HPV The step daughter of the TB epidemic

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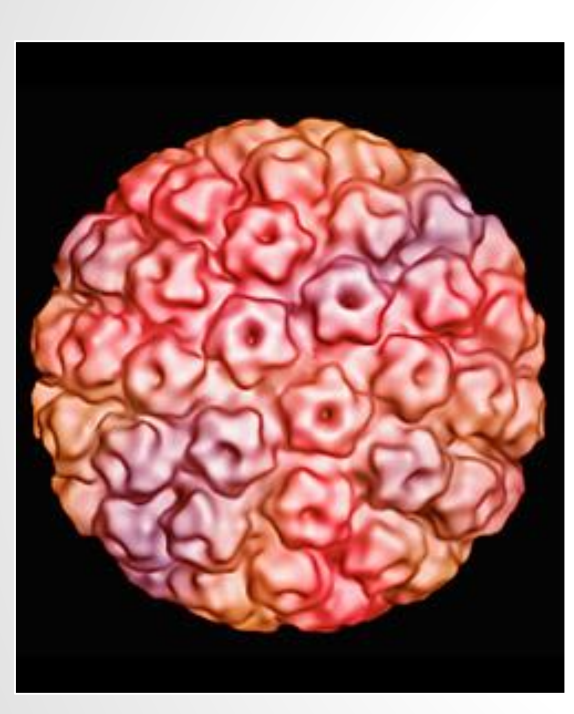
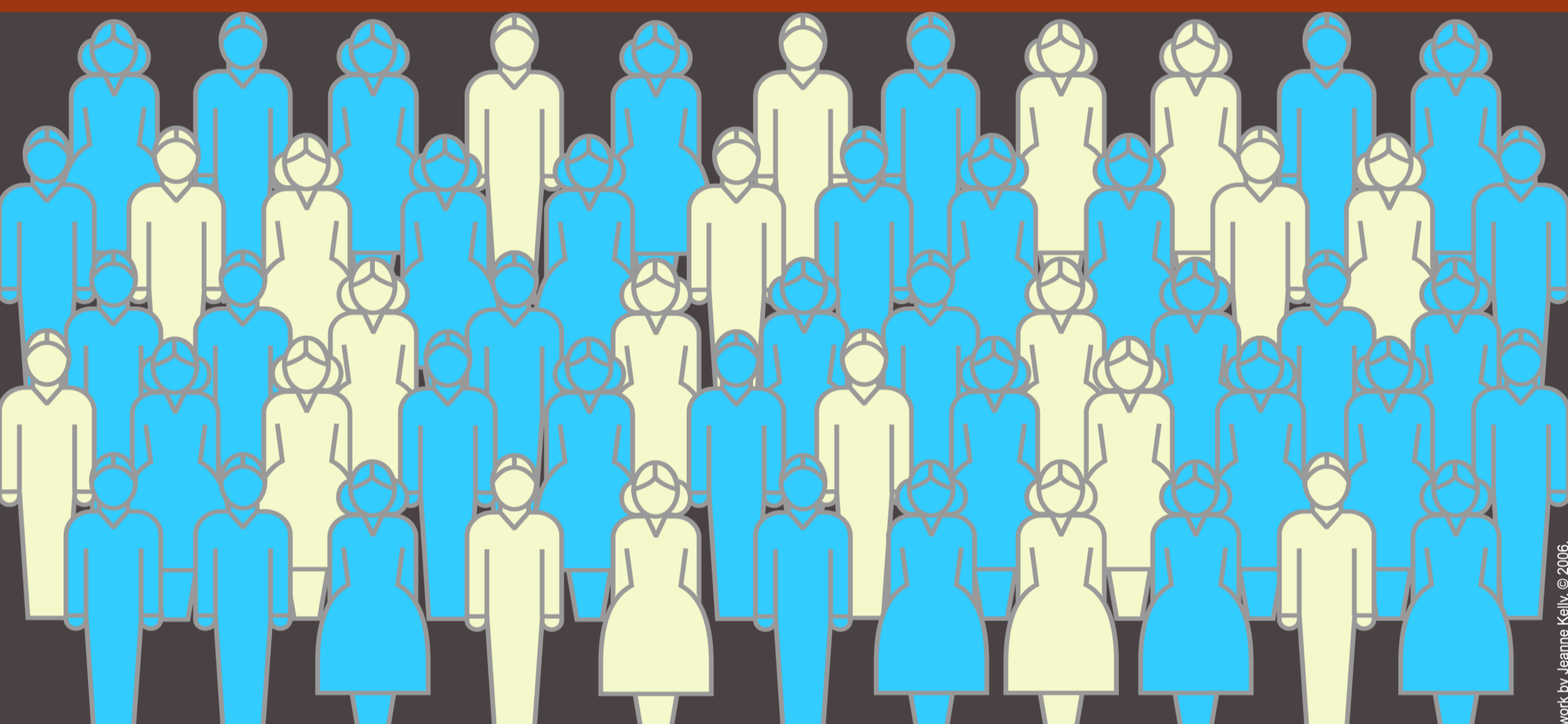
South African Clinician HIV Society
Sept 2014

Human papillomavirus (HPV)



- **Nonenveloped double-stranded DNA virus**
- **Epitheliotropic, obligatory intracellular parasite**
- >150 types identified
- ~ 40 anogenital types
  - Oncogenic (“High-risk”) types: **16, 18**, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
  - Possibly oncogenic types: 26,53, 66,67, 70,73, 82
  - Non-oncogenic /unknown oncogenic types include: 6, 11, 40, 42, 54, 55,61, 62, 64, 69, 71, 72, 81, 83, 84, CP6108, IS39

- HPV is the most common sexually transmitted virus
- At least 70 percent of sexually active persons will be infected with genital HPV at some time in their lives. HPV infects both men and women.
- Not all women with HPV will get Ca Cervix but almost all cervical cancers have detectable “high-risk” HPV DNA



Estimates of Global Burden of HPV Associated Cancer Munoz-Iarc

- 100% cervical cancers (Type 16, 18)
  (275,000 deaths world wide 88% in RLCs predicted to increase to 430,000 deaths by 2030 if nothing done)
- 86% anal cancers (60X risk in HIV MSM in USA)
- 30% of cancers of the vulva, vagina and penis
- 55% of cancers of the oropharynx
- 10% of cancers of larynx and oral cavity
- ? Squamous Cell Carcinoma of the Conjunctiva

Proportion of total cancer cases due to HPV

Giuliano et al Int J Cancer 2014

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TREATING HEALTH SERIOUSLY

Region	Female	Male
India	26.9	1.8
Sub-Saharan Africa	25.0	0.6
Other Oceania	17.5	0.5
Other Central Asia	16.2	0.7
South. America	15.6	0.6
Other East. Asia	10.1	0.5
China	6.5	0.1
North. Africa and West. Asia	5.4	0.3
Europe	4.5	0.7
Japan	3.8	0.3
North. America	2.5	0.9
Australia / New Zealand	2.1	0.5

Female Male

World Prevalence of Cervical Cancer

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TREATING HEALTH SERIOUSLY

Europe
59,931 cases/yr
HPV 16/18
74%

North America
14,670 cases/yr
HPV 16/18
76%

Asia
265,884
cases/yr
HPV
16/18
67%

Latin America
71,862 cases/yr
HPV
16/18
65%

Africa
78,897 cases/yr
HPV 16/18
70%

Oceania
2004 cases/yr
HPV 16/18
78%

Cases per 100,000 women

- <10.0
- 10.1–20.0
- 20.1–30.0
- 30.1–40.0
- >40.0
- No data

Cancer Mortality in Sub-Saharan Africa

International Agency for Research on Cancer
World Health Organization

Mortality

66,698 (30.4%)
50,233 (22.9%)
35,427 (16.1%)
14,719 (6.7%)
10,472 (4.8%)
7,766 (3.5%)
8,688 (4.0%)
7,484 (3.4%)
8,622 (3.9%)
9,259 (4.2%)

- Cervix uteri
- Breast
- Liver
- Kaposi sarcoma
- Non-Hodgkin lymphoma
- Colorectum
- Ovary
- Oesophagus
- Stomach
- Other and unspecified

International Agency for Research on Cancer
World Health Organization

Incidence

91,233 (29.6%)
75,141 (24.4%)
64,620 (21.0%)
15,024 (4.9%)
8,198 (2.7%)
9,109 (3.0%)
9,961 (3.2%)
11,045 (3.6%)
11,125 (3.6%)
12,305 (4.0%)

The Benefit of teamwork?

TREATING HEALTH SERIOUSLY

- The benefit is for the viruses –not the host

HIV positive women have higher rates of HPV and significant diversity

- Our clinic in Jo'burg (191 women screened)
  Over 80% our women screened have an HR type of HPV
  Two women had 8 different oncogenic types
  Different types also 40% 16 then 56, 66 Firnhaber Cancer cause and prevention 2010
- ZAMBIA- 85% had HR HPV types 52, 58 ParhamGynecol Oncol 103 (1017-10220)
- BRAZIL - 38.6% HR HPV personal communication Breatriz Grinsztejn
- THAILAND- 51% HR HPV
- INDIA - 41.8% HR HPV Sahasrabuddhe et al. PLoS One 2010 5(1): e8634

Types 16 and 18 seen but also 33,35,52,53 and 81

Prevalence of HPV types by CD4 count levels

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Firnhaber et al Cancer Cause and Prevention 2010

100%
80%
60%
40%
20%
0%

HPV 16 (p<0.01)
HPV 18 (p=0.15)
HPV 33 (p=0.9)
HPV 56 (p=0.9)
HPV 59 (p=0.5)
HPV 66 (p=0.04)
Any HPV (p<0.01)
Oncogenic (p<0.01)
Multiple oncogenic (p<0.01)

<200 200-500 >500

HIV Clinical Effect on Cervical Dysplasia

- **USA** –16.2% Dysplasia (LSIL 14.1%, HSIL 2.1%)
- 4% Dysplasia in HIV negative Massad et al AIDS 2004
- **Brazil** 26.7% Dysplasia (LSIL 21% HSIL 5.7%) personal communication Professor Breatriz Grinsztejn
- **Zambia** 76% Dysplasia (HSIL 33% 43% LSIL) Parham et al Gynecol Oncol 2008
- **South Africa** 51% Dysplasia (HSIL 18% and 23.5% LSIL) Firnhaber et al Cancer Causes Control epub 1 Dec 2009

SA Rural areas unpublished confirmed reports of 60% HSIL

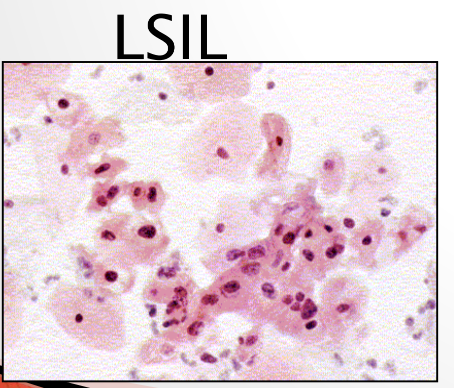
CD4 : A Risk Factor for Cervical Dysplasia

- CD4 count level was inversely associated with an increased risk of abnormal cervical cytology.
- For CD4 >500 versus <200:

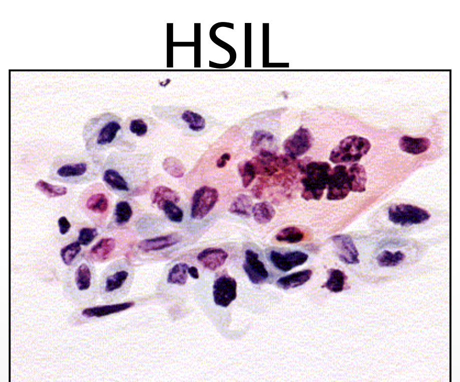
  LSIL : OR=1.3 (1.1-1.6)

  HSIL: OR=3.2 (1.4-7.2)

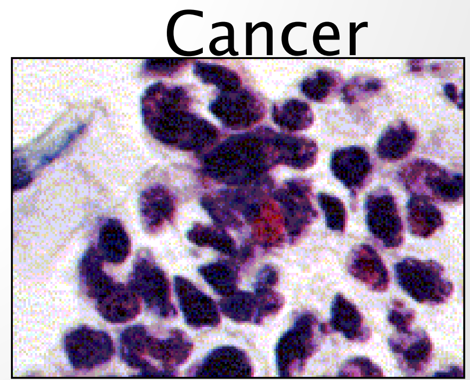
LSIL



HSIL



Cancer



Progression Rates

CD4 and Progression

- any from Normal or LSIL

Rate
(per 100 woman-years)

25
20
15
10
5
0

<200
200-349
350-499
≥500
OVERALL

CD4

= 95% CI

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HAART and Progression

25
20
15
10
5
0

ART
No ART
OVERALL

= 95% CI

Cervical Cancer and HIV

"The doctor of the future will give no medicine, but will interest his patients in the care of the human body, in diet, and in the cause and prevention of disease."

Challenges for Screening

- Zambia –Women need permission to screen from male partner
- India – Reluctance for male health care providers to perform screening/procedures
- South Africa- myths of loss of fertility and sexual drive
- Another disease
- Infrastructure issues (electricity, water)
- Another queue
- Transportation costs, time of work and child care

When the woman gets to the clinic

- She may not get the Pap smear due to long queues/overwhelm staff (Coverage in many clinics less than 30% or so)
- Pap smear if done- high rates of inadequacy (>50% in some clinics)
- Results sit at clinic and never placed in file
- Referred for Colposcopy /LEEP appointment in 6 to 12 months

Visual Inspection of the Cervix– VIA See and Treat

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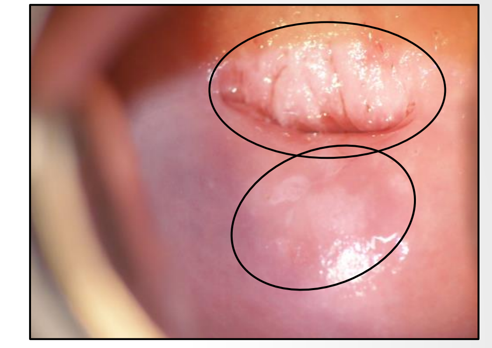
Place 5% acetic acid or Iodine on the cervix

White areas consider abnormal

Freeze with cryotherapy

using N2O or CO2



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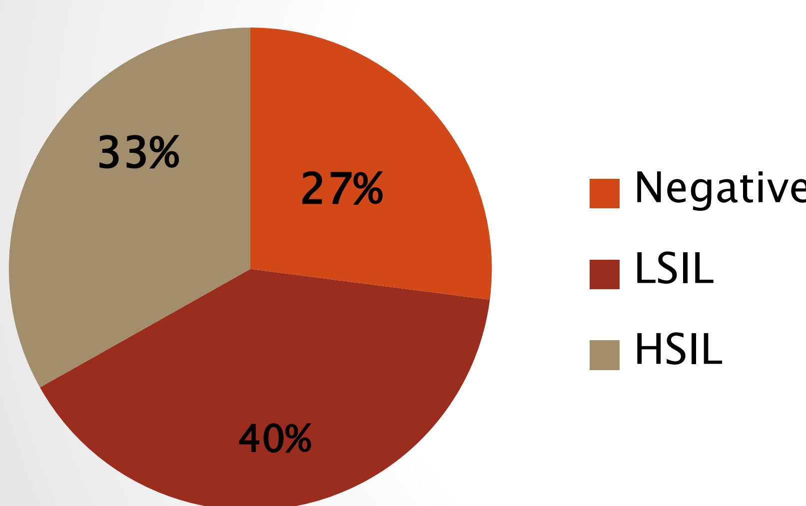
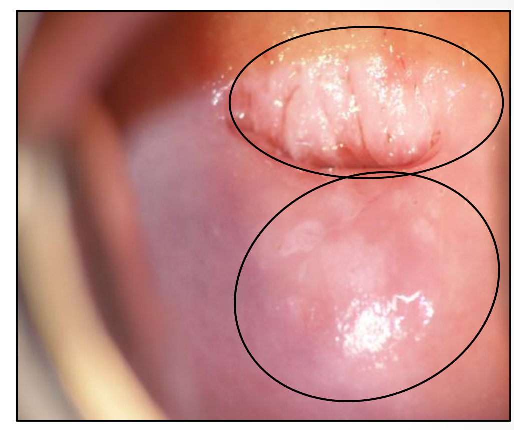
Results

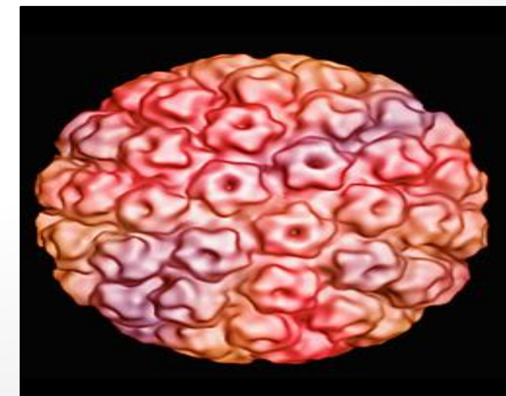
Pap smear Results



- VIA + 45.0%



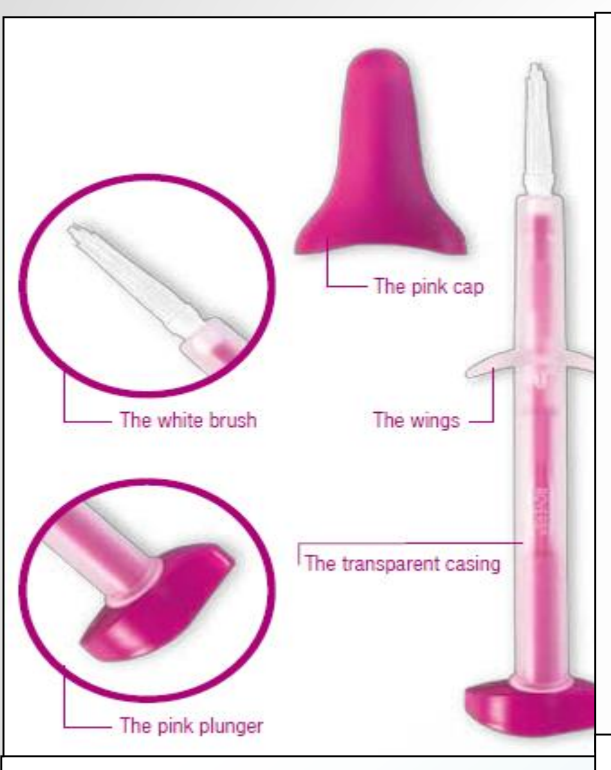
- HPV + 60.9%

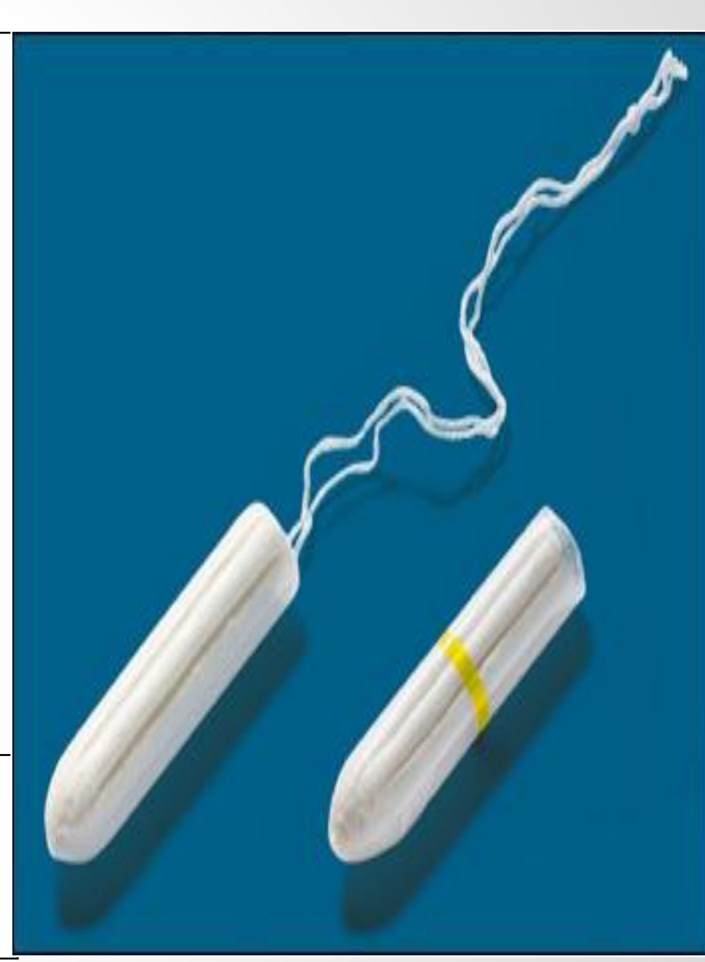


Sensitivity /Specificity

	CIN2+ (N=310)		CIN3+ (N=102)	
	Sensitivity 95% CI	Specificity 95% CI	Sensitivity 95% CI	Specificity 95% CI
Cytology	75.8% (70.8-80.8)	83.4% (80.9-85.9)	94.5% (89.8-99.2)	72.7% (70.0-75.3)
VIA	75.5% (70.5-80.4)	68.1% (65.0-71.3)	76.2% (67.9-84.5)	58.9% (56.0-61.9)
HPV	91.9% (88.5-95.3)	51.4% (48.0-54.8)	97.9% (95.0-100)	42.8% (39.8-45.7)

HPV Self testing





HPV testing Xpert

- Xpert for HPV Tests 14 different HR HPV
- FDA approved for TB machines all over Sub-Saharan Africa
- Potential for POC results 1 hour
- Validation done against Cobas and Digene HC with histology CIN 2+ (at 7 sites in USA N=697) Einstein MH et al JCM June 2014
- Sensitivity the same for Cobas (90.8%) better than Digene 90.8 vs 81.6%)
- Specificity better than cobas (42.6% vs 39.6%)
- Less specific than dHC (42.2% vs 47.7%)

Early results of Anal study

Goeieman B et al Croi 2014

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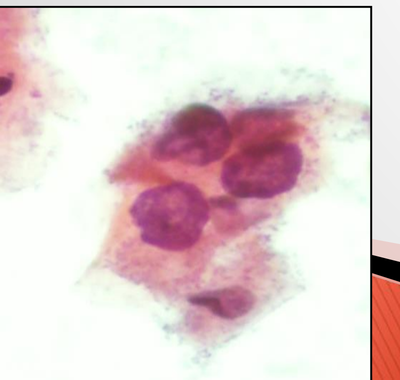
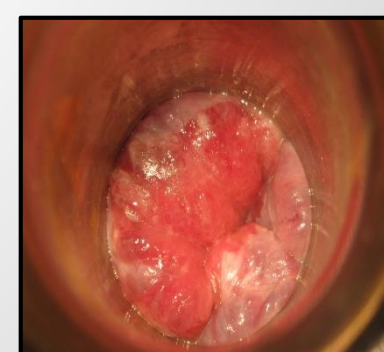
TREATING HEALTH SERIOUSLY

- Performed at HIV clinic in Johannesburg
- 88 women results 42% infected with HR HPV
- 90% had abnormal cytology (72% LSIL and 18% HSIL)
- 10% HGAIN on HRA
- Decrease rates of HR HPV with higher CD4 and longer time on ARV
- Decrease rates of HSIL with higher CD4
- 200 women on cohort now analysis pending





Let us prevent another epidemic—SCREEN/TREAT!

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- Cervical Cancer screening/treatment imperative!
- HIV seropositive women are living longer now RLC
- Completely Preventable cancer
- No diagnostic/screening system is perfect
- We need to push for the political will to start screening

"Every woman has the right to live a life free from cervical cancer"

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THANK YOU

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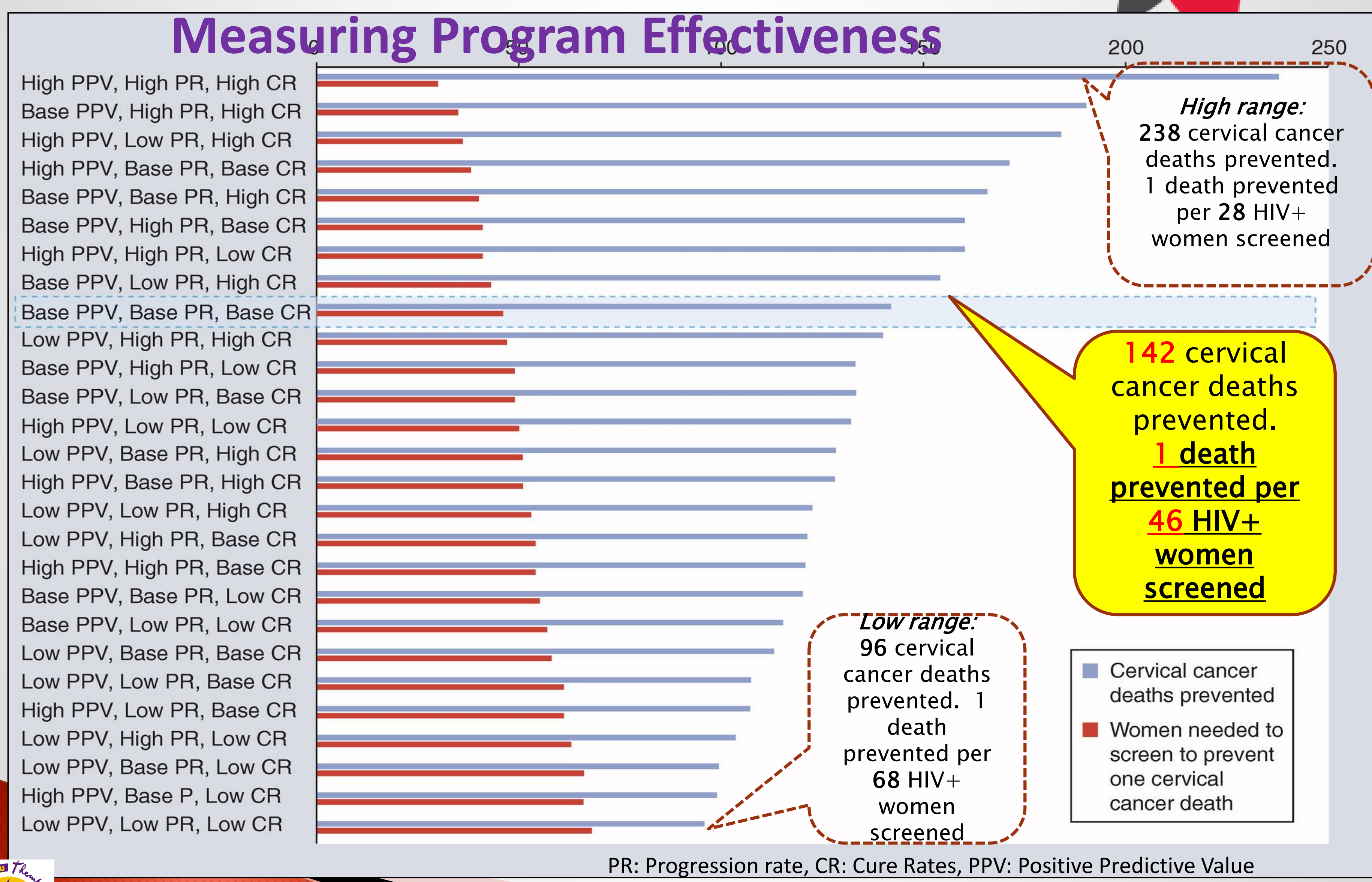
TREATING HEALTH SERIOUSLY

- Department of Health Gauteng South Africa
- Melinda Wilson Pepfar/ USAID
- Patients at the Themba Lethu Clinic Helen Joseph Hospital
- <u>Cervical Cancer Implementation/ Research team</u>
- Sr Sophie William/ Maureen Siminya/ Nthombiyenkosi Rakhombe/ Sibongile Ramotshela/Patricia Kegorilwe - Right to Care
- Avril Swarts-Clinical HIV Research Unit
- Dr Tim Wilkin- Cornell University NY
- Dr Mark Faesen - Right to Care - OB/GYN
- Prof Simon Levin - Right to Care/University of Wits/ Department OB/GYN
- Dr Bridgette Goeieman MO - Right to Care
- Jennifer Smith/Lu Mao/Michael Hudgens - University of North Carolina
- Anna-Lise Williamson/Bruce Allan - University of Cape Town
- First for Women

HIV-infected women undergoing cervical cancer screening in Zambia



PR: Progression rate, CR: Cure Rates, PPV: Positive Predictive Value

Parham GP, Mwanahamuntu MH, Sahasrabuddhe VV, et al. HIV Therapy. 2010; 4, 713-722.

HPV vaccine controversy in India

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- HPV vaccine implementation project halted by Indian Govt. in April 2010—after reports of 5 deaths among vaccinated girls
  - Deaths later proved to be unrelated to vaccination (2 suicides, 1 malaria, 1 snake bite, 1 drowning)
  - Other HPV vaccine studies/trials in India also halted, but private sector availability not halted
- In response to outcry (mainly by anti-vaccine groups) ---> probe by Indian Parliamentary investigative committee---released in 2013—blamed poor project review/approvals, sloppy project implementation, and ethical issues re: consent of vulnerable, tribal populations.
- Supreme Court of India, in response to Public Interest Litigations, is now reviewing the 2008 HPV vaccine licensure decisions by the Indian regulatory body (e.g., why no efficacy trials were conducted in India)--final decision scheduled for late October 2014.