HPV The step daughter of the TB epidemic

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South African Clinician HIV Society
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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
100% cervical cancers (Type 16, 18) (275,000 deaths worldwide, 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

<table>
<thead>
<tr>
<th>Region</th>
<th>Female (Proportion)</th>
<th>Male (Proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>26.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>25.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Other Oceania</td>
<td>17.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Other Central Asia</td>
<td>16.2</td>
<td>0.7</td>
</tr>
<tr>
<td>South. America</td>
<td>15.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Other East. Asia</td>
<td>10.1</td>
<td>0.5</td>
</tr>
<tr>
<td>China</td>
<td>6.5</td>
<td>0.1</td>
</tr>
<tr>
<td>North. Africa and West. Asia</td>
<td>5.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Europe</td>
<td>4.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Japan</td>
<td>3.8</td>
<td>0.3</td>
</tr>
<tr>
<td>North. America</td>
<td>2.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Australia / New Zealand</td>
<td>2.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>
World Prevalence of Cervical Cancer

North America
14,670 cases/yr

Europe
59,931 cases/yr

Asia
265,884 cases/yr

Latin America
71,862 cases/yr

Africa
78,897 cases/yr

Oceania
2004 cases/yr

Cases per 100,000 women:
- <10.0
- 10.1–20.0
- 20.1–30.0
- 30.1–40.0
- >40.0
- No data

HPV 16/18
- 76%
- 74%
- 67%
- 65%
- 70%
- 78%
Cancer Mortality in Sub-Saharan Africa

Mortality

- Cervix uteri: 66,698 (30.4%)
- Breast: 8,888 (4.0%)
- Liver: 7,404 (3.4%)
- Kaposi sarcoma: 7,404 (3.4%)
- Non-Hodgkin lymphoma: 8,622 (3.8%)
- Colorectum: 9,256 (4.2%)
- Ovary: 14,718 (6.7%)
- Oesophagus: 10,472 (4.8%)
- Stomach: 50,233 (22.8%)
- Other and unspecified: 35,427 (16.1%)

Incidence

- Cervix uteri: 91,233 (29.6%)
- Breast: 75,141 (24.4%)
- Liver: 8,188 (2.7%)
- Kaposi sarcoma: 9,108 (3.0%)
- Non-Hodgkin lymphoma: 8,881 (3.2%)
- Colorectum: 11,045 (3.6%)
- Ovary: 11,125 (3.6%)
- Oesophagus: 15,024 (4.9%)
- Stomach: 64,620 (21.0%)
- Other and unspecified: 12,005 (4.0%)
The Benefit of teamwork?

- 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
  - (1017–10220)
  - Parham Gynecol Oncol 103

- **BRAZIL** – 38.6% HR HPV
  - personal communication Breatriz Grinsztejn

- **THAILAND** – 51% HR HPV

- **INDIA** – 41.8% HR HPV

Types 16 and 18 seen but also 33, 35, 52, 53 and 81
Firnhaber et al Cancer Cause and Prevention 2010

Prevalence of HPV types by CD4 count levels
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 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)
Progression Rates

Rate (per 100 woman-years)

= 95% CI

Baseline Pap

Rate

LSIL/HSIL

LSIL

HSIL

LSIL/HSIL (OVERALL)
CD4 and Progression

Progression Rates
- any from Normal or LSIL

Rate
(per 100 woman-years)

= 95% CI

CD4
HAART and Progression

Rate
(per 100 woman-years)

= 95% CI

<table>
<thead>
<tr>
<th></th>
<th>ART</th>
<th>No ART</th>
<th>OVERALL</th>
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<tbody>
<tr>
<td>Rate</td>
<td>15</td>
<td>25</td>
<td>10</td>
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</table>

= 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

Place 5% acetic acid or Iodine on the cervix
White areas consider abnormal
Freeze with cryotherapy using N2O or CO2
Results

Pap smear Results

- VIA + 45.0%
- HPV + 60.9%

- 33% Negative
- 27% LSIL
- 40% HSIL
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<th>CIN2+ (N=310)</th>
<th>CIN3+ (N=102)</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity 95% CI</td>
<td>Specificity 95% CI</td>
</tr>
<tr>
<td>Cytology</td>
<td>75.8% (70.8-80.8)</td>
<td>83.4% (80.9-85.9)</td>
</tr>
<tr>
<td>VIA</td>
<td>75.5% (70.5-80.4)</td>
<td>68.1% (65.0-71.3)</td>
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<tr>
<td>HPV</td>
<td>91.9% (88.5-95.3)</td>
<td>51.4% (48.0-54.8)</td>
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HPV Self testing

- The pink cap
- The white brush
- The wings
- The transparent casing
- The pink plunger

evalyn® brush

delphi bioscience
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%)
Perform 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!

- 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”
THANK YOU

- Department of Health Gauteng South Africa
- Melinda Wilson Pepfar/ USAID
- Patients at the Themba Lethu Clinic Helen Joseph Hospital
- **Cervical Cancer Implementation/ Research team**
  - 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

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<tr>
<th>Measuring Program Effectiveness</th>
<th>PR: Progression rate, CR: Cure Rates, PPV: Positive Predictive Value</th>
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<tbody>
<tr>
<td>High PPV, High PR, High CR</td>
<td>142 cervical cancer deaths prevented. 1 death prevented per 46 HIV+ women screened</td>
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<tr>
<td>Base PPV, High PR, High CR</td>
<td></td>
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<tr>
<td>High PPV, Low PR, High CR</td>
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<tr>
<td>Base PPV, Base PR, Base CR</td>
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<tr>
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<tr>
<td>Low PPV, Low PR, Low CR</td>
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High range: 238 cervical cancer deaths prevented. 1 death prevented per 28 HIV+ women screened.

Low range: 96 cervical cancer deaths prevented. 1 death prevented per 68 HIV+ women screened.

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

HPV vaccine controversy in India

- 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.