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Our Issues, Our Drugs, Our Patients

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Cervical Cancer and HIV

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South African Clinician HIV Society
April 2016
Age-standardized incidence rate of cervical cancer

Globocan 2012; WHO/ICO, 2014
Cancer Mortality in Sub-Saharan Africa

**Mortality**
- Cervix uteri: 50,233 (22.8%)
- Breast: 35,427 (16.1%)
- Liver: 14,718 (6.7%)
- Kaposi sarcoma: 10,472 (4.8%)
- Non-Hodgkin lymphoma: 9,222 (3.9%)
- Colorectum: 8,622 (3.9%)
- Ovary: 8,622 (3.9%)
- Oesophagus: 9,259 (4.2%)

**Incidence**
- Cervix uteri: 91,233 (29.6%)
- Breast: 75,141 (24.4%)
- Liver: 64,620 (21.0%)
- Kaposi sarcoma: 15,024 (4.9%)
- Non-Hodgkin lymphoma: 11,045 (3.6%)
- Colorectum: 11,125 (3.6%)
- Ovary: 11,125 (3.6%)
- Oesophagus: 12,305 (4.0%)
- Other and unspecified: 8,198 (2.7%)
- Stomach: 9,109 (3.0%)
- Other and unspecified: 9,961 (3.2%)

*Source: International Agency for Research on Cancer (IARC)*
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
Proportion of total cancer cases due to HPV

Giuliano et al Int J Cancer 2014
The Benefit of teamwork?

• The benefit is for the viruses – not the host
215 women with cervical cancer were enrolled, (67.9%) HIV-infected, (27.0%) HIV-uninfected, and (5.1%) with unknown HIV status.

Only 8 (3.7%) cancers were identified by screening and symptoms prompted diagnosis in remaining 207 (96.3%).

HIV-infected women were younger than women without HIV—median age 41.3 and 57.6 years, respectively (P<0.001).

Median CD4 count for HIV-infected women was 406 cells/μL (IQR 283 - 550 cells/μL)
Results Continue

Dryden-Peterson et al CROI 2016 abstract 711

- 86.8% were receiving ART (median duration 4.4 years).
- 35.0% HIV-infected and 16.1% HIV-uninfected women died during follow-up (most cancer related).
- Median survival for HIV-infected women was shorter 16.6 versus 24.3 months, respectively (P=0.007).
- HIV-infection associated with increased mortality (HR 2.66, 95% CI 1.3 - 5.5, P=0.008).
- Among women with HIV, CD4 cell count or ART duration was not associated with survival.
Survival Probability

MONTHS

1: HIV-Infected
2: HIV-Uninfected

Censored
Logrank p=0.0067
8479 incident cases recorded in Botswana National Cancer Registry from 2003 to 2009 were utilized.

- A total of 850 patients with HIV and cancer were followed.
  - Median 12.2 months (IQR 6.1 to 24.3 months)
  - 1.2% loss to follow-up
Mortality Rates (with 5 year survival rates)  

<table>
<thead>
<tr>
<th>Disease</th>
<th>5-Year Mortality</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>KS</td>
<td>52.5%</td>
<td>(39.0 - 59.9%)</td>
</tr>
<tr>
<td>Cervix</td>
<td>5.7%</td>
<td>(1.3 - 12.9%)</td>
</tr>
<tr>
<td>NHL</td>
<td>40.5%</td>
<td>(13.1 - 53.0%)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>5.2%</td>
<td>(0.0 - 25.8%)</td>
</tr>
<tr>
<td>Breast</td>
<td>20.5%</td>
<td>(2.1 - 37.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>17.0%</td>
<td>(7.9 - 25.9%)</td>
</tr>
</tbody>
</table>

For each condition, the mortality rate is shown along with the 95% confidence interval (CI).
Overall cancer mortality increased, 1.2% annually (95% CI 0.7 to 3.1%), and mortality due to tuberculosis declined markedly.

- Cervical cancer mortality increased substantially, 13.3% annually (95% CI 11.7 to 14.9%)
Cervical Cancer and HIV in South Africa

- Significantly increased risk CaCx in HIV infected women (OR 1.6 95% CI 1.2 – 2.3) (Setas et al., 2000,2007).

- In JHB, invasive cervical cancer presents almost 10 years earlier than HIV seronegative women (Lomalisa et al., 2000).

- HIV positive women are at a greater risk of lower genital tract neoplasias including vulvar and anal cancers. (Ferenczy et al.,2003).

- Our clinic seeing rates of 135/100,000 per women of Invasive cervical cancer
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.”
Infection with HPV

Persistent / Recurrent HPV infection

HIV negative around late 40s-50s

HIV positive late 20s – mid 30s

Invasive Cervical Cancer
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
Xpert HR-HPV

1. Obtain one appropriately collected and labeled cervical specimen.*
2. Transfer 1 mL of cervical specimen to the cartridge.
3. Insert cartridge and start assay. Results in less than 60 minutes.

Participants: 1161 HIV-positive women

Xpert® HPV is a qualitative real-time PCR test for automated and rapid detection of Human Papillomaviruses (HPV).
Overall agreement was 90% between two tests.

The agreement beyond chance (Cohen’s kappa) was 0.78 (95% CI: 0.74-0.82) indicating excellent agreement.

Discordant results were due to the influence of lower HPV DNA amounts as indicated by lower RLU in hc2 and high Ct in Xpert (P<0.0001).
## Xpert performance for CIN2/3

<table>
<thead>
<tr>
<th></th>
<th>CIN2/3</th>
<th></th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>hc2 positive</strong></td>
<td></td>
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</tr>
<tr>
<td>Sensitivity</td>
<td>91.5% (87.2-95.8)</td>
<td>51.0% (47.6-54.5)</td>
<td>42.1% (38.4-45.8)</td>
<td>93.9% (90.7-97.1)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Xpert HR-HPV positive</strong></td>
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<tr>
<td>Sensitivity</td>
<td>88.3% (83.6-93.0)</td>
<td>48.4% (44.9-51.9)</td>
<td>40.1% (36.5-43.8)</td>
<td>91.3% (87.6-95.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>P1 (HPV16)</strong></td>
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<tr>
<td>Sensitivity</td>
<td>31.5% (26.3-36.7)</td>
<td>93.5% (91.8-95.2)</td>
<td>65.5% (56.7-74.2)</td>
<td>77.7% (74.9-80.5)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
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<tr>
<td><strong>P2 (HPV18/45)</strong></td>
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<tr>
<td>Sensitivity</td>
<td>30.1% (25.0-35.3)</td>
<td>85.6% (83.2-88.0)</td>
<td>45.0% (38.1-51.8)</td>
<td>75.8% (72.8-78.9)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
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<tr>
<td><strong>P3 (HPV31/33/35/52/58)</strong></td>
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<tr>
<td>Sensitivity</td>
<td>61.1% (55.4-66.8)</td>
<td>71.9% (68.8-75.0)</td>
<td>45.9% (41.0-50.7)</td>
<td>82.6% (79.4-85.8)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P4 (HPV51/59)</strong></td>
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</tr>
<tr>
<td>Sensitivity</td>
<td>18.8% (14.5-23.2)</td>
<td>89.7% (87.6-91.8)</td>
<td>41.7% (33.5-49.9)</td>
<td>73.9% (70.9-76.8)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P5 (HPV39/68/56/66)</strong></td>
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<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>33.6% (28.3-38.9)</td>
<td>80.7% (78.0-83.5)</td>
<td>40.7% (34.7-46.7)</td>
<td>75.6% (72.4-78.8)</td>
</tr>
</tbody>
</table>

CIN: cervical intraepithelial neoplasia
Relationship between the amount of DNA and the prevalence of CIN2+

Women infected with HPV16, HPV18/45 or HPV31/33/35/52/58 were found to have significantly higher amounts of HPV DNA detected for those with CIN2+ compared to those without CIN2+, P<0.0001 for each.
“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
<table>
<thead>
<tr>
<th></th>
<th>CIN2+ (N=310)</th>
<th></th>
<th>CIN3+ (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cytology</td>
<td>75.8%</td>
<td>83.4%</td>
<td>94.5%</td>
</tr>
<tr>
<td></td>
<td>(70.8-80.8)</td>
<td>(80.9-85.9)</td>
<td>(89.8-99.2)</td>
</tr>
<tr>
<td>VIA</td>
<td>75.5%</td>
<td>68.1%</td>
<td>76.2%</td>
</tr>
<tr>
<td></td>
<td>(70.5-80.4)</td>
<td>(65.0-71.3)</td>
<td>(67.9-84.5)</td>
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<tr>
<td>HPV</td>
<td>91.9%</td>
<td>51.4%</td>
<td>97.9%</td>
</tr>
<tr>
<td></td>
<td>(88.5-95.3)</td>
<td>(48.0-54.8)</td>
<td>(95.0-100)</td>
</tr>
</tbody>
</table>
HIV-infected women undergoing cervical cancer screening in Zambia: Measuring Program Effectiveness


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