Cervical cancer and HPV Associated disease in HIV positive women

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HIV and Cervical Cancer

Studies have shown that among HIV positive women 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)

Global Estimates of HIV for Adults and Children 2009 and New Infections and Deaths in 2011*

- People living with HIV: 33.3 million
  - Adults: 30.8 million
    - Women: 15.9 million
  - Children < 15 years: 2.5 million
- New HIV infections 2011: 2.6 million
- Deaths due to AIDS 2011: 1.8 million

Adults and children estimated to be living with HIV, 2011*

- Sub-Saharan Africa: 23.5 million
- Eastern Europe & Central Asia: 1.4 million
- Middle East & North Africa: 300,000
- North America: 1.4 million
- Caribbean: 230,000
- South & South-East Asia: 4.0 million
- Latin America: 1.4 million
- East Asia: 830,000
- Oceania: 53,000

Total: 34 million (31.4 – 35.9 million)

*UNAIDS Global Report 2012
Sub-Saharan Africa AIDS statistics

- Epidemic in SSA varies considerably with Southern Africa the most severely affected
- Southern Africa in **2009**
  - 11.3 million people living with HIV
  - 34% of people living with HIV resided in the 10 countries of Southern Africa
  - 31% of new infections and 34% of AIDS-related deaths documented
  - 40% of all adult women living with HIV live in Southern Africa
- 5.6 m people living with HIV live in South Africa – largest proportion in the world
Cervical Cancer

- Worldwide per year
  - 2.3 million prevalent cases
  - 500,000 new cases
  - 250,000 deaths
- 80% of new cases and deaths
- Less than 5% of global cancer resources
- Disease of *inequity of access* to health care
ASIR of cervical cancer in Africa

*Globocan 2008
ASIR and ASR of Deaths from Cervical cancer per 100 000 in different regions of Africa

- N.Africa
- Middle Africa
- W.Africa
- S.Africa
- East Africa

ASR Deaths
ASIR
## Cervical cancer in HIV positive women

<table>
<thead>
<tr>
<th>Source</th>
<th>No. women with HIV/cervical cancer</th>
<th>RR, OR or SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frisch et al (2000)* USA</td>
<td>355 cases cervix cancer</td>
<td>RR 5.4 (95% CI 3.9 – 7.2) Match cancer and AIDS registers</td>
</tr>
<tr>
<td>Tanon et al (2012)^ Benin/Coted’Ivoire</td>
<td>152 cases of cervical cancer</td>
<td>OR 7.9 (95% CI:3.8 – 16.7) multivariate analysis</td>
</tr>
<tr>
<td>Odida et al (2011)+ Uganda</td>
<td>55 women with ICC and 54 controls</td>
<td>OR 1.6 (95% CI:1.0 – 2.6) (adjusted for age and CD4 count)</td>
</tr>
<tr>
<td>Adjorlolo-Johnson et al (2010) Cote d’Ivoire#</td>
<td>132 with ICC/ 120 controls</td>
<td>OR 3.4 (95% CI:1.1 – 10.8) Logistic regression and in women positive for hr-HPV infection</td>
</tr>
<tr>
<td>Kahesa et al (2008)@ Tanzania</td>
<td>138 cases ICC/138 controls</td>
<td>OR 2.9 (95% CI: 1.4 – 5.9) Logistic regression analysis</td>
</tr>
</tbody>
</table>

*Frisch et al, J Natl Cancer Institute, 2000;92 (18):1500 -10; ^ Tanon et al PLOS one2012;7(10) e48108
@Kahesa et al. BMC Pulbic Health 2008;8:262
Prevalence and incidence of HPV infection

- Meta-analysis* of 157,879 women with normal cytology (78 studies) who underwent HPV DNA testing and the prevalence of HPV estimated:
  - Globally: 10.4%
  - Africa: 22.1%
  - Central America and Mexico: 20.4%
  - Northern America: 11.3%
  - Europe: 8.1%
  - Asia: 8.0%

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Women</th>
<th>HPV prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>489</td>
<td>56.6</td>
</tr>
<tr>
<td>Asia</td>
<td>238</td>
<td>31.1</td>
</tr>
<tr>
<td>Europe</td>
<td>340</td>
<td>32.4</td>
</tr>
<tr>
<td>North America</td>
<td>2039</td>
<td>31.4</td>
</tr>
<tr>
<td>South/Central America</td>
<td>124</td>
<td>57.3</td>
</tr>
<tr>
<td>All regions</td>
<td>3230</td>
<td>36.3</td>
</tr>
</tbody>
</table>

*Clifford et al AIDS 2006;20:2337-44
## HPV type distribution in SCC in women in Africa

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>SCC n = 570 (%)*</th>
<th>SCC N = 2402 (%)^</th>
<th>SCC N = 544 (%)+</th>
<th>SCC N = 410 (%)#</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16</td>
<td>51.2</td>
<td>53.1</td>
<td>48.0</td>
<td>49.0</td>
</tr>
<tr>
<td>HPV 18</td>
<td>15.0</td>
<td>19.8</td>
<td>23.0</td>
<td>23.0</td>
</tr>
<tr>
<td>HPV 45</td>
<td>7.1</td>
<td>11</td>
<td>10.0</td>
<td>13.0</td>
</tr>
<tr>
<td>HPV 35</td>
<td>8.7</td>
<td>4.1</td>
<td>5.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

+ de Sanjose et al. Lancet Oncol 2010 # Muwonge et al IPV 2010
HIV and Cervical Cancer Precursors

- Cytological diagnosis at baseline in 400 HIV positive women followed over 36 months in Cape Town*
  - LSIL 35%
  - HSIL 13%
  - ASC-US 7%
  - Normal 45%

Denny et al Obstet Gynecol 2008;111^6):1380 - 87
HPV Genotypes (Roche Reverse Line Blot Assay)

- Baseline HPV types (n = 397)
  - HPV 16: 60 (15%)
  - HPV 52: 60 (15%)
  - HPV 53: 59 (15%)
  - HPV 35: 57 (14%)
  - HPV 18: 44 (11%)

- Number of HPV types:
  - One: 27%
  - Two: 21%
  - Three: 12%
  - Four: 10%
  - Five and eight: 8%

- Strongly associated with Low CD4 count and high viral loads (p < 0.001)
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 +

* Denny et al, JAMA 2010
HR-HPV prevalence in HIV-positive and HIV-negative women.
Risk of CIN2+ in HIV-positive and HIV-negative women

Cumulative risk CIN2+ (%) over time:

- HIV-positive
- HIV-negative

6 months:
- HIV-positive: 3%
- HIV-negative: 2%

12 months:
- HIV-positive: 7%
- HIV-negative: 4%

24 months:
- HIV-positive: 10%
- HIV-negative: 5%

36 months:
- HIV-positive: 14%
- HIV-negative: 5%

SA HIV Clinicians 2012
<table>
<thead>
<tr>
<th>Site</th>
<th>No. of new cases 2008</th>
<th>Attributable to HPV (%)</th>
<th>No. attributable to HPV</th>
<th>Less Developed regions</th>
<th>More Developed regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>530 000</td>
<td>100%</td>
<td>530 000</td>
<td>470 000</td>
<td>180 000</td>
</tr>
<tr>
<td>Vulva</td>
<td>27 000</td>
<td>43%</td>
<td>12 000</td>
<td>4 100</td>
<td>7 500</td>
</tr>
<tr>
<td>Vagina</td>
<td>13 000</td>
<td>70%</td>
<td>9 000</td>
<td>5 700</td>
<td>3 400</td>
</tr>
<tr>
<td>Anus</td>
<td>27 000</td>
<td>88%</td>
<td>24 000</td>
<td>12 000</td>
<td>12 000</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>84 000</td>
<td>86%</td>
<td>72 000</td>
<td>66 000</td>
<td>5 900</td>
</tr>
<tr>
<td>Oro-pharynx</td>
<td>85 000</td>
<td>26%</td>
<td>22 000</td>
<td>6 400</td>
<td>15 000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>669 000</strong></td>
<td></td>
<td><strong>564 200</strong></td>
<td><strong>223 800</strong></td>
<td></td>
</tr>
</tbody>
</table>

*de Martel et al. Lancet Oncol 2012, May 9th, 1 - 9
Ano-genital Cancers

- Proportion of anal cancers associated with HPV 16 or 18 is as high as the proportion associated with cervical cancer
- Incidence of anal cancer increasing by 2% per year among men and women in general population
- Incidence highest in MSM and in HIV positive women/men
- 7 fold increase in Penile cancer in HIV infected men
- 60 fold increase in anal cancer in HIV infected men
- High rates of genital warts in both men and women, often resistant to conventional therapies

Prevention of cervical cancer in HIV positive women

• Primary prevention
  • HPV Vaccination
  • Published studies on quadrivalent vaccine in three groups
    • Children 7 – 12 years old
    • Women older than 16 years
    • Men over age 18
  • Show vaccine is safe with no impact on HIV status in terms of CD4 cell count and HIV viral load
  • Immunogenic, although may be need for booster doses
  • Longer term follow up and efficacy data awaited
Prevention of cervical cancer in HIV positive women

• Secondary prevention
  • Cytology, HPV DNA testing and VIA
  • Followed by colposcopy
  • Infrastructure for secondary prevention not available in most SSA settings
  • Currently, due to PEPFAR funding ART available free in many countries but NOT cervical cancer screening
  • Linkage between the two not structurally integrated and women cannot afford to pay for screening and ‘ecosystem’ around screening e.g treatment, histology, follow up
  • As women live longer due to ART, scenario of increasing incidence of cervical cancer if no screening and linkage between the two virally-associated diseases not made
Conclusions

• HIV and cervix cancer worlds need to work together

• Ideal method of preventing cervical cancer in HIV positive women not fully defined

• Screen and treat or even prophylactic ablation of the transformation zone in HIV positive women likely to be effective however, more long term data required

• **Cervical cancer screening and prevention should be an integral part of chronic care package for HIV positive women**