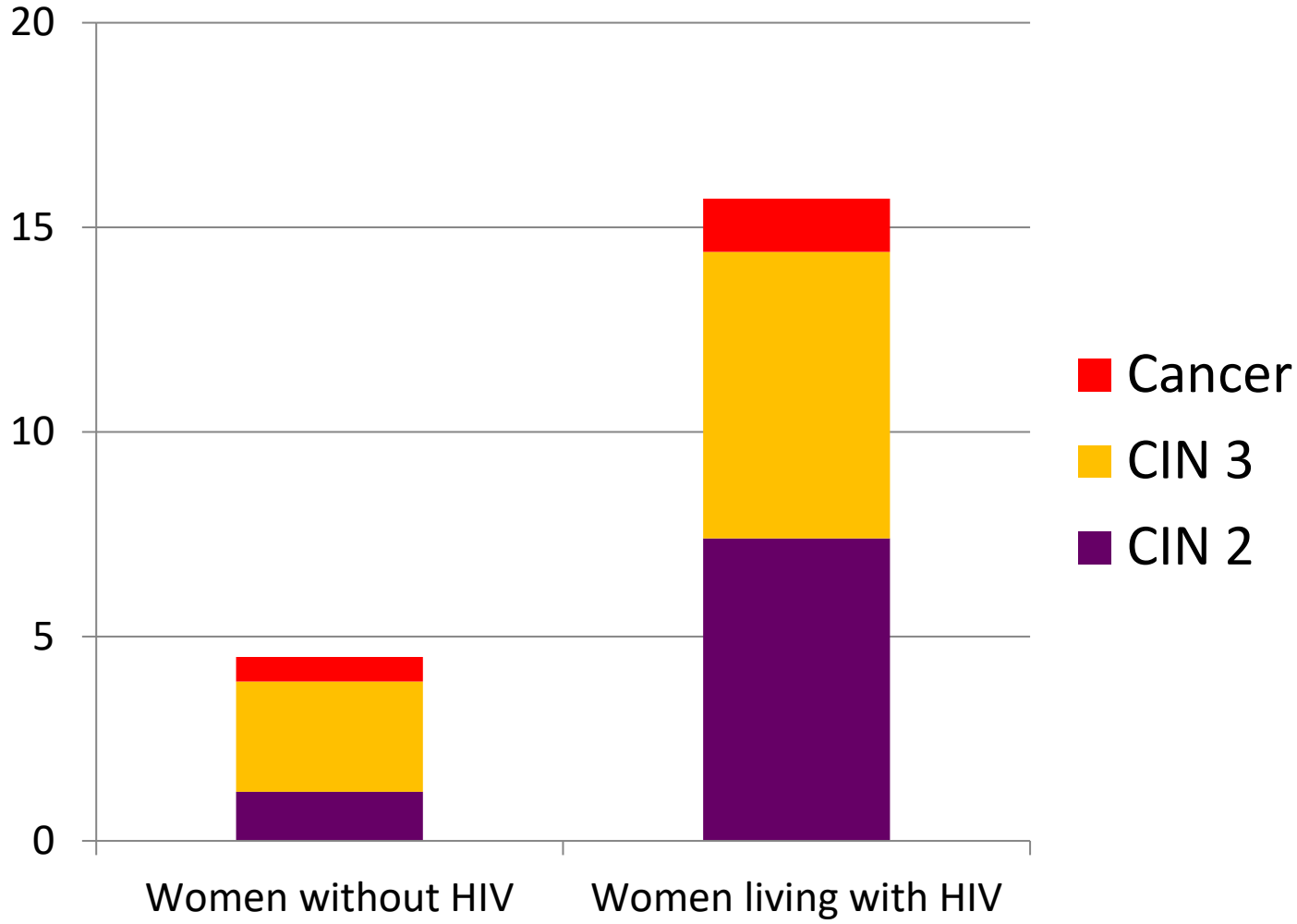
Tackling intersecting epidemics: High prevalence HPV infection among women living with HIV



Presented at 4th Annual Symposium on Global Cancer Research

8 April 2016, San Francisco, CA

High prevalence of cervical intraepithelial neoplasia grade 2 or 3 or cancer (CIN2+) in a screening population in Khayelitsha (30-65 years)



Historical perspective

- 20 years ago, we dreamed about a “HPV dipstix”
- We went on to show that HPV “screen-and-treat” is highly effective

Screen-and-Treat Approaches for Cervical Cancer Prevention in Low-Resource Settings

A Randomized Controlled Trial

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Context Non–cytology-based screen-and-treat approaches for cervical cancer prevention have been developed for low-resource settings, but few have directly addressed efficacy.

Objective To determine the safety and efficacy of 2 screen-and-treat approaches for cervical cancer prevention that were designed to be more resource-appropriate than conventional cytology-based screening programs.

Design, Setting, and Patients Randomized clinical trial of 6555 nonpregnant women, aged 35 to 65 years, recruited through community outreach and conducted between

- But we didn’t have a “HPV dipstix” then
- Now we do

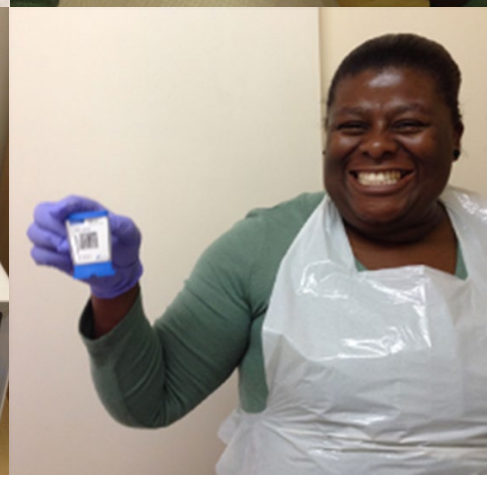
Point-of-care HPV tests are now available

Cartridge preloaded with all required reagents

No specialized lab skills required

Fully automated real-time PCR instrument Doesn't require "batching"

GeneXpert Instrument

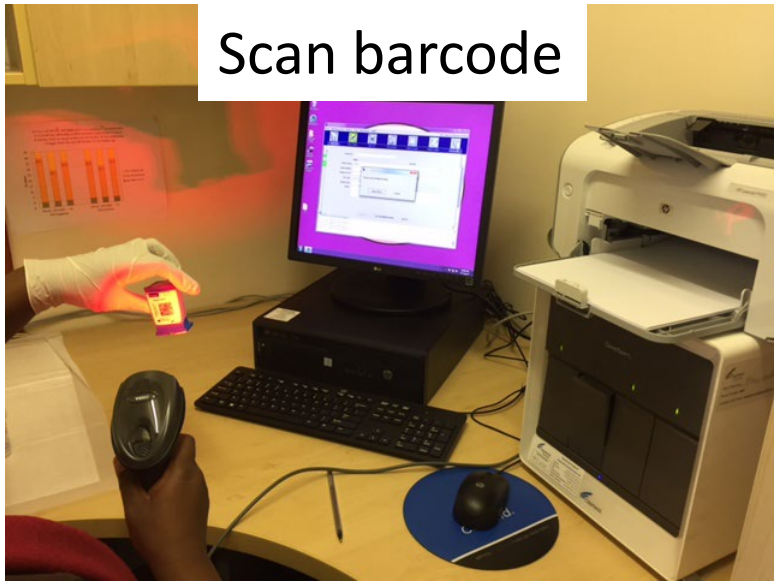


<1 min of operator "hands-on" time

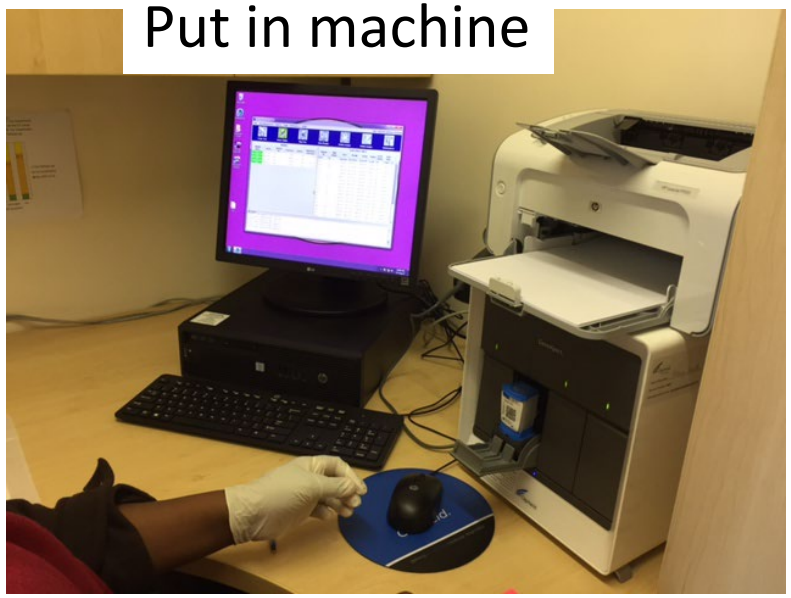
Put 1 ml Preservcyt in cartridge

Point-of-care HPV DNA test
HPV Xpert

Scan barcode



Put in machine



60 minutes later:

HPV 16
HPV 18/45
HPV 31/33/35/52/58
HPV 51/59
HPV 39/56/66/68

How to improve specificity of HPV testing (*risk stratification, triage*)

- Come up with a better test (biomarkers etc.)
- Repeat HPV test
- Add VIA
- Select only certain genotypes
- Select only those with high HPV viral load

Using data from our previous studies, we considered whether specificity of HPV testing* could be improved by:

	Sensitivity	Specificity	Over-treatment
Adding VIA			
HPV testing only	90	84	16
HPV testing + VIA	48	95	5
Changing viral load cut-offs	**Without losing sensitivity!**		
HPV testing RLU >1**	90	84	16
HPV testing RLU >2	86	86	14
HPV testing RLU >5	81	89	11
HPV testing RLU >10	71	90	9

*HPV testing done with Hybrid Capture II **Relative Light Unit (RLU) > 1 = standard cut-off

Assay Information

Assay	Assay Version	Assay Type
HPV HR AND GENOTYPE RUO ASSAY	2	Research Use Only

Test Result:

HPV 16 NEG;
HPV 18_45 POS;
OTHER HR HPV POS

Cycle threshold (Ct)

Test and Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SAC	36.8	45.0	NA	PASS
HPV 16	0.0	0.0	NEG	PASS
HPV 18_45	30.9	322.0	POS	PASS
P3	26.6	366.0	POS	PASS
P4	0.0	7.0	NEG	PASS
P5	0.0	-3.0	NEG	PASS

User:	Signoria vathiswa kamkam		
Status:	Done	Start Time:	17/03/15 09:34:31
Expiration Date*:	26/12/49	End Time:	17/03/15 10:34:58
S/W Version:	4.4a	Instrument S/N:	805050
Cartridge S/N*:	234594192	Module S/N:	645194
Reagent Lot ID*:	11051	Module Name:	A1
Notes:			
Error Status:	OK		

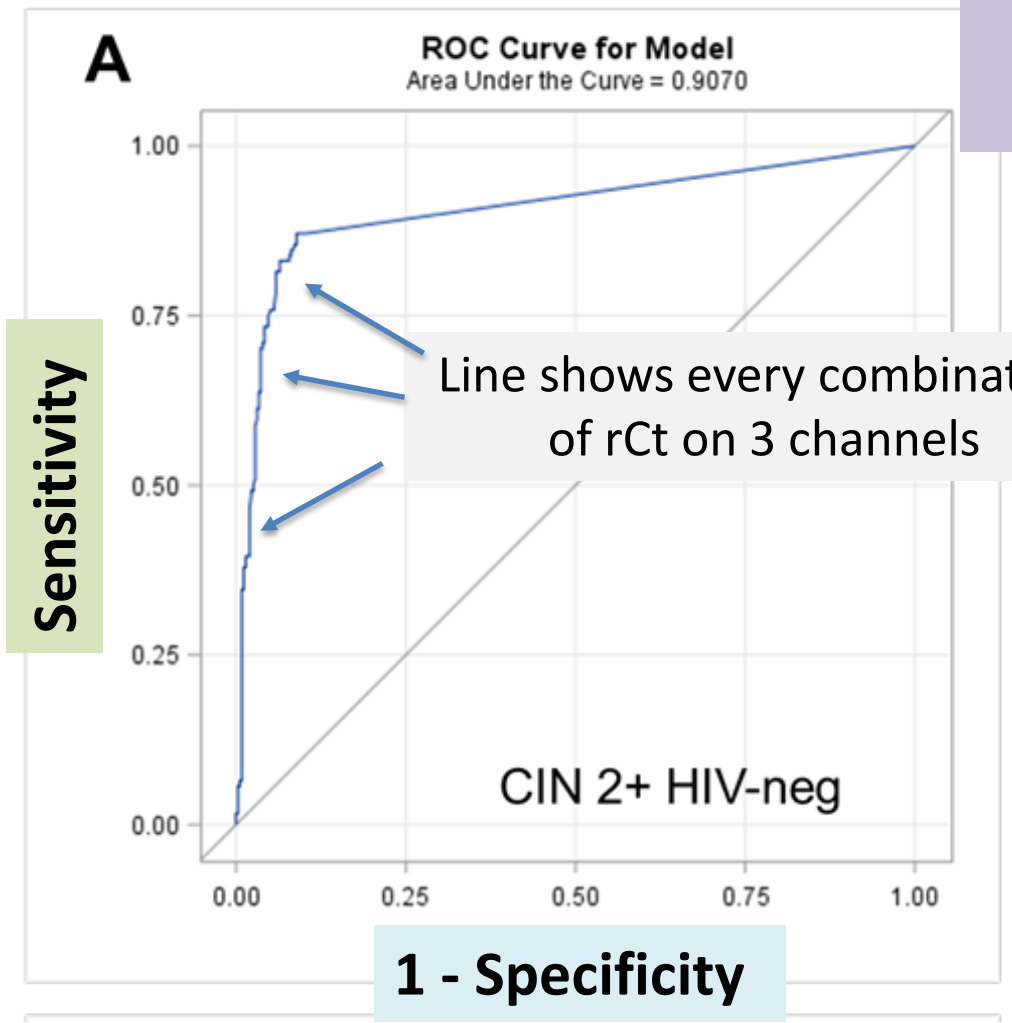
Errors
<None>

Improving specificity by changing the viral load thresholds on HPV Xpert

Real-time PCR for 14 targeted HPV types in 5 channels plus sufficiency control:

HPV16;
HPV18 45;
[P3] HPV31, 33, 35, 52, 58;
[P4] HPV51 59;
[P5] HPV39, 56, 66, 68

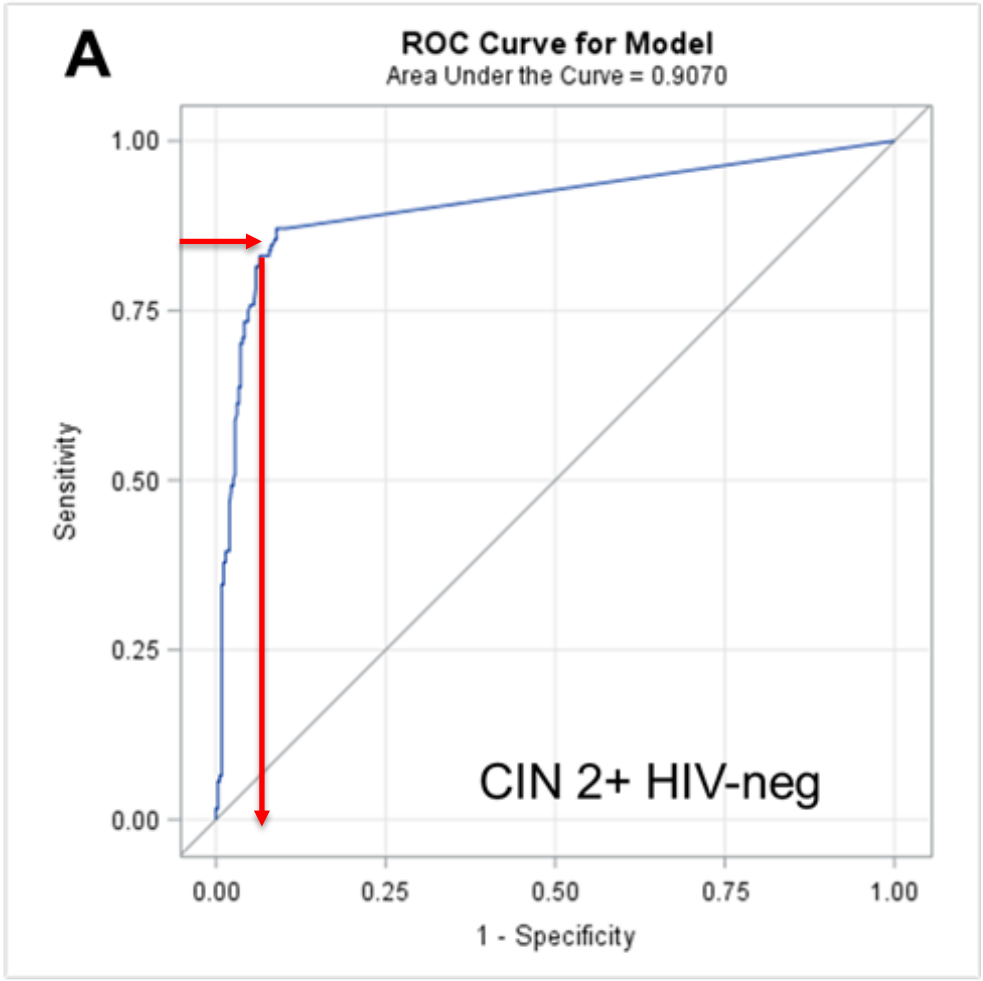
From logistic regression model, calculate a Receiver Operating Characteristic (ROC) Curve

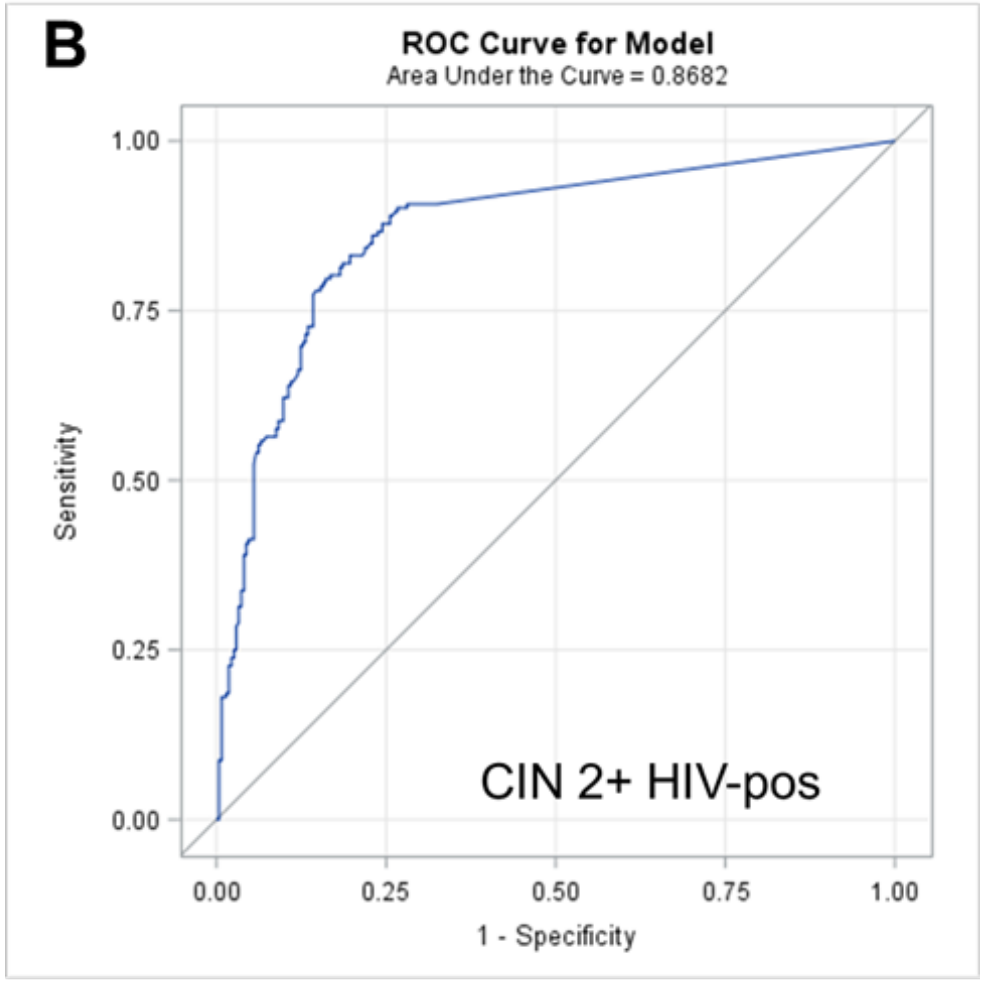


Area under the curve (AUC) =0.91

Line shows every combination of rCt on 3 channels

More stringent cycle threshold (Ct) values makes the sensitivity/specificity balance more favorable for screen and treat





Cutoffs could be selected for different settings appropriate to resource availability and community preferences

	Sensitivity	Specificity	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Screen positive (95% CI)
CIN2+					
HIV-negative					
	65	96.4	50.0 (42.3-57.7)	98.0 (96.5-99.5)	6.9 (4.5-9.2)
	70	96.4	51.9 (33.3-59.5)	98.3 (97.0-99.7)	7.1 (4.7-9.5)
	75	95.3	47.2 (40.2-54.2)	98.6 (97.4-99.8)	8.4 (5.7-11.1)
	80	**94.1**	**43.1 (36.7-49.5)**	**98.8 (97.6-100)**	**9.8 (6.9-12.8)**
	85	91.3	35.4 (30.0-40.8)	99.1 (98.1-100)	12.7 (9.3-16.1)
HIV-positive					
	65	88.3	53.3 (46.6-60.1)	92.5 (89.3-95.7)	20.7 (16.5-25.0)
	70	87.2	52.9 (46.4-59.4)	93.4 (90.4-96.4)	22.5 (18.0-27.0)
	75	85.8	52.0 (45.8-58.2)	94.4 (91.5-97.3)	24.5 (19.8-29.2)
	80	**83.2**	**49.4 (43.5-55.3)**	**95.3 (92.6-98.0)**	**27.5 (22.5-32.5)**
	85	77.0	43.1 (37.8-48.4)	96.2 (93.7-98.7)	33.5 (28.1-39.0)

Kuhn L et al Lancet Global Health. 2020 Feb;8(2):e296-e304.

Khayelitsha Site B Clinic

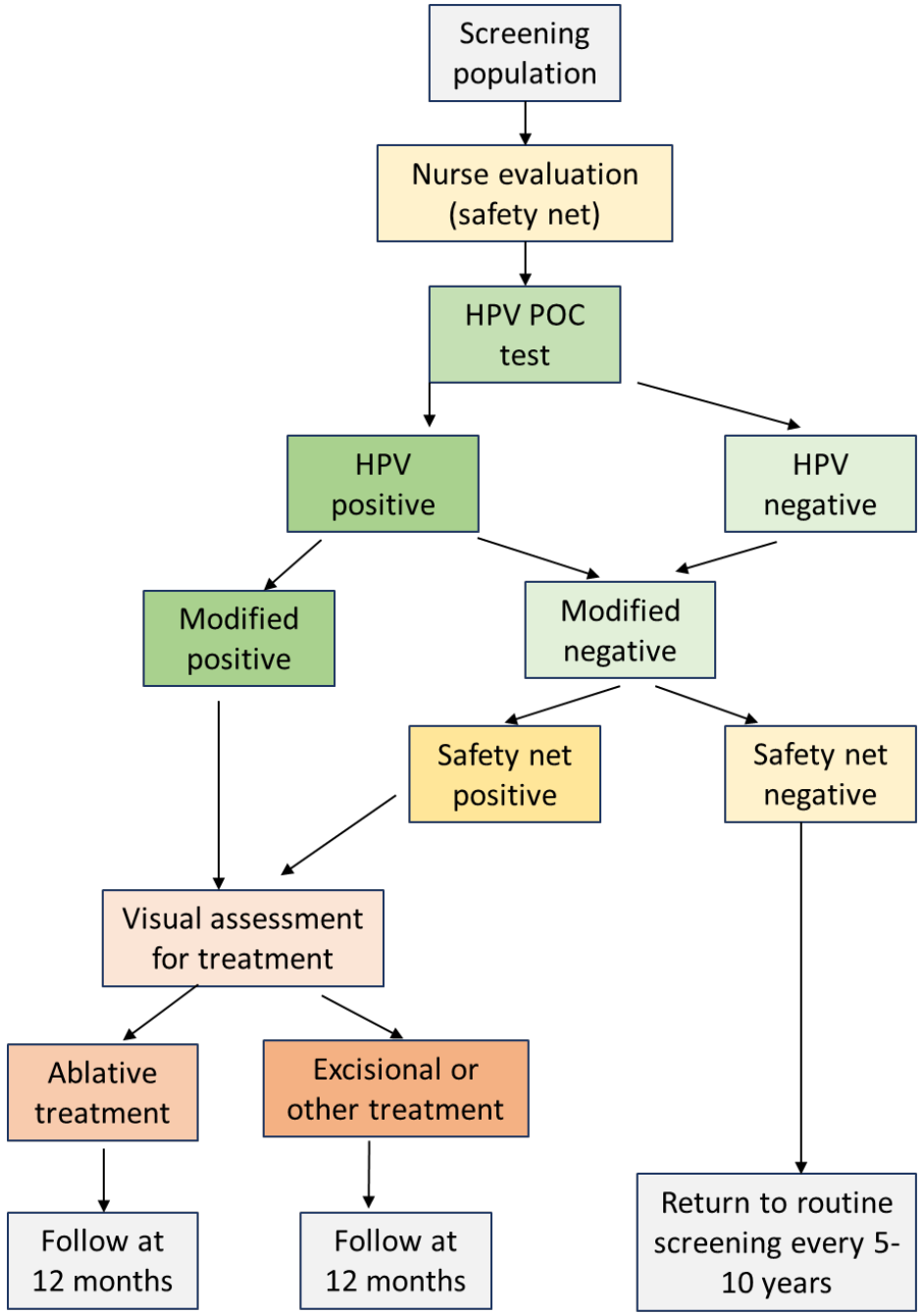
Research Facilities

Phambili Ngempilo Yabafazi

Screen-and-treat team

- Nurse
- Community health workers
- Doctor

Point-of-care HPV screen-and-treat algorithm



Step 1: Nurse safety evaluation suitability for screening

- Primary Rationale: Detect HPV negative cancers
- Secondary Rationale: Address comorbidities
- Will not be possible if self-collected vaginal swabs are used
- Requires suitably trained providers

Step 2: Point-of-Care HPV test

Why we chose Xpert HPV

- Validated and approved
- Easily done at POC (only commercially-available HPV test that can be easily-done at the POC)
- Partial HPV typing as provides results in 5 channels
- Provides HPV viral load data (PCR cycle threshold values) for further risk stratification triage
- Implemented modified cut-offs expected to attain 85% sensitivity

Step 3: Interpret HPV test result

- Women are asked to wait for result
- When results are available, interpret as to whether or not treatment is required
- Explain to women meaning of result
- Explain need for treatment

Step 4: Visual Assessment for Treatment (VAT)

Nurse exam of cervix after application of acetic acid

Criteria for suitability for ablative treatment:

1] cervix is accessible

2] no evidence or suspicion of invasive cancer

3] squamocolumnar junction is visible

4] no marked inflammation, infection or severe atrophy

5] any visible aceto-white lesion >75% of the cervix and does not extend into the endocervical canal

Step 5: If suitable, treated on-site, same day with thermocoagulation

Why ablative therapy?

- One of the approved treatment modalities for cervical cancer precursor lesions
- Considered to have acceptable efficacy
- Equipment needed is relatively inexpensive
- Can be done by nurses – does not require specialist skills
- Is safer than other treatment options

Step 6: If eligible but not suitable for same-day ablative therapy

Reviewed by on-site doctor to determine appropriate next steps

- Antibiotic treatment and ablative treatment 7-14 days later
- On-site LLETZ
- Referral to colposcopy and possible LLETZ or cone biopsy
- Referral for suspicious for cancer
- Other referrals

Results of demonstration study in Khayelitsha

From May 2017 to September 2018, 3062 women were enrolled

~200 women per month ~50 per week

1346 Women Living With HIV (WLWH) (44%)

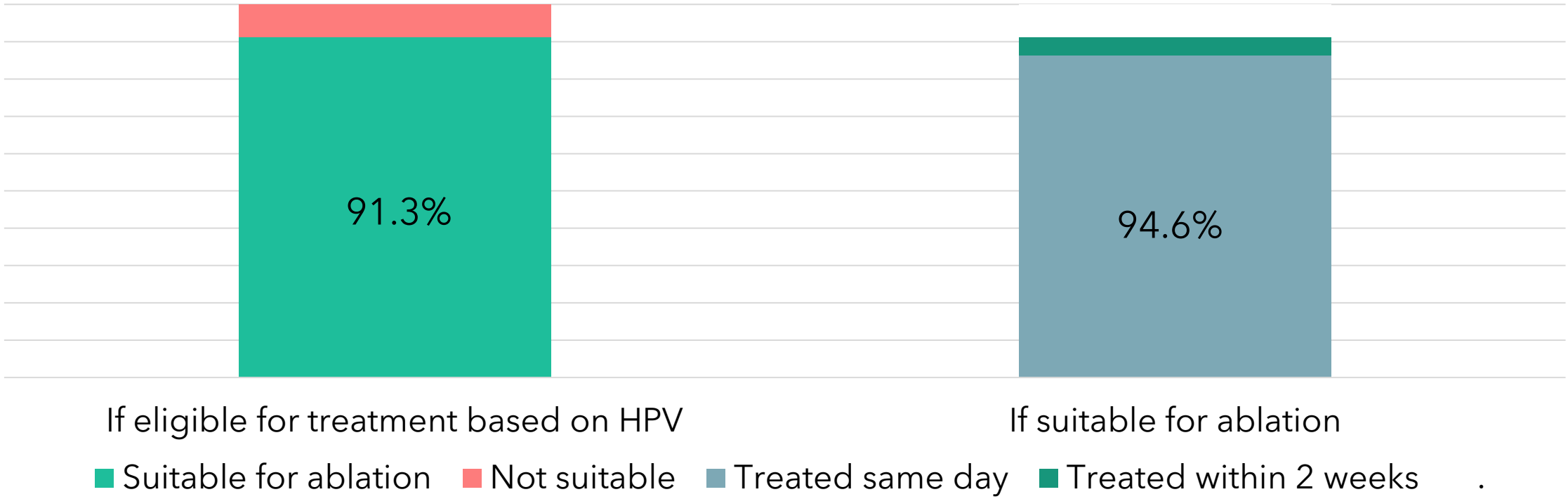
1716 Women Not Living without HIV (WNLH)

Almost all women stayed to receive their HPV results

Variable	Total Population	Women living with HIV (WLWH)	Women not living with HIV (WNLH)
Valid results obtained			
Valid on 1st run	3005 (98.1)	1320 (98.1)	1685 (98.2)
Valid on 2nd run	52 (1.7)	23 (1.7)	29 (1.7)
Valid on 3rd run	4	3	1
New sample needed	1	0	1
Woman received results on the same day			
Yes	3056 (99.8%)	1345 (99.9%)	1711 (99.7%)
No	6 (0.2%)	1 (0.1%)	5 (0.3%)
Any high risk HPV+ (any of the 5 channels+)			
Yes	857 (28.0%)	559 (41.5%)	298 (17.4%)
No	2205 (72.0%)	787 (57.5%)	1418 (82.6%)
Meet modified HPV c			
High viral load on			
52, 58+			(10.4%)
No	2532 (82.7%)	994 (73.8%)	1507 (89.6%)

Median waiting time from sample collection to receiving results
1.52 hours (IQR 1.35 – 1.80 hours)

>90% were treated with thermocoagulation on the same day



8.7% of treatment-eligible but not suitable for ablation were reviewed by on-site doctor:

- 3 cancers were detected by HPV testing and by nurse evaluation as unsuitable for ablation
- 1 cancer was detected by nurse on initial safety screen and was HPV negative
- 35% suitable for ablation after antibiotic treatment
- 24% managed on-site (LLETZ)
- 41% higher level of specialist gynae care

Complications of ablative therapy were rare

- <1 % had minor complications of thermal ablation at the time of the procedure (3 moderate or excessive pain and one mild vaginal wall burn)
- <6% had complications that they sought health care for (most treated with antibiotics)
- No serious adverse events

Conclusions

- Outstanding fidelity to an HPV-based screen-and-treat protocol could be attained
- Task-shifting of HPV testing to a non-laboratory trained CHW was successful
- Task-shifting of sample collection and ablative treatment to a trained study nurse was successful
- Complications of ablative therapy were minimal
- Numbers of women needing referral to specialized gynae services was reduced
- Counseling and education needs were considerable

Areas in need of further research

- How to implement within routine services
- When resources permit, less stringent risk stratification may be desirable
- Need increased attention to improving treatment modalities for pre-cancerous disease

Acknowledgements

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Lynette Denny, Rakiya Saidu, Ros Boa, Jennifer Moodley

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Epidemiology, Pathology, Gynecology

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Thank you!

Phambili Ngempilo
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