Key Points:

- HPV Relevant & Common in Caribbean
- Many HPV Disease Assoc- Importantly Cancer
- Special Considerations for People Living With HIV/AIDS
- We Can Screen for / Prevent HPV and Associated Diseases
- Discuss Effective Means of Prevention
Human Papillomavirus 101

- Most Common STI Worldwide
  - Caribbean among highest incidence
- Double Stranded DNA Virus
- > 100 types
  - 40 affect genital area
- Major Etiological Agent of Cervical Cancer/Anogenital
- More Common in HIV Infection
Global Epidemiology:


- 10% Worldwide Prevalence - (291 million ♀ Carriers)

  - 22.1% Africa (North)
  - 20.4% Central America and Mexico
  - 11.3% North America
  - 8.1% Europe
  - 8.0% Asia
Caribbean Epidemiology

- 14 Caribbean Country Review by C. Ragin et al. HPV Prevalence in Healthy Women:
  - 57.5% Overall Higher than US Statistics
  - 81% Jamaica (2009)
  - 35% Tobago (2007)

  - 40.6% Trinidad
<table>
<thead>
<tr>
<th>Publication</th>
<th>N</th>
<th>Source</th>
<th>Population Prevalence (%)</th>
<th>Median Age (years)</th>
<th>Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jamaica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strickler et al. 1999</td>
<td>94</td>
<td>HP</td>
<td>13.8 (7.6–22.5)</td>
<td>37</td>
<td>PCR</td>
</tr>
<tr>
<td>Watt et al. 2007</td>
<td>236</td>
<td>HP</td>
<td>87.7 (82.8–91.6)</td>
<td>49</td>
<td>PCR</td>
</tr>
<tr>
<td>Overall adjusted</td>
<td>330</td>
<td></td>
<td>70.8 (63.7–77.0)</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobago</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ragin et al. 2007</td>
<td>212</td>
<td>GP</td>
<td>35.4 (29.0–42.2)</td>
<td>41.5</td>
<td>PCR</td>
</tr>
<tr>
<td>Total population</td>
<td>542</td>
<td></td>
<td>57.5 (51.9–62.9)</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

All values are measures of DNA prevalence.

GP = general population; HP = hospital population; PCR = polymerase chain reaction.

*a* adjusted for each study, publication year, median age and population.

*b* adjusted for each study, publication year, country, median age and population source.
## Risk of cervical cancer with human papillomavirus

<table>
<thead>
<tr>
<th>High-risk (oncogenic or cancer-associated) types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low-risk (non-oncogenic) types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common types: 6, 11, 40, 42, 43, 44, 54, 61, 72, 81</td>
</tr>
</tbody>
</table>

Regional HPV Strain Prevalence Studies

- **Trinidad Pilot Study**
  - 310 Sexually Active Women, ages 18 – 64 yrs, health facilities
  - HPV genotyping
  - HPV Strains: HPV 52 (12.5%), HPV16 (10.3%), HPV18 and HPV 66 (8.7%) & HPV 58 (7.9%)

- **Belize City Pilot Study (Cathro et al 2008)**
  - 527 Sexually Active Women
  - HPV 16/18 prevalence
    - 2.6% normal cytology vs. 50% HGSIL
  - Most common types HPV 16, HPV 35 and HPV 58
  - Multiple infections common
# High risk HPV DNA prevalence in some Caribbean Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Specimen</th>
<th># specs</th>
<th>Any HPV%</th>
<th>16 %</th>
<th>18</th>
<th>31</th>
<th>33</th>
<th>35</th>
<th>39</th>
<th>45</th>
<th>51</th>
<th>52</th>
<th>56</th>
<th>58</th>
<th>59</th>
</tr>
</thead>
<tbody>
<tr>
<td>B'dos</td>
<td>Genital carcinoma</td>
<td>20</td>
<td>90</td>
<td>65</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cervico Vaginal lavages</td>
<td>200</td>
<td>68</td>
<td>12</td>
<td>13.5</td>
<td>12</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6.7</td>
<td>1.4</td>
<td>1.4</td>
<td>5.4</td>
<td>8.1</td>
<td>4.0</td>
</tr>
<tr>
<td>J'ca</td>
<td>CIN3/Ca</td>
<td>39</td>
<td>92</td>
<td>36</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td>13</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CIN 2</td>
<td>27</td>
<td>63</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>7</td>
<td>15</td>
<td>4</td>
<td>11</td>
<td>4.0</td>
<td>4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CIN 1</td>
<td>62</td>
<td>50</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>10</td>
<td>6.0</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASCUS</td>
<td>10</td>
<td>50</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sur</td>
<td>Cervical carcinoma</td>
<td>130</td>
<td>82</td>
<td>49</td>
<td>19</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tobago</td>
<td>Cervical cells</td>
<td>212</td>
<td>35</td>
<td>6.7</td>
<td>2.7</td>
<td>5.3</td>
<td>2.7</td>
<td>6.7</td>
<td>5.3</td>
<td>10.7</td>
<td>2.7</td>
<td>6.7</td>
<td>2.7</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>T'dad</td>
<td>Exfoliate Cervical cells</td>
<td>328</td>
<td>6.7</td>
<td>3.6</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HPV and HIV

- HPV more common in HIV sero-positive persons (Mbulawa et al 2009)

- HPV increases risk of HIV acquisition (Smith et al 2010)
HIV & HPV- A Bidirectional Relationship

- HPV prevalent in HIV infection
  - HPV Factors-
    - Viral Oncogenes:
      - E6 & E7-
        - Immortalise keratinocytes
        - p53 & Retinoblastoma protein interaction
  - HIV Factors-
    - HPV infxn. Persists-immune
    - Tat proteins drive HPV 16 & 17 replication/oncogenesis
    - E7 overexpression
HPV & HIV Co-Infection in the Caribbean

- Dames et al.
  - Bahamas (2007)
  - 67% high risk HPV prevalence among 100 HIV +ve females
  - 100% incidence high risk HPV- HGSIL

- Paulino et al.
  - Dominican republic (2010)
  - HIV +ve MSM
  - 100% incidence- HPV infection
### Some Risks for HPV Infection:

<table>
<thead>
<tr>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Median Age- 43 yrs (Caribbean Studies)</td>
<td></td>
</tr>
<tr>
<td>▫ Differs than N. American Data</td>
<td></td>
</tr>
<tr>
<td>• Sexual Activity</td>
<td></td>
</tr>
<tr>
<td>▫ Partner Number</td>
<td></td>
</tr>
<tr>
<td>• &gt; 5 Lifetime</td>
<td></td>
</tr>
<tr>
<td>▫ New Partners</td>
<td></td>
</tr>
<tr>
<td>• HIV</td>
<td></td>
</tr>
<tr>
<td>• Sexual Activity</td>
<td></td>
</tr>
<tr>
<td>▫ Partner Number</td>
<td></td>
</tr>
<tr>
<td>▫ Condom usage</td>
<td></td>
</tr>
<tr>
<td>▫ Prior STIs</td>
<td></td>
</tr>
<tr>
<td>▫ MSM</td>
<td></td>
</tr>
<tr>
<td>• Uncircumcised</td>
<td></td>
</tr>
</tbody>
</table>
HPV Manifestations

2 Major Clinical Syndromes

- Common Warts
- Genital Warts (HPV 6 & 11)
- Cervical/Genital/Anal Cancers - (HPV 16 & 18)
- Oropharyngeal Ca
- Respiratory Papillomatosis
HPV—human papilloma virus

HPV has a circular, double stranded DNA, protected by capsid proteins. More than 100 HPV-types are known. HPV16 and 18 cause 70% of all cervix cancers.

Infection by HPV
HPV infects epithelial cells in the cervical mucosa. HPV DNA integrates into the cellular genome when causing cancer.

Viral replication

~90% heal within two years

HPV DNA integrated into tumour cell DNA

0.8% develop cancer

© The Nobel Committee for Physiology or Medicine 2008
Illustration: Annika Röhl
HPV & HIV & The Cervix

- Invasive Cervical Ca
  - AIDS Defining Condition
  - RR 5.4 (Frisch et al- 2001)

- ↑ CIN Prevalence (Mandelblatt 1999)
  - Immunodeficiency Related
  - Lower clearance
Cervical Cancer

- Caribbean 3x higher than N. America
  - 85% of disease burden (Arbyn et al. 2011)
- Major Morbidity and Mortality Worldwide
- Caribbean Sub- region high mortality
Projected Cervical Cancer Burden in Latin America and the Caribbean, 2010–2030

New cases per year

Deaths per year

Number of cases/deaths

2010: 71,774
2015: 80,000
2020: 90,000
2025: 100,000
2030: 110,000

2010: 33,557
2015: 40,000
2020: 45,000
2025: 50,000
2030: 55,000

HPV & HIV & Anus

- Squamous Cell Cancer of the Anus (SCCA)
  - Biological similarities to Cervical Ca
  - Higher incidence in HIV +ve MSM (Machalek et al 2012)
    - ↑ Incidence in CART era (Screening? Survivability)

- Anal Intra-epithelial Neoplasia (AIN) prevalent in MSM (Chin-Hong et al 2004)
  - RR 3.7 vs. HIV –ve MSM
HPV- Maybe Asymptomatic

ZERO SYMPTOMS

Because HPV has no symptoms, it's hard to know if you—or your partner—is infected.
## HPV: Tackling an Epidemic

### Strategies

<table>
<thead>
<tr>
<th>Behavior Modification</th>
<th>Screening for HPV/ Cervical &amp; Anal Ca</th>
<th>Vaccines</th>
<th>Circumcision</th>
</tr>
</thead>
</table>


Behavioral Modification

• Minimize Exposure
  ▫ Number of Partners (CDC Recommendation)
  ▫ Monogamy
  ▫ Condom Use
  ▫ Counsel Patients
    • Prevention

Winer et al. Condom Use and the risk of Genital Papillomavirus Infxn. in Young Women. NEJM. 2006; 354 (25): 2654-54
Who Should be Screened for HPV?

- HPV testing routine:
  - **Women > 30 yrs w/ pap test q 5 yearly** (ACS/ASCCP/ASCP/ACOG-2012)
  - **Women ≥ 21yrs w/ ASGUS**

- **PLWHA:**
  - **Women**
    - Initial Visit & q6 monthly
  - **Men & Women**
    - Annual Anal Pap Smears recommended (Bosch et al 1995)
HPV Detection

- DNA Testing-
  - 1st test developed for routine use
  - Cervical Cancer Precursors-
    - Sensitive, not specific (high false +)
  - FDA approved (Cevista, Hybrid Capture 2, Cobas)

- RNA Testing (Novel Method)
  - Detects E6 and E7 RNA (active oncogenes)
  - Sensitivity/specificity improved

- Cellular Marker Detection (Novel)
  - p16 (product of E7 protein cellular disruption) staining
Cervical Cancer & HPV Screening
A Promise of Global Prevention for Limited Resources

- Screen at Cervical Ca Peak Incidence in Low-Resource Regions
  - 35 - 40 yrs
- One Visit “screen & treat” Strategy
- In-expensive
- Safe
- Reliably Effective
- May lower incidence by 50%
Human Papillomavirus Vaccines

- **Gardasil** – 3 doses (0, 2, 6 mo) $450.56
  - Quadrivalent
  - Targets HPV types 6, 11, 16 & 18
  - 97 to 100% Efficacy of prevention cervical precursor lesions or cancer in HPV-naïve women
  - 44% Efficacy patients w/ or w/o HPV women
  - Men-Efficacy of ano-genital lesion prevention too

- **Cervarix** – 3 doses (0, 1, 6 mo) $360
  - Bivalent
  - Targets HPV types 16 & 18
  - Comparable to Quadrivalent Vaccine
Human Papillomavirus Vaccination Recommendations

- **Women**
  - **ACS/ACIP/AAP/ACOG**
    - 11 – 12 yrs
    - “Catch-up”: 13 – 26 yrs.
  - **WHO**
    - 9 – 13 yrs.

- **Men**
  - **ACIP**
    - Males 11 -12 yrs (as young as 9yrs)
    - “Catch up”: 13- 21 yrs.
    - Some opposing views (Dz. Burden, cost effectiveness)

- **HIV Infected (Immuno-compromised)**
  - Recommended through age 26 yrs

- **Special Considerations**
  - Age > 26 yrs, pre-existing cervical abnormalities/genital warts
<table>
<thead>
<tr>
<th>Country</th>
<th>Year of implementation</th>
<th>Target population and age group</th>
<th>Catch-up age group</th>
<th>Geographic scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States*</td>
<td>2006</td>
<td>Females, 11--12 yrs</td>
<td>13--26 yrs</td>
<td>National</td>
</tr>
<tr>
<td>Canada†</td>
<td>2007</td>
<td>Females, 9--15 yrs</td>
<td>Varies</td>
<td>National</td>
</tr>
<tr>
<td>Panama</td>
<td>2008</td>
<td>Females, 10 yrs</td>
<td>None</td>
<td>National</td>
</tr>
<tr>
<td>Mexico§</td>
<td>2008</td>
<td>Females, 9--12 yrs</td>
<td>Varies</td>
<td>Partial (5%)</td>
</tr>
</tbody>
</table>

* In the United States, quadrivalent HPV vaccine is approved by the Food and Drug Administration for use in females and males; the Advisory Committee on Immunization Practices (ACIP) states that quadrivalent HPV vaccine may be given to males aged 9--26 years, but currently it is not part of the routine immunization schedule for males.

† In Canada, quadrivalent HPV vaccine is approved for use in both females and males aged 9--26 years and females up to age 45 years by Health Canada; no recommendations from the National Advisory Committee on Immunization currently exist for women aged >26 years or for males of any age. Target ages vary across provinces and territories; the upper catch-up age in some jurisdictions ranges from 15 to 26 years.

§ In Mexico, target age and catch-up age ranges varied by year, with an upper catch-up age as high as 16 years.
HPV Vaccination Programmes

- **Strategies**
  - Ladner et al. 2012
  - Eight HPV Vaccination Programs in Low Income Countries
  - 87,580 girls
  - 3 Programs (school delivery, health facility based, both “mixed models”)
  - Mean vaccine coverage - 87.8%
  - Adherence b/t dose 1 and 3 – 90.9%
  - “Mixed models- highest success
MINISTER of Health Dr Perry Gomez (at microphone) said the Government of The Bahamas and officials from the Ministry of Health are in negotiations with the Merck pharmaceutical company that will lead to the introduction of the Human Papilloma Virus (HPV) vaccine into the public health system. The availability of the vaccine at public facilities is expected to decrease the incidence of cancer of the cervix and eventually lead to the elimination of cancer of the cervix. Dr Delon Brennen, Deputy Chief Medical Officer, Ministry of Health is pictured at left of photo.

Photo: Patrick Hanna/BIS

Govt in talks over HPV vaccine

THE government is in discussions with the pharmaceutical company Merck regarding the introduction of the Human Papilloma Virus (HPV). Vaccine for women who are most at risk of contracting cervical cancer, Minister of Health, Dr Perry Gomez said.

Officials say the introduction of HPV vaccine into the public health system will provide equal access for those women not able to afford private visits, and is expected to improve the health of women while also decreasing the mental as well as public health, when only the private well-off girl has access to a vaccine that can prevent her from getting cancer of the cervix and the one who is unable to afford it, not have the same access? That cannot be right,” Dr Gomez said.

“I am convinced that this will improve the health of cancer of the cervix.” Dr Gomez said the opportunity for the introduction of the HPV vaccine came about as a result of his attendance at an international conference at which representatives from the world’s leading pharmaceutical companies and leading healthcare personnel, including many phy-
HPV Vaccination Challenges

- Cost of Vaccine
  - Expensive
  - Need Cost Benefit Analyses

- Vaccine Alliances/Procurement
  - Pan American Health Organisation (PAHO)
  - Global Alliance for Vaccines and Immunisation (GAVI)
HPV Vaccination Challenges

• Serotypes covered? Cross-protection
• Availability of Vaccines to Wider Public
• Pace of Global Vaccine Introduction may be slow
• Knowledge & Attitudes Towards Vaccine
• Experience in Adolescent Health Care Delivery
Male Circumcision

• Circumcised vs. No Circumcision
  ▫ Less HPV acquisition, more clearance
  ▫ HIV –ve (Gray et al. Rakai, Uganda)
    • 19.7 cases/100 person yrs intervention vs. 29.4 cases control
  ▫ HIV +ve (Serwadda et al. (Rakai, Uganda)
    • 55.3% intervention vs. 71.7% control
  ▫ Effective in reducing transmission to female partners
    • 21 infections vs. 27 infections per 100 person yrs
Summary

• HPV is common & results in high burdens of disease especially cervical cancer in our region
• HPV & HIV have a bi-directional relationship & co-infection may be more likely to cause malignant lesions
• Epidemiology of HPV different in Caribbean
• Infection maybe asymptomatic
• Behavior change, cost effective HPV testing, vaccination and male circumcision are steps towards tackling an epidemic