PRIMARY HPV mRNA SCREENING WITH DIFFERENT GENOTYPE COMBINATIONS to ENHANCE CERVICAL CANCER PREVENTION IN SOUTH AFRICAN WOMEN

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Disclosures

- The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Cervical Cancer Prevention South Africa

SOUTH AFRICA:

- We suffer a double epidemic of Cervical Cancer and HIV-infections
  - 12 000 new cervical cancer cases per year
  - age-standardized incidence rate of 35.3 per 100 000 women (2020)
  - more than half of patients with cervical cancer are women living with HIV with HPV prevalence doubled
- The high prevalence of co-infections challenges the use of sensitive HPV-testing, leading to massive over-treatment of test-positives
- Accurate local data on HPV prevalence and types by HIV status are essential to identify implementable strategies to improve cervical cancer control

HPV genotype distribution

BACKGROUND:

- **mRNA E6/E7** HPV detection has shown higher specificity in detecting clinically relevant disease CIN2+ compared to conventional HPV-DNA testing

- **Genotype combination** is critical in prevention strategies:
  - Inherent oncogenicity
  - Prevalence per geography
  - Prevention program tolerance

- HPV-types identified in invasive cancer cases from South Africa* rank **16>18>45>35>33>52>31>58**>51 as the most prevalent types - together responsible for > 90% of ICC

*HPV types in cervical cancer tissue in South Africa: A head-to-head comparison by mRNA and DNA tests. Medicine 96(47):p e8752, November 2017. DOI: 10.1097/MD.0000000000008752

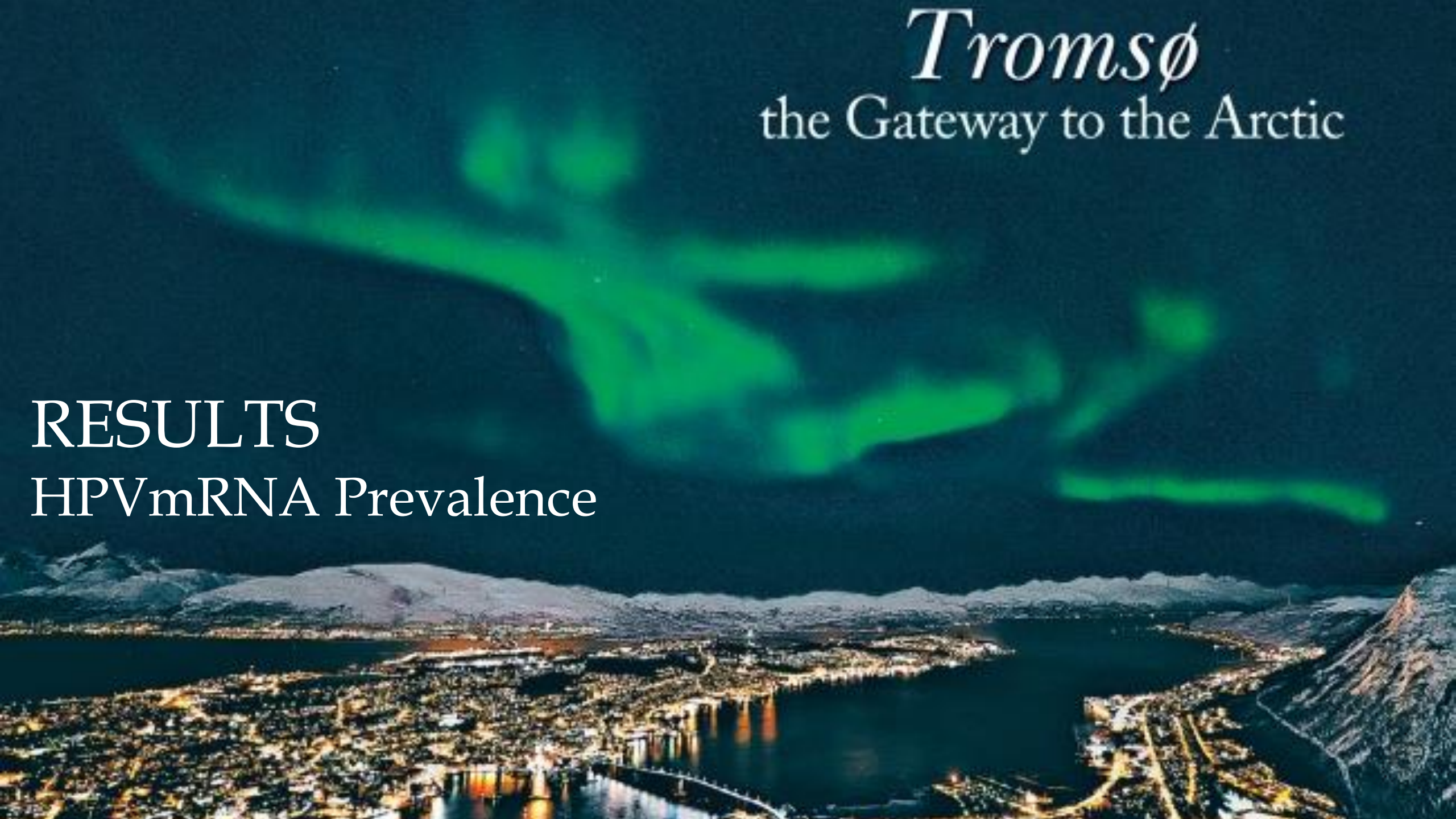
The DiaVACCS Trial:
Diagnosis in **V**accine **A**nd **C**ervical **C**ancer **S**creen

A screening trial among HIV-positive and HIV-negative women Gauteng and Western Cape provinces

A collaboration between Stellenbosch University & University of Pretoria, SA

Publications:

Phase 1 Baseline results: S Afr Med J 2022;112(7):478-486. https://doi.org/10.7196/SAMJ.2022.v112i7.16478
HPV mRNA results: Cancers. 2023; 15(22):5453. https://doi.org/10.3390/cancers15225453



RESULTS

HPVmRNA Prevalence

Study Objectives

mRNA TESTING IN DIFFERENT GENOTYPE COMBINATIONS:

Primary:

- ❑ Explore the potential of a screen-and-treat strategy using mRNA HPV tests to impact cervical cancer prevention in a high-prevalence HIV population

Secondary:

- ❑ Optimize the selection of HPV types to predict CIN3+ during screening among both HIV-positive and negative women:
  - evaluate various combinations of HPV types based on HIV status
  - model the effectiveness of a screen-and-treat approach
  - assess the number mRNA positive cases needed to be treated

Aimed at:

- ❑ Prevention of progression of CIN3 to invasive cervical cancer
- ❑ In resource-constrained settings with limited access to colposcopy & biopsy

ClinicalTrials.gov identification number NCT02956031

Cancers. 2023; 15(22):5453. https://doi.org/10.3390/cancers15225453

Study Methods

Type:

- Multicentric screening trial among HIV negative and positive women at Tshwane District Hospital, Kalafong Provincial Tertiary Hospital and Tygerberg Academic Hospital

Screening:

- Visual inspection, Molecular and cytological screening tests.
- Colposcopy and biopsy at the initial visit (consenting participants), treatment if required (LLETZ)
- HPV mRNA E6/E7 testing for **TOP 8** types:

  PreTect SEE-SA and PreTect HPV-Proofer'7, plus HPV 35

  (PreTect AS, Klokkarstua, Norway)

Diagnosis:

- Final histology result: most severe finding among punch biopsies and LLETZ specimens

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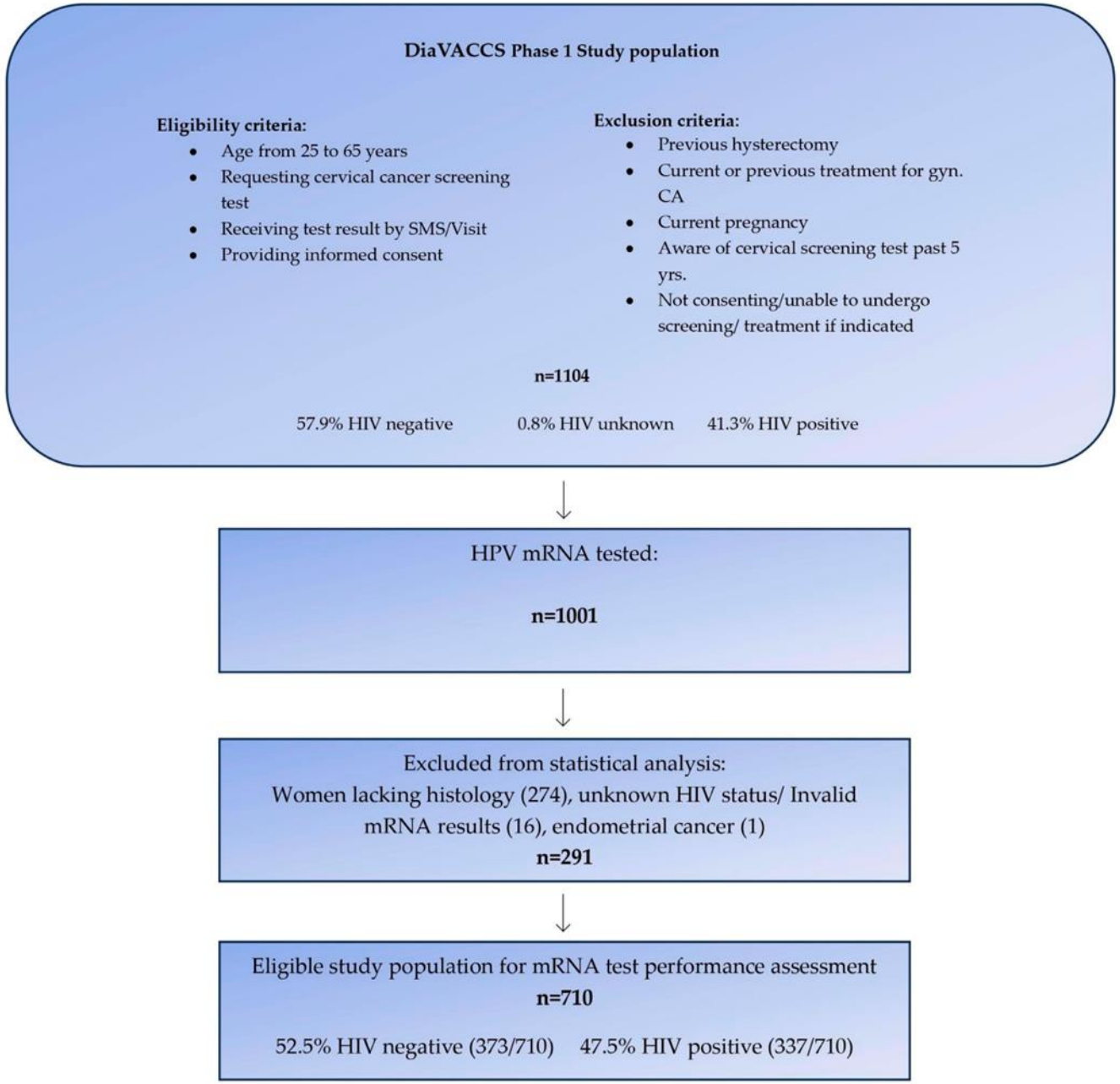
Study diagramme

2016-2020
n=1001



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1. HPV mRNA type frequency

mRNA HPV Type	n	%
16	48	6.8
45	33	4.6
58	29	4.1
18	27	3.8
52	27	3.8
31	24	3.3
35	21	3.0
33	15	2.1
Negative	486	68.5
Overall positive	224	31.5

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2. Age, positivity rate for mRNA combinations, and most severe histology, all by HIV status.

Characteristics	HIV Negative	HIV Positive	Total	*p*-Value
Women (n)	373	337	710	
Age (years)	n (%)	n (%)	n (%)	
25–39	181 (48.5)	171 (50.7)	352 (49.6)	$p = 0.60$
40–65	192 (51.5)	166 (49.3)	358 (50.4)	
mRNA HPV types	n (%)	n (%)	n (%)	
16, 18, 45	33 (8.8)	75 (22.3)	108 (15.2)	
16, 18, 45, **35**	40 (10.7)	101 (30.0)	141 (19.9)	
16, 18, 45, 31, 33	46 (12.3)	101 (30.0)	147 (20.7)	$p < 0.01$
16, 18, 45, 31, 33, **35**	52 (13.9)	123 (36.5)	175 (24.6)	
16, 18, 45, 31, 33, 52, 58	67 (18.0)	136 (40.4)	203 (28.6)	
16, 18, 45, 31, 33, 52, 58, **35**	71 (19.0)	153 (45.4)	224 (31.5)	
Most severe histology	n (%)	n (%)	n (%)	
Normal	139 (37.3)	98 (29.1)	237 (33.4)	
CIN1	123 (33.0)	72 (21.4)	195 (27.5)	
CIN2	63 (16.9)	78 (23.1)	141 (19.9)	$p < 0.0$ CIN2+/<CIN2
CIN3	44 (11.8)	81 (24.0)	125 (17.6)	$p < 0.01$ CIN3+/<CIN3
ICC	4 (1.1)	8 (2.4)	12 (1.7)	

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3. Detection rate of mRNA HPV genotype combinations by final histology result according to HIV status.

Histology	Normal		CIN1		CIN2		CIN3		ICC	
HIV Status	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.
Women (n)	139	98	123	72	63	78	44	81	4	8
mRNA HPV+	%	%	%	%	%	%	%	%	%	%
16, 18, 45	2.2	6.1	4.1	2.8	15.9	33.3	27.3	44.4	75	62.5
16, 18, 45, **35**	2.9	9.2	4.1	4.2	20.6	47.4	34.1	56.8	75	75
16, 18, 45, 31, 33	3.6	7.1	5.7	12.5	17.5	42.3	45.5	54.3	75	100
16, 18, 45, 31, 33, **35**	4.3	10.2	5.7	13.9	22.2	55.1	50	64.2	75	100
16, 18, 45, 31, 33, 52, 58	6.5	10.2	9.8	18.1	23.8	56.4	63.6	75.3	75	100
16, 18, 45, 31, 33, 52, 58, **35**	7.2	13.3	9.8	19.4	27	65.4	65.9	82.7	75	100

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4. Test performance: Sensitivity, Specificity and Positive and Negative predictive values for CIN3+, by HIV status

	Sensitivity			Specificity			PPV			NPV		
HIV Status	**Neg.**	**Pos.**	**Total**	**Neg.**	**Pos.**	**Total**	**Neg.**	**Pos.**	**Total**	**Neg.**	**Pos.**	**Total**
mRNA HPV+	%	%	%	%	%	%	%	%	%	%	%	%
16, 18, 45	31.3	46.1	40.9	94.5	86.3	90.9	45.5	54.7	51.9	90.3	81.7	86.5
16, 18, 45, **35**	37.5	58.4	41.1	93.2	80.2	87.6	45.0	51.5	49.6	91.0	84.3	88.2
16, 18, 45, 31, 33	47.5	58.4	54.7	92.9	80.2	87.4	50.0	51.5	51.0	92.4	84.3	89.0
16, 18, 45, 31, 33, **35**	52.1	67.4	62.0	91.7	74.6	84.3	48.1	48.8	48.6	92.8	86.4	90.3
16, 18, 45, 31, 33, 52, 58	64.6	77.5	73.0	88.9	73.0	82.0	46.3	50.7	49.3	94.4	90.0	92.7
16, 18, 45, 31, 33, 52, 58, **35**	66.6	84.3	78.1	88.0	68.5	79.6	45.1	49.0	47.8	94.7	92.4	93.8

5. Number of mRNA positive cases needed to treat to address one existing CIN3+ case
Estimated proportion of cervical cancers prevented by detection

	Positivity Rate mRNA			Sensitivity			NNT * to Address One Case CIN3+			Estimated % CC Prevented **		
HIV Status	**Neg.**	**Pos.**	**Total**	**Neg.**	**Pos.**	**Total**	**Neg.**	**Pos.**	**Total**	**Neg.**	**Pos.**	**Total**
Women (N)	373	337	710	48	89	137	NA	NA	NA	96	65	161
mRNA HPV+	%	%	%	%	%	%	%	%	%	%	%	%
16, 18, 45	8.8	22.3	15.2	31.3	46.1	40.9	2.2	1.8	1.9	66.7	70.8	68.3
16, 18, 45, **35**	10.7	30.0	19.9	37.5	58.4	41.1	2.2	1.9	2.0	78.1	76.9	77.6
16, 18, 45, 31, 33	12.3	30.0	20.7	47.5	58.4	54.7	2.0	1.9	2.0	72.9	80.0	75.8
16, 18, 45, 31, 33, **35**	13.9	36.5	24.6	52.1	67.4	62.0	2.1	2.1	2.1	84.4	86.2	85.1
16, 18, 45, 31, 33, 52, 58	18.0	40.4	28.6	64.6	77.5	73.0	2.2	2.0	2.0	78.1	83.1	80.1
16, 18, 45, 31, 33, 52, 58, **35**	19.0	45.4	31.5	66.6	84.3	78.1	2.2	2.0	2.1	89.6	89.2	89.4

*NNT= Number Needed to Treat to address one case of CIN3+ ; ** Estimated proportion of cervical cancers prevented by detection and treatment

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DISCUSSION AND CONCLUSIONS

Study conclusions

- This study demonstrated that by screening the study population with the 6-type mRNA test, **treatment of 25%** of the total population is needed
- This approach has the potential to prevent **85% of ICC cases**
- Without any further triage, around 2 women will need to be treated to manage a single **current CIN3+ case**
- This low number highlights the **programmatic efficiency** and **clinical impact** of mRNA-based screening using a limited number of genotypes
- The data for HIV-positive women and HIV-negative women should be used separately to generalize these findings
- **Screen-and-treat using mRNA testing with a limited number of HPV types (either 6 types or 8 types) is a promising strategy for cervical cancer prevention in resource-constrained settings**

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