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Our Issues, Our Drugs, Our Patients

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HPV Infection and associated disease among HIV positive individuals

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Wits RHI
Outline of presentation

• Introduction

• Burden of HPV associated diseases

• The role of HIV and its interaction in HPV associated diseases

• Current prevention and treatment for HPV associated diseases

• Conclusion and Acknowledgements
Introduction

- Human papillomavirus (HPV) classified a Group 1 by IARC in 1995.
- Causative role in cervical cancer described in 1999.
- Extensive data on the burden of HPV associated diseases among women including:
  - anogenital warts, cancers of the cervix, vulva, vagina, anus, head & neck
- The recognition that HPV infection also causes a significant and growing burden of disease in men has led to increasing interest in HPV infection and disease in both heterosexual men and men who have sex with men (MSM).
- New evidence suggests that:
  - men are also have high a prevalence of HPV infection
  - Additionally they are frequently are infected with multiple HPV types
Human Papillomaviruses

• Viral structure:
  – circular double-stranded DNA genome
  – 2 capsid proteins (L1, L2)
  – 3 oncogenes (E5, E6 and E7) modulate the transformation process

• Subtype classification based on L1:
  – 100 genotypes: 40 genital, >13 linked to cancer

• “High-risk” types (HPV 16, 18, etc)
  – Cervical, anal, vulvar, vaginal, penile cancers and their precursor lesions

• “Low-risk” types (HPV 6, 11, etc)
  – Anogenital warts (AGWs)

Cancer Facts, ACS, 2003
# Incidence cancer attributable to HPV in 2008

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Number of cases</th>
<th>Number attributable to HPV</th>
<th>PAF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix uteri</td>
<td>530 000</td>
<td>530 000</td>
<td>100</td>
</tr>
<tr>
<td>Vulva</td>
<td>27 000</td>
<td>12 000</td>
<td>43</td>
</tr>
<tr>
<td>Anus</td>
<td>27 000</td>
<td>24 000</td>
<td>88</td>
</tr>
<tr>
<td>Penis</td>
<td>22 000</td>
<td>11 000</td>
<td>50</td>
</tr>
<tr>
<td>Vagina</td>
<td>13 000</td>
<td>9 000</td>
<td>70</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>85 000</td>
<td>22 000</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>700 000</strong></td>
<td><strong>610 000</strong></td>
<td><strong>86</strong></td>
</tr>
</tbody>
</table>

Forman et al., Vaccine, 2012
Incidence of AGWs

• Global estimates from a systematic review of 37 studies:
  – 160 to 289 per 100 000

• AGWs are benign but are responsible for a huge burden of morbidity and costs due to:
  – Frequent recurrence
  – Often multiple visits to the health care facilities for treatment
  – Pyschosocial distress

• Among HIV positive individuals AGWs are florid and even have a prolonged clinical course.

Patel et al., BMC Infectious disease, 2013
HIV, HPV and associated disease

• Impaired immune response increases susceptibility to
  – acquisition of HPV infection
  – reactivation of latent HPV infection

• Impaired clearance of oncogenic viral infections

• Chronic inflammation promotes carcinogenesis by
  – generation of genotoxic reactive oxygen and nitrogen species
  – procarcinogenic cytokines and growth factors

• HIV +ve individuals are more likely to have
  – prevalent and persistent HPV infection
  – to progress in pre-cancerous lesions or cancer

Phanuphak et al., J Acquir Immune Defic Syndr, 2014
Vessely et al., Annu Rev Immunol, 2011
Schottenfield et al., CA Cancer J Clin, 2006
Dubrow et al., Curr Opin Oncol, 2012
Prevalence of cervical HPV DNA by age and HIV status among 349 women in BF

Prevalence (%)

HIV+      HIV-

Age Groups

<20  20-24  25-29  30-39  >40

HIV prevalence =16%

Didelot-Rousseau et al., Br J Cancer, 2006
Prevalence of HR-HPV among 1371 HIV+ and 8050 HIV- women in Cape Town

HIV prevalence = 14.6%

McDonald AC et al., Frontiers Oncol 2014
High risk of HPV Cervical Cancer among HIV positive individuals

- Linkage studies of ART and Cancer registries show:
  - A 2- to 22-fold increase in Ca CX in HIV+ compared to HIV women.
  - Women in Southern Africa are at markedly higher risk than women in HICs.
  - Among Southern African women, incidence rates do not decline with time on ART.

<table>
<thead>
<tr>
<th>Region</th>
<th>HR (95% CI) at 2yrs after ART initiation</th>
<th>HR (95% CI) at 5yrs after ART initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>North America</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Latin America</td>
<td>2.1 (0.8-5.0)</td>
<td>2.2 (1.2-4.2)</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>8.9 (6.0-13.3)</td>
<td>12.4 (7.8-20.0)</td>
</tr>
</tbody>
</table>

Rhoner et al., CROI, 2016
Cancers among HIV positive individuals in SA

Figure: Cancer Incidence Rate in HIV-positive men and women

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Incidence Rate (Men)</th>
<th>Incidence Rate (Women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>1240</td>
<td>1353</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>437</td>
<td>246</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>477</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>141</td>
<td>126</td>
</tr>
<tr>
<td>Lip, oral cavity</td>
<td>58</td>
<td>25</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Anorectal</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Penis</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Stomach</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Breast</td>
<td>159</td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>68</td>
<td>18</td>
</tr>
<tr>
<td>Prostate</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

Incidence rate per 100,000 person years

Sengayi et al., CROI, 2016
Biological interaction between HPV and HIV

• HIV infection modifies significantly the distribution of HPV types in cervical cancer
• Low CD4+ counts are the strongest independent predictor for HPV infection and AGWs
• HPV infection is independently associated with an increased risk of HIV acquisition
• It is hypothesized that postulated new infections elicit a local immune response to clear the HPV infection
• This response recruits immune cells which may be vulnerable to infection with HIV

Naulcer et al., Journal of General Virology, 2011
Sahasrabuddhe et al., Br J Cancer, 2007
De Sanjose et al., Lancet Oncol, 2010
Smith et al., J Infect Dis, 2010
Smith-McCune., Plos 1, 2010
Risk of Acquiring HPV After First Intercourse in Female Adolescents

Cumulative risk of cervical HPV infection in female adolescents with only 1 sexual partner

Collins et al., Br J Obstet Gynaecol, 2002
HPV in Adolescents

- HIV +ve adolescents are 3 times more likely to have cytological abnormalities compared to their HIV -ve counterparts.

- A study done in Cape Town on 83 HIV +ve young women of mean age (sd) 19.9(1.1) has confirmed this.

Alder et al., Infectious Dis Obstet Gyneco, 2014
Nachman et al., Archiv Pediatrc Adolesc Med, 2009
HPV infection and the anal canal

- 1983: Areas of epithelial transformation susceptible to HPV infection share similarities with transformation zone (TZ) of cervix
- This epithelium undergoes metaplasia
- Almost all anal carcinomas arise in the TZ
- 2007 IARC concludes sufficient evidence for carcinogenicity of HPV in penis, anus, oral cavity, oropharynx, tonsils

Yang et al., *Mod Pathol*, 2015
Darragh et al., *J Low Genit Tract Dis*, 2012
Anal cancer incidence is rising

Incidence highest in MSM HIV infected individuals

Partridge, 2006
HPV infection in the head & neck

• Preference for the oropharynx not clearly understood
  – could be due to the transitional epithelium

• Tonsillar epithelium is histologically similar to the cervical and anal epithelia

• Invagination of the mucosal surface.
  – may favor virus capture and maintenance by promoting access to and infection of basal cells
  – Detection rate of HPV is much higher in oral rinse than with swabs

Frisch et al., Journal of the National Cancer Institute, 2000
Chu et al., Oncology, 2013
Read et al., Plos 1, 2012
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Frisch et al., Journal of the National Cancer Institute, 2000
Chu et al., Oncology, 2013
Read et al., Plos 1, 2012
Rising oropharyngeal cancer especially in men

Maura et al., JCO, 2015
Associations between number of oral sex partners and oral HPV prevalence

Maura et al., JCO. 2015
Effect of ART on HPV associated disease

- ART induced immune reconstitution has reduced incidence of AIDS related cancers e.g. KS and NHL
- Immune reconstitution leads to clearance of oncogenic viral infections
- ART improves life expectancy
  - lengthening exposure time to HR-HPV
  - allows for accumulation of genetic changes that increase the likelihood of cancer

Palefsky., Adv Dent Res. 2006
Shiels et al., J Natl Cancer Inst, 2011
ART and HPV associated cancer

• Effect on HPV associated cancers is be unclear

• Cervical dysplasia and Cancer:
  – Some studies have reported a protective effect on prevalence and progression of CIN2+ lesions but this has not been confirmed in by other studies

• Anal cancer:
  – incidence has increased

• Head & Neck cancer:
  – incidence has increased.

Firnhaber et al., JIAS, 2012
Ezechi et al., Plos 1, 2014
Zhang et al., APJCP, 2012
De Vuyst et al., Br J Cancer, 2012
Piketty et al., AIDS, 2013
Beachler et al., Curr Opin Oncol, 2013
Treatment and prevention options
Treatment for anogenital warts and neoplastic lesions

• Topical agents
  – TCA, podophylin, podophylotoxin, 5-FU

• Ablative therapies
  – CO2 laser

• Surgical excision

• Immune modulators
  – Imiquimod, intra-lesional interferon
Screening

• Anal intraepithelial neoplasia (AIN), like its cervical counterpart, CIN, is a potential precursor lesion of squamous cell carcinoma of the anus

• AIN screening analogous to pap smear programs for CIN have been recommended in high-risk populations to reduce the incidence of anal carcinoma in certain high income countries
  – Cytological analysis followed by high resolution anoscopy (HRA) in case of anal dysplasia

• Despite these guidelines challenges still remain:
  – HRA is expensive and unavailable in low & middle income countries
  – Utility of screening is questionable given the emerging evidence that some of AIN regresses spontaneously.
  – Absences of molecular biomarkers to stratify individuals at high risk of progression

Machalek et al., Lancet Oncol, 2012
Prevention options: condoms

• Results from several studies now suggest that increased condom usage is associated with lower rates of HPV DNA detection

• There is also evidence that using condoms leads to a more rapid regression of both penile and cervical intraepithelial lesions, as well as a more rapid clearance of genital HPV infection in women

• It is important to note that condoms provide a protective barrier against the transmission of HPV by skin to skin contact; however, individuals can be infected with HPV on areas not protected by a condom
Condom protection is partial

Consistent Condom Use Partially Reduces the Risk of HPV Infection

Adjusted hazard ratio

<table>
<thead>
<tr>
<th>Frequency of condom use by partner</th>
<th>Adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>5%-49%</td>
<td>1.0</td>
</tr>
<tr>
<td>50%-99%</td>
<td>0.5</td>
</tr>
<tr>
<td>100%</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* P = .02 compared with frequency of <5%.
† P = .003 compared with frequency of <5%.
‡ Adjusted for number of new and previous sexual partners.
N = 82 women (18-22 years of age).

Winer et al, N Engl J Med, 2005
Prevention options: male circumcision

- MC trials in SA and Uganda have shown a reduction in the prevalence of both HR- and LR- HPV types with circumcision in HIV-seronegative men.

- In Rakai, MC was found to reduce both the prevalence and incidence of multiple HR-HPV types in those men who were HIV-seropositive.
Prevention options: HPV vaccines

- Globally 3 vaccines are available estimated to prevent up to 80% of HPV associated cancers
  - Bivalent (Cervarix®), Quadrivalent (Gardasil®) & nonavalent (Gardasil ®9) LR 6, 11, and HR 16, 18, 31, 33, 45, 52 and 58

- All vaccines have been shown to be safe and immunogenic in HIV positive individuals

- Quadrivalent protects HIV +ve women against cervical and anogenital disease

- WHO recommends three-dose schedule
  - (0, 1–2, 6 months) for HIV +ve girls (regardless of whether they are on ART)

- Questions still remains on whether to include boys, men or HIV positive individuals esp in LMICs

Denny et al., Vaccine, 2013
Olsson et al., Human Vaccines, 2009
Conclusions

• There is an increased burden of HPV related diseases
  – among women, men and adolescents
• The burden is even higher among PLWHA
• The role of ART in reducing the burden of HPV associated cancers is unclear
• Condoms and male circumcision prevent HPV infection
• More data is required on:
  – the utility of screening for AIN in HIV+ men
  – whether boys or HIV + positive men should be vaccinated
Acknowledgements

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