HPV Screening, Triage and HIV Infection

Lynette Denny
Department Obstetrics and Gynaecology, University of Cape Town/Groote Schuur Hospital
Director SA Medical Research Council Gynaecological Cancer Research Centre

Cancer in 2012 – Global Perspective*

- 14.1 million new incident cases of cancer
- 8.2 million deaths
- 32.6 million living with cancer (within 5 years of diagnosis)
- Of these majority occurred in LMICs
- 8 million new cancers (56%)
- 5.3 million of the deaths from cancer (65%)
- 15.6 million of the 5 year prevalent cases (48%)

*www.globocan.iarc.fr/

Top Ten Cancers in Women Globally – Globocan data 2012*

Breast 1924710
Colorectal 614304
Lung 583100
Stomach 514504
Cervix 167683

Top Ten Cancers in Women in Africa, Globocan 2012*

Breast 103257
Cervix 9981
Colorectal 228082
Liver 229923

HIV and Cervical Cancer

- Studies have shown that among HIV positive women there is a consistently higher incidence of:
  - HPV infection
  - Persistent HPV infection with high risk types
  - Infection with multiple types HPV
  - Cervical cancer precursors (CIN or SIL)
  - Greater failure rate of treatment
  - Cervical cancer
- Invasive cancer of the cervix proclaimed an AIDS-defining illness in 1993 (CDC)

*www.globocan.iarc.fr/
Human papillomavirus (HPV) related genital disease in the immuno-compromised host*

- Immune status has a significant impact on expression of HPV disease and response to treatment
- Reduced cytotoxic T-lymphocyte reactivity to HPV oncoproteins E6 and E7 leads to impaired ability to clear HPV
- Organ transplant patients and patients with HIV/AIDS suffer from increased rates of HPV infection with increased severity and duration of disease
- These patients are frequently infected with multiple HPV types and have been found to have a higher prevalence of HR HPV-16

HPV Control Board, 2020

Immune status has a significant impact on expression of HPV disease and response to treatment. Reduced cytotoxic T-lymphocyte reactivity to HPV oncoproteins E6 and E7 leads to impaired ability to clear HPV. Organ transplant patients and patients with HIV/AIDS suffer from increased rates of HPV infection with increased severity and duration of disease. These patients are frequently infected with multiple HPV types and have been found to have a higher prevalence of HR HPV-16.


Global Estimates of HIV for Adults and Children 2019*

- People newly infected with HIV 1.7 million
- People living with HIV 38 million
- 10.2 million adults
- 1.8 million children (0 – 14 years)
- Deaths due to AIDS-related illnesses 690 000
- 81% of all people living with HIV knew their status and about 7.1 million did not know they were living with HIV
- Access to ART 20.6 million
- Since start of epidemics 75.7 million infected and 32.7 million have died from AIDS-related illnesses

Global HIV & AIDS statistics – 2019*

- 2009: 6.4 million people accessed ART and this increased to 25.4 million in 2019
- 80% of pregnant women living with HIV have access to ART
- New antiretroviral treatments have been reduced by 80% since the peak in 1999
- In 2019 there were 1.7 million people newly infected with HIV compared to 2.8 million in 1998
- On a weekly basis 5500 women aged 15 – 24 years become infected with HIV and in SSA 5/6 new infections occur in girls aged 15 – 19 years
- TB remains leading cause of death among people living with HIV (1 in 3 AIDS-related deaths)

HPV Prevalence in HIV positive women

- Among 796 cases of invasive cervical cancer, 770 came from Africa of whom 702 (91.2%) were HPV positive
- HPV prevalence among women with LSIL cytology was 85% and in women with HSIL cytology it was 92.2%
- In women with histologically confirmed CIN 3 HPV prevalence was 98%

HPV Control Board, 2020

Cape Town Screen and Treat Study

- Randomized clinical trial
- 6553 unscreened women 35-65 years in Cape Town, South Africa*
- 14% HIV-positive at baseline
- Comparison of HPV prevalence and CIN
- 956 HIV-positive vs. 5596 negative women

* Source: www.unaids.org

**Region** | **Number of Women** | **HPV prevalence**
--- | --- | ---
Africa | 2986 | 16/02 (56.6%)
Asia | 2523 | 636 (25.2%)
Europe | 2137 | 591 (27.6%)
North America | 2427 | 821 (33.8%)
South/Central America | 1666 | 1558 (83.5%)
All regions | 11739 | 4798 (40.8%)
HR-HPV prevalence in HIV-positive and HIV-negative women:

<table>
<thead>
<tr>
<th>HIV-positive</th>
<th>HIV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 years</td>
<td>0-5 years</td>
</tr>
<tr>
<td>6-12 years</td>
<td>6-12 years</td>
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<tr>
<td>13-19 years</td>
<td>13-19 years</td>
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<tr>
<td>20-29 years</td>
<td>20-29 years</td>
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<td>30-34 years</td>
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<tr>
<td>35-39 years</td>
<td>35-39 years</td>
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<tr>
<td>40-49 years</td>
<td>40-49 years</td>
</tr>
<tr>
<td>50-59 years</td>
<td>50-59 years</td>
</tr>
<tr>
<td>60-65 years</td>
<td>60-65 years</td>
</tr>
<tr>
<td>66+ years</td>
<td>66+ years</td>
</tr>
</tbody>
</table>

Risk of CIN2+ in HIV-positive and HIV-negative women:

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>HIV-positive</th>
<th>HIV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.39</td>
<td>4.04</td>
</tr>
<tr>
<td>6</td>
<td>4.04</td>
<td>4.18</td>
</tr>
<tr>
<td>12</td>
<td>4.18</td>
<td>4.57</td>
</tr>
<tr>
<td>24</td>
<td>4.57</td>
<td>5.00</td>
</tr>
<tr>
<td>36</td>
<td>5.00</td>
<td>5.40</td>
</tr>
</tbody>
</table>

HPV-associated disease:

- Persistent infection with high-risk types of HPV is a necessary event in the pathogenesis of cervical cancer.
- Up to 80% of sexually active persons over the age of 15 will be infected with HPV at some point in their lives.
- Transmission is by skin to skin contact.
- Most infected individuals clear the infection within 8 months and the infection has no clinical consequences.
- A minority of infected individuals will demonstrate HPV-related disease.
- Glandular warts
- Respiratory papillomatosis
- Anogenital invasive disease and/or precancer.
- Head and neck cancers

Relationship HIV and HPV infection in women seroconverting:

- SA Study*

  - 5595 women aged 35–65 followed over 36 months.
  - 517 HIV-positive at enrolment.
  - 125 HIV sero-converted during trial.
  - Prior to sero-conversion, high-risk HPV positive 20.3%.
  - During sero-conversion, high-risk HPV positive 23.6%.
  - Post-sero-conversion, high-risk HPV positive 49.1%.

Elimination of Cervical Cancer: WHO Draft Strategy:

- By 2030:
  - 90% coverage of girls 9–14 years.
  - Screening with high performance test at least once in 35 years.
  - 90% coverage and 90% treatment of screen-positive women.
  - 90% coverage of affected women.
**Triage of HPV positive women in cervical cancer screening**

- Recommended strategies include:
  - HPV genotyping with HPV 16/18 and cytology
  - P16/ki-67 dual staining cytology
  - Host methylation
  - Viral methylation testing
  - Use of risk thresholds for return to primary screening, repeat testing, referral to colposcopy, immediate treatment

**Modifying HPV DNA testing to optimise specificity**

- WHO has recommended HPV-based screen and treat approach in low resource settings
- The concern however is the relatively low specificity of HPV testing in general and specifically in HIV positive women, which leads to overtreatment
- There are a number of ways of addressing this problem
- One is to use a triage test in HPV positive women (DNA, Cytology, or additional HPV tests) prior to treatment
- Our group evaluated using HPV type restriction and more stringent cut-offs on the Xpert-HPV (Cepheid) to define a positive test prior to treatment, in order to optimise specificity

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**About Xpert-HPV assay (Cepheid)**

- PCR assay that detects and types 15 types of high-risk HPV DNA
- The different HPV DNA types are grouped into 5 channels:
  - HPV 16
  - HPV 18 and/or 45
  - HPV 31, 33, 35, 52, and/or 58 (P3)
  - HPV 51 and/or 59 (P4)
  - HPV 39, 56, 66 and/or 68 (P5)
- For each channel a cycle threshold (CT) value is generated and values below CT cut-offs are defined as “positive”.

**Advantages of Xpert-HPV as POC test**

- Cartridge is preloaded with all required reagents
- Fully automated real-time PCR instrument doesn’t require “batching”
- <1 min of operator “hands-on” time
- No specialized lab skills required

**Evaluate Xpert-HPV “as is”**

<table>
<thead>
<tr>
<th>HIV-positive (CIN2+)</th>
<th>HIV-negative (CIN2+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity %</strong></td>
<td><strong>Specificity %</strong></td>
</tr>
<tr>
<td>93</td>
<td>88.3</td>
</tr>
<tr>
<td>88.3</td>
<td>63.6</td>
</tr>
<tr>
<td>87.3</td>
<td>87.3</td>
</tr>
</tbody>
</table>

- Sensitivity/Specificity %
  - Positive for any of 16, 18, 45, 31, 33, 35, 52, 58, 39, 56, 66, 68
Restrict to specific HPV types

- By restricting the result to specific HPV types in the first three channels and by changing the cycle thresholds for defining screen-positive, we attained an 85% sensitivity for the detection of histologically confirmed HSIL in the whole group.
- Specificity for HIV-negative women was 93% and for HIV-positive women was 82%.
- The best algorithm optimized Ct values for the three channels that detected HPV types 16, 18, 45, 31, 33, 35, 52, 58, 51, 59, 39, 56, 66, 68.
- These data showed that by altering the definition of a positive HPV-Expert test, specificity could be significantly increased without loss of sensitivity in both HIV-positive and HIV-negative women.
- This algorithm is ideal for low resource settings where a positive test can be linked to immediate/same day treatment, obviating the need for return visits and reducing lost to follow up.

Main findings

- Visual Assessment of Cervix is an intrinsic component of cervical cancer screening and takes on different forms:
  - Naked eye inspection of the cervix
  - VIA (with 3–5% acetic acid)
  - Colposcopic assessment with acetic acid (with or without histological sampling)

New Technologies

- Automated Visual Evaluation (AVE)
  - Capitalizes on mobile phone technology
  - MobileODT has developed the Enhanced Visual Assessment system (EVA)
  - Device is essentially a cellphone with excellent optical magnification and an enhanced light source
  - Access to internet and software has been added to the phone to augment clinical utility
  - EVA enables storage of digital images for record purposes and quality control and the potential to upload images to the cloud-based system
  - The database is able to retain patient information with key clinical information and allow for expert review
New Technologies

- The AVE system applies advances in machine-learning methods and artificial intelligence, enabling the system to perform an automated diagnosis based on digital imaging of the cervix.
- We plan to evaluate the MobileODT as an adjunct to assist and possibly replace the diagnosis of specialist colposcopy.
- To train nurse clinicians to evaluate women participating in screen and treat programmes who are HR-HPV positive.
- Utility of AVE system to detect disease in women who have undergone prior ablative therapy due to HPV positivity.

Conclusions

- Molecular testing for detection of high-risk HPV DNA is the future.
- Issue of most reliable triage will depend on resources available and desired outcome.
- Implementation of screen and treat requires more health systems evaluation.
- Qualitative research with diverse women to understand barriers and/or acceptance of screen and same-day treatment.
- How to integrate screen and treat programmes with HPV vaccination.
- Critical to success is widespread coverage with high-quality treatment of presumed preinvasive lesions.

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