



# Southern African HIV Clinicians Society 3rd Biennial Conference

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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



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# Outline of presentation

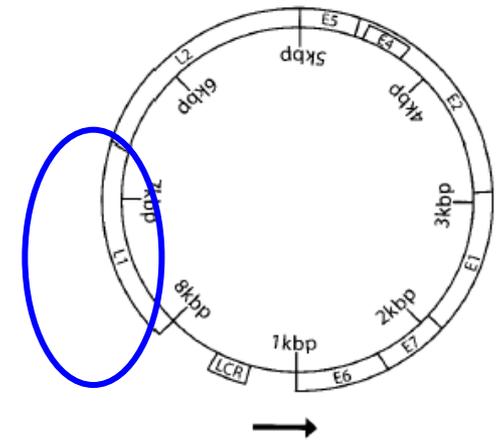
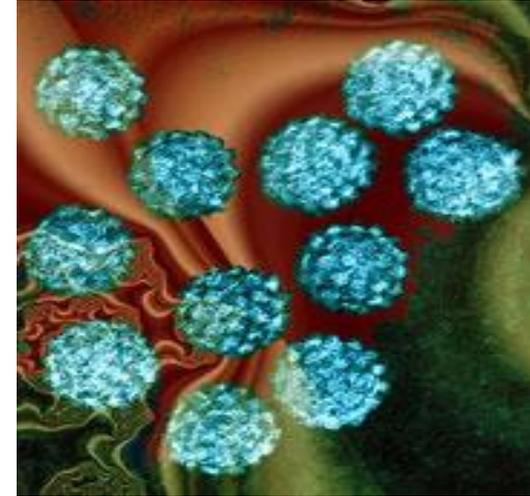
- Introduction
- Burden of HPV associated diseases
- The role of HIV and its interaction in HPV associated diseases
- Current prevention and treatment for HPV associated diseases
- Conclusion and Acknowledgements

# 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)



# Incidence cancer attributable to HPV in 2008

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

Forman et al., Vaccine, 2012



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# 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
  - Psychosocial distress
- Among HIV positive individuals AGWs are florid and even have a prolonged clinical course.

Patel et al., BMC Infectious disease, 2013



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# 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

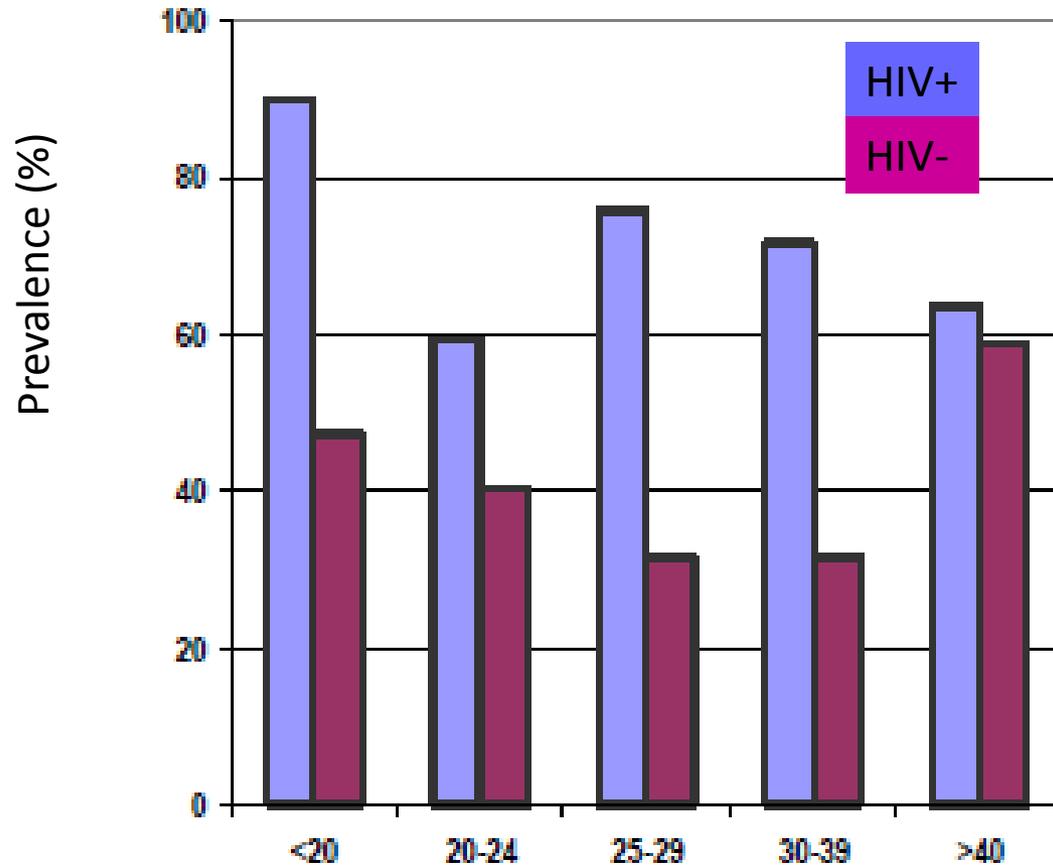
Schottenfield et al., CA Cancer J Clin ,2006

Dubrow et al., Curr Opin Oncol ,2012



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# Prevalence of cervical HPV DNA by age and HIV status among 349 women in BF



HIV prevalence = 16%

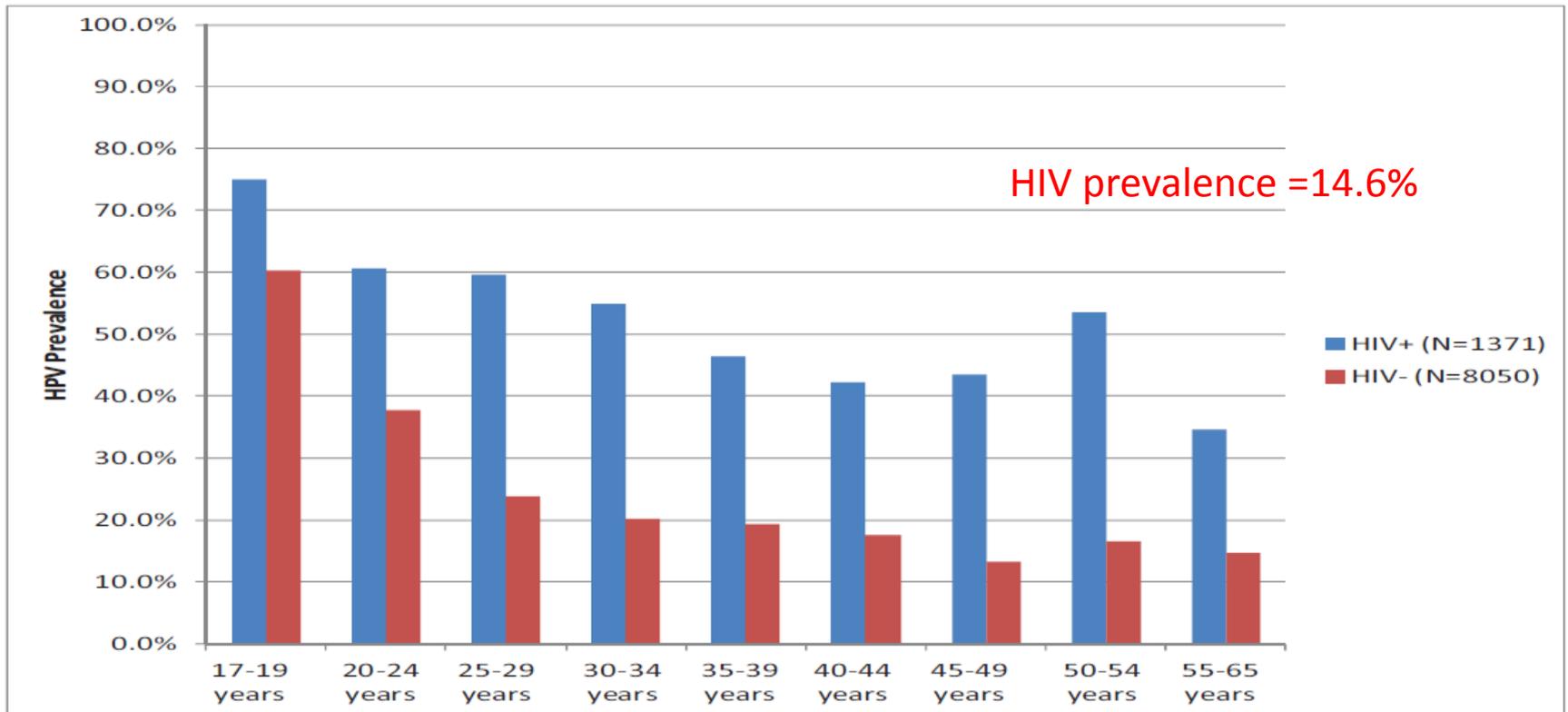
Didelot-Rousseau et al., Br J Cancer, 2006

Age Groups



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# Prevalence of HR-HPV among 1371 HIV+ and 8050 HIV- women in Cape Town

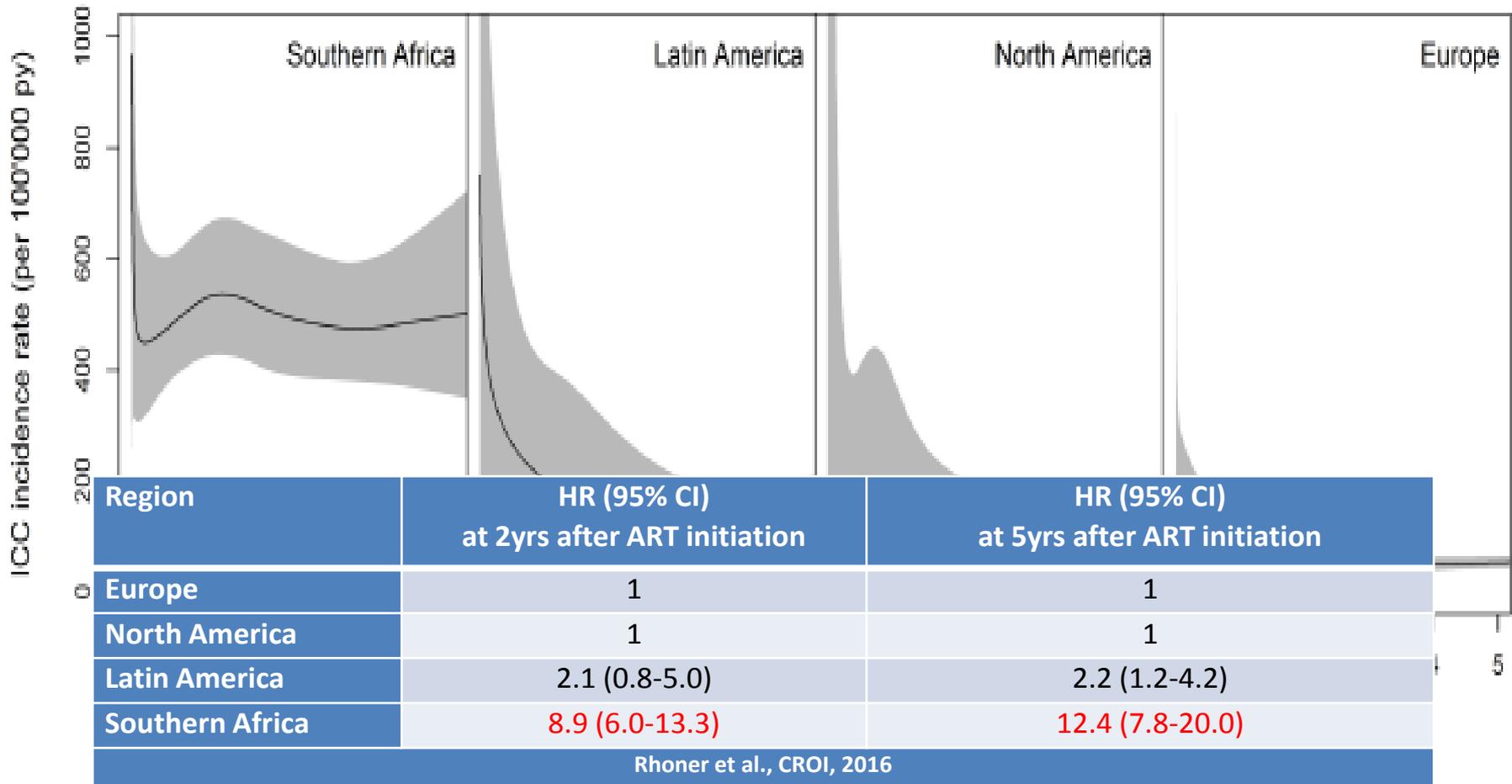


McDonald AC et al., Frontiers Oncol 2014



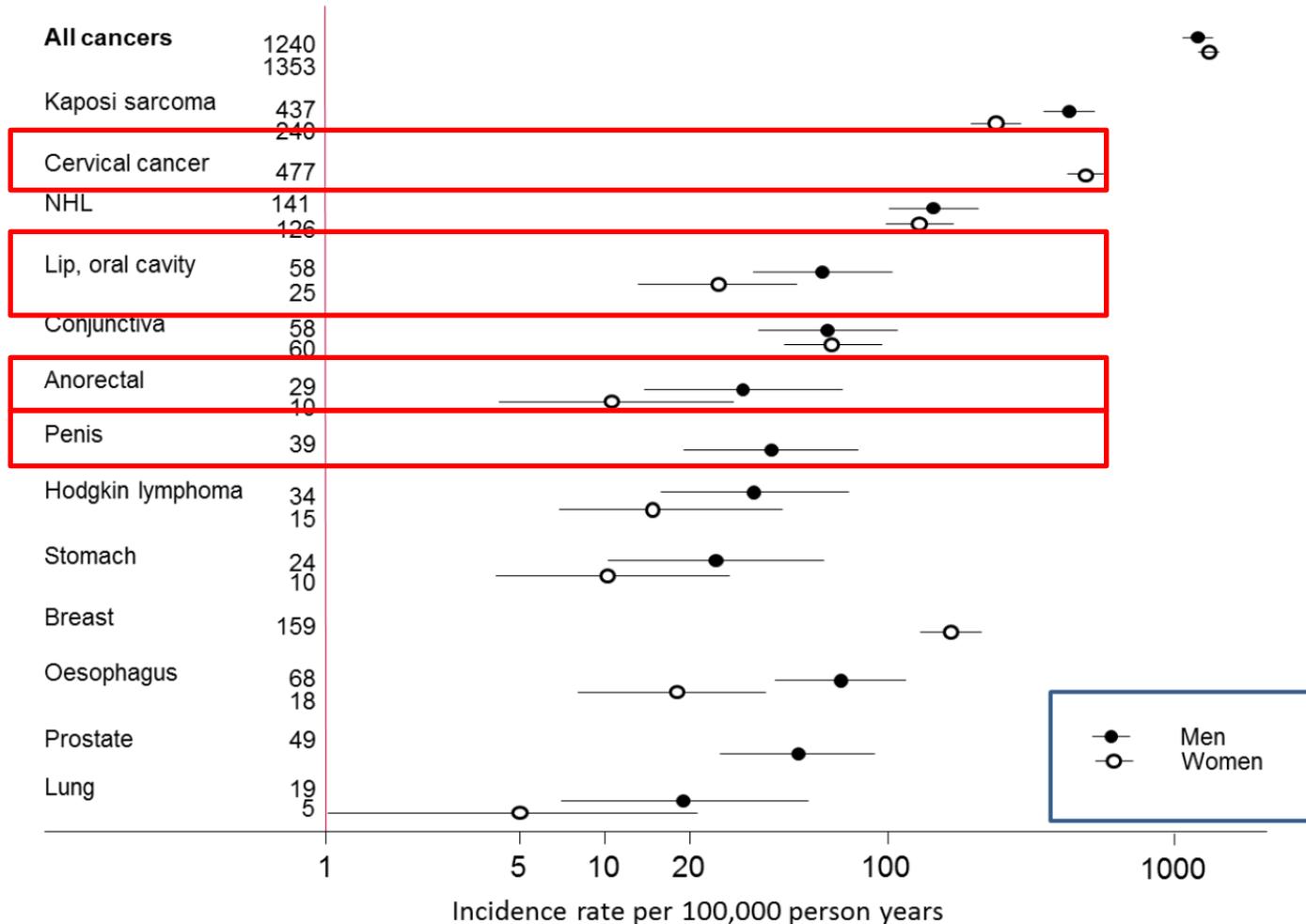
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# High risk of HPV Cervical Cancer among HIV positive individuals



# Cancers among HIV positive individuals in SA

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



# 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

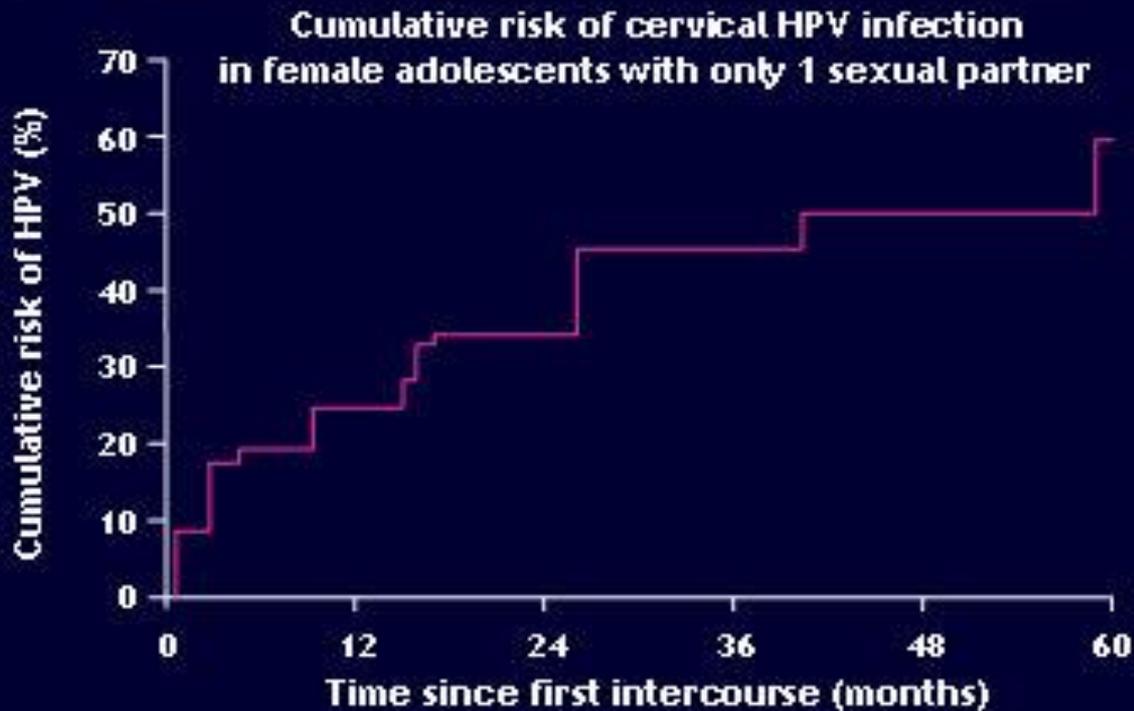
Smith et al., J Infect Dis, 2010

Smith-McCune., Plos 1, 2010



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# Risk of Acquiring HPV After First Intercourse in Female Adolescents

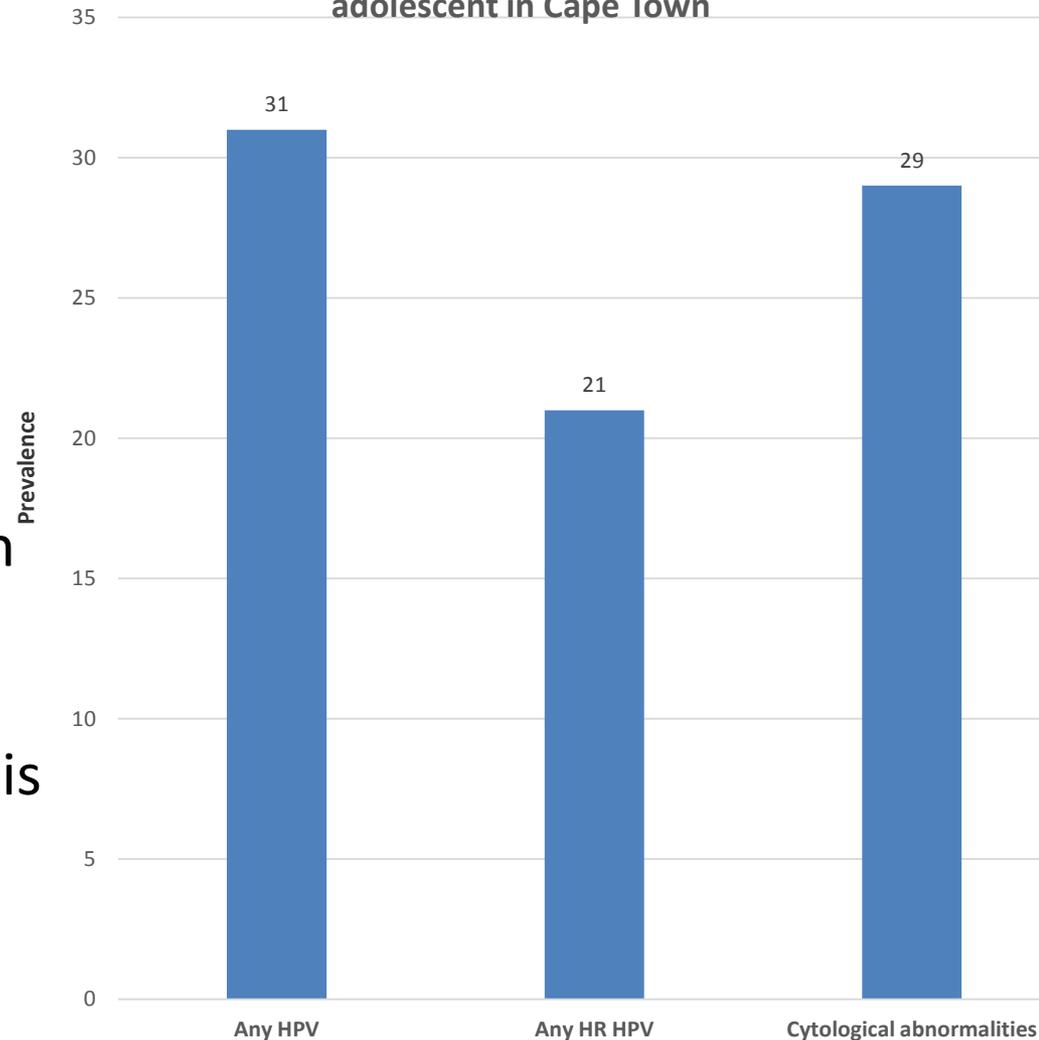


Collins et al., Br J Obstet Gynaecol, 2002

# 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

HPV infection and cervical disease among HIV positive adolescent in Cape Town



Alder et al., *Infectious Dis Obstet Gyneco*, 2014

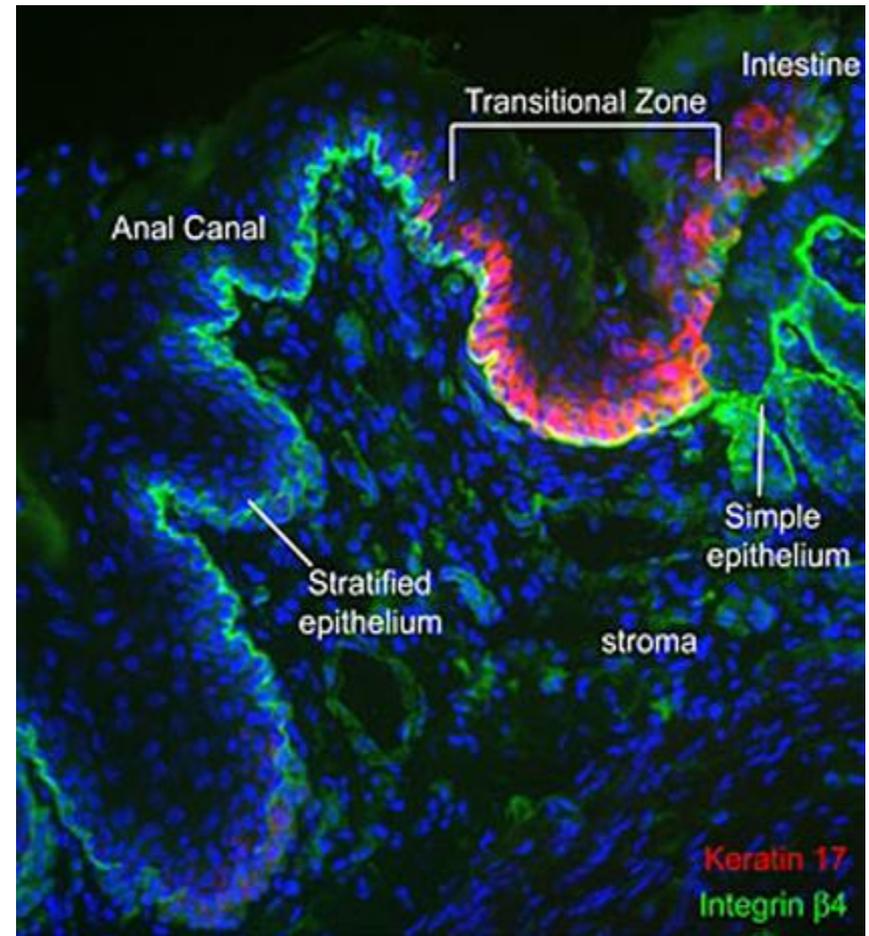
Nachman et al., *Archiv Pediatr Adolesc Med*, 2009



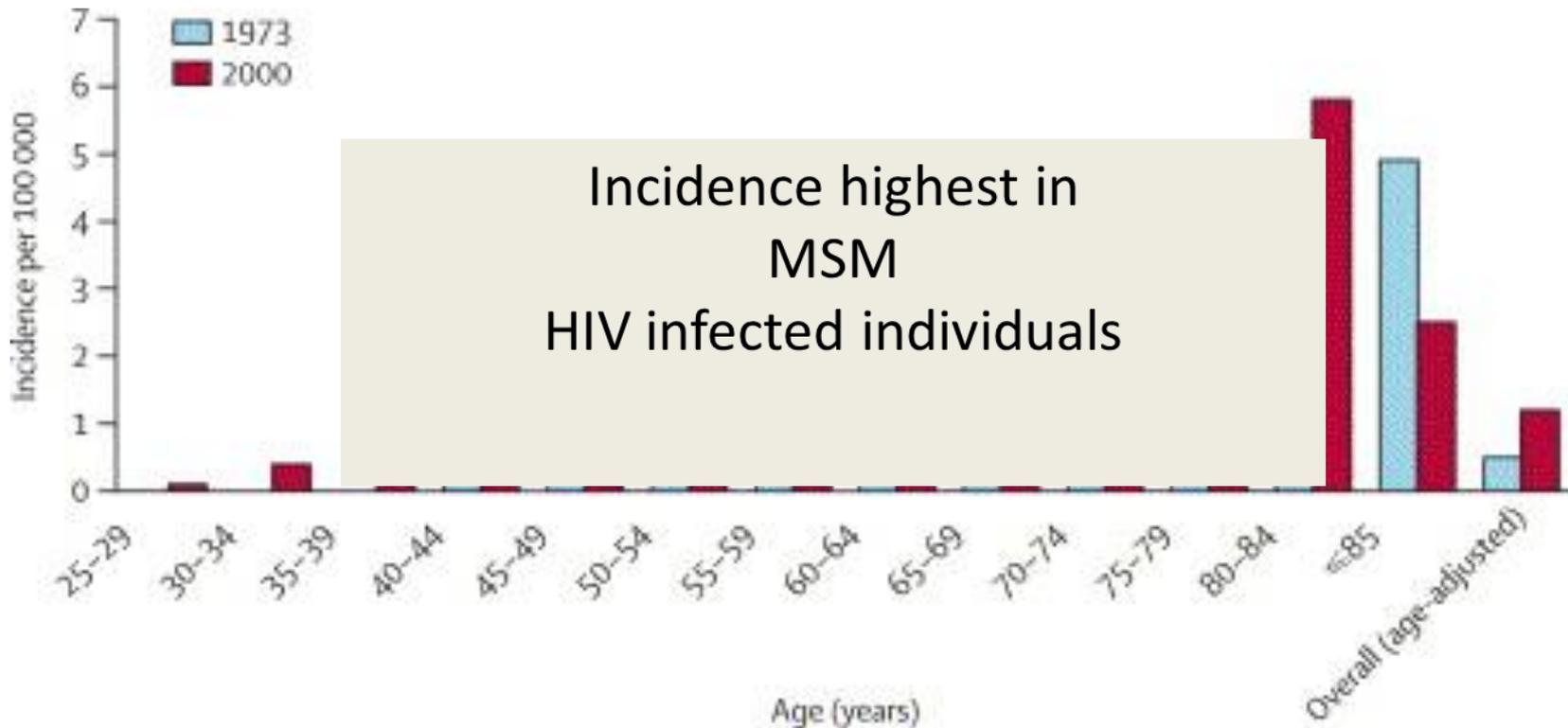
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# HPV infection and the anal canal

- 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



# Anal cancer incidence is rising



Partridge, 2006



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# 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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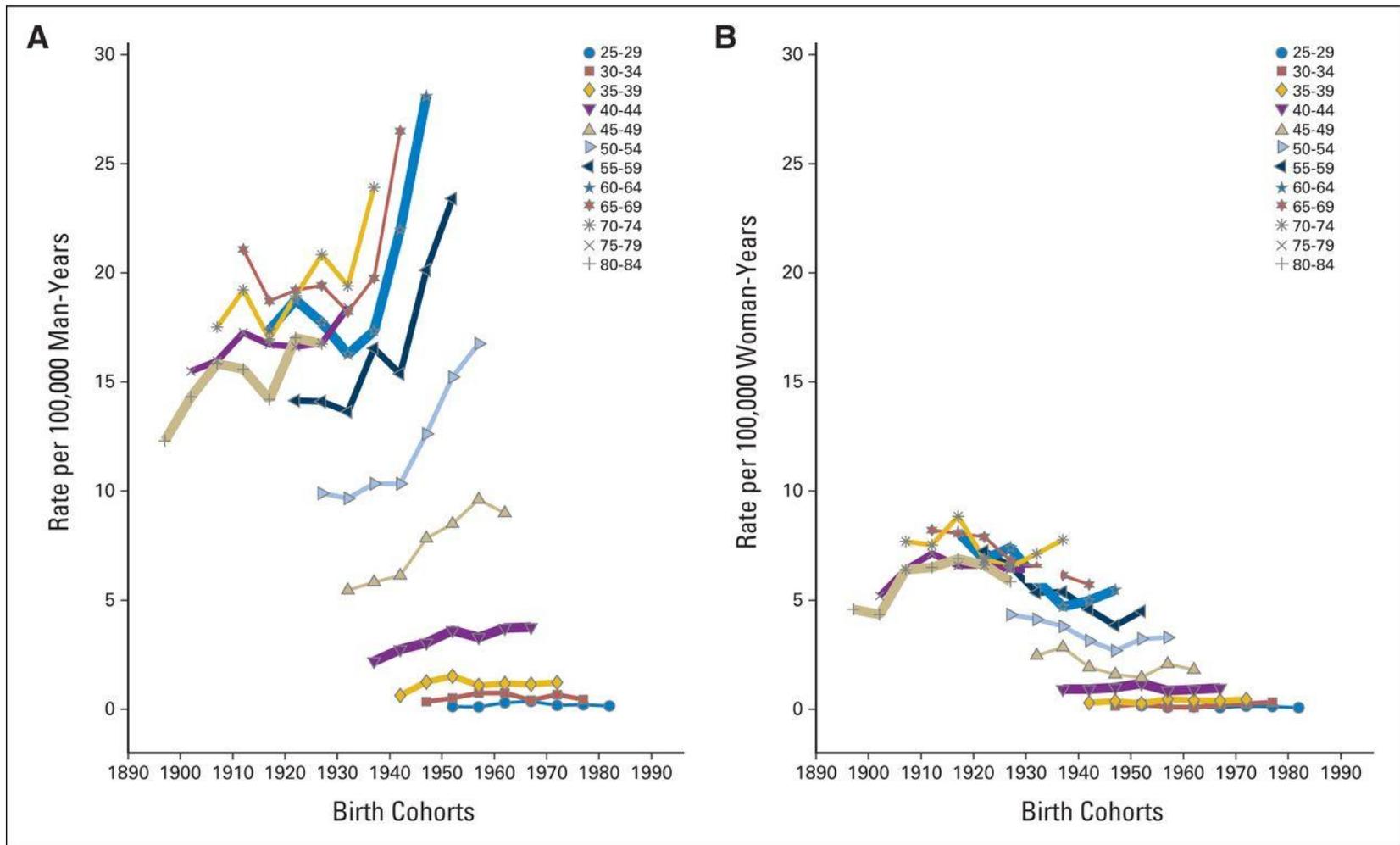
Chu et al., Oncology, 2013

Read et al., Plos 1, 2012



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# Rising oropharyngeal cancer especially in men

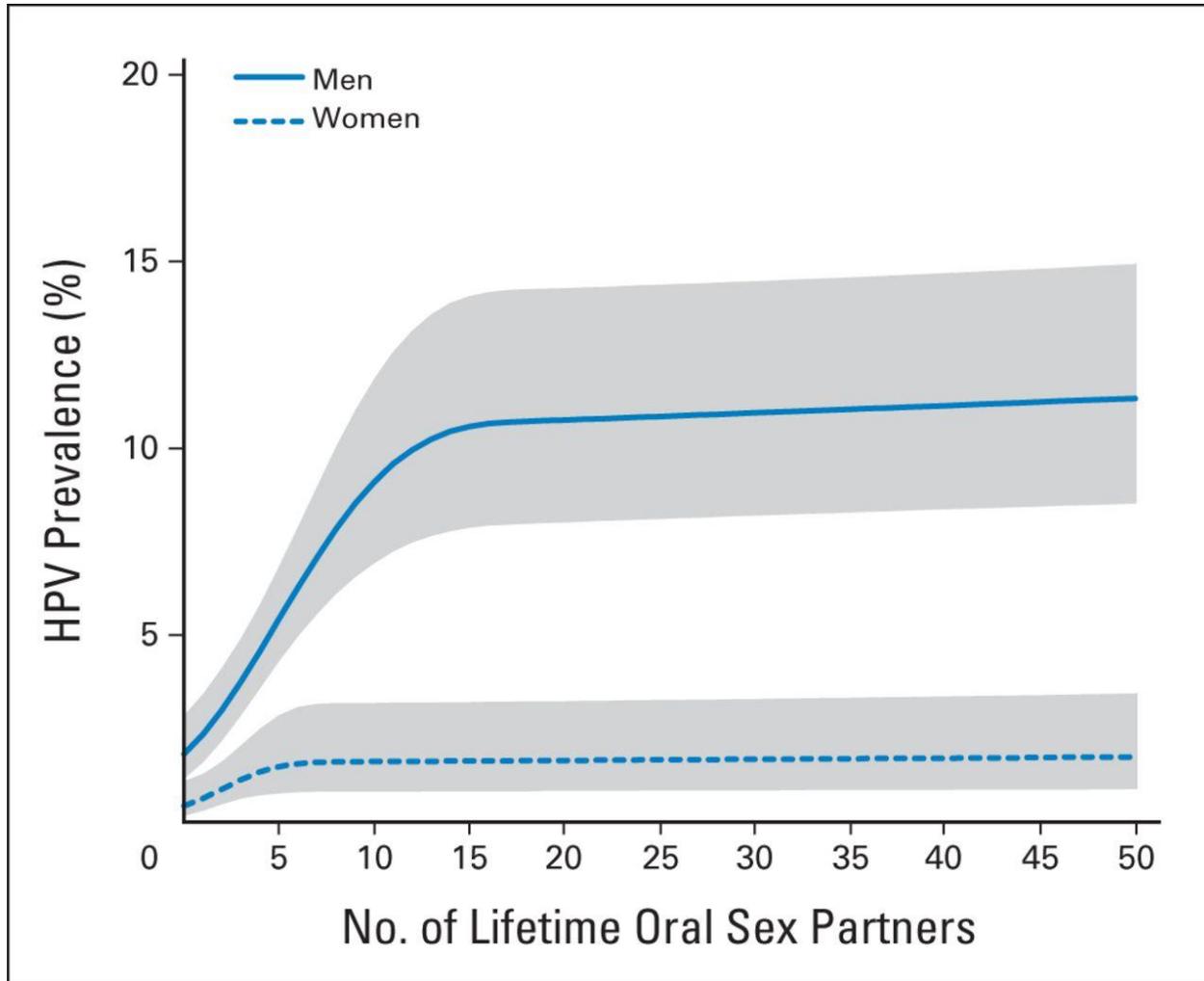


Maura et al., JCO, 2015



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# Associations between number of oral sex partners and oral HPV prevalence



Maura et al., JCO. 2015



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# 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



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# 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



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# Treatment and prevention options

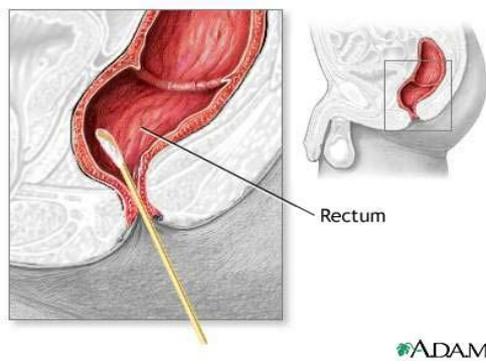


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# Treatment for anogenital warts and neoplastic lesions

- Topical agents
  - TCA, podophylin, podophylotoxin, 5-FU
- Ablative therapies
  - CO2 laser
- Surgical excision
- Immune modulators
  - Imiquimod, intra-lesional interferon

# Screening



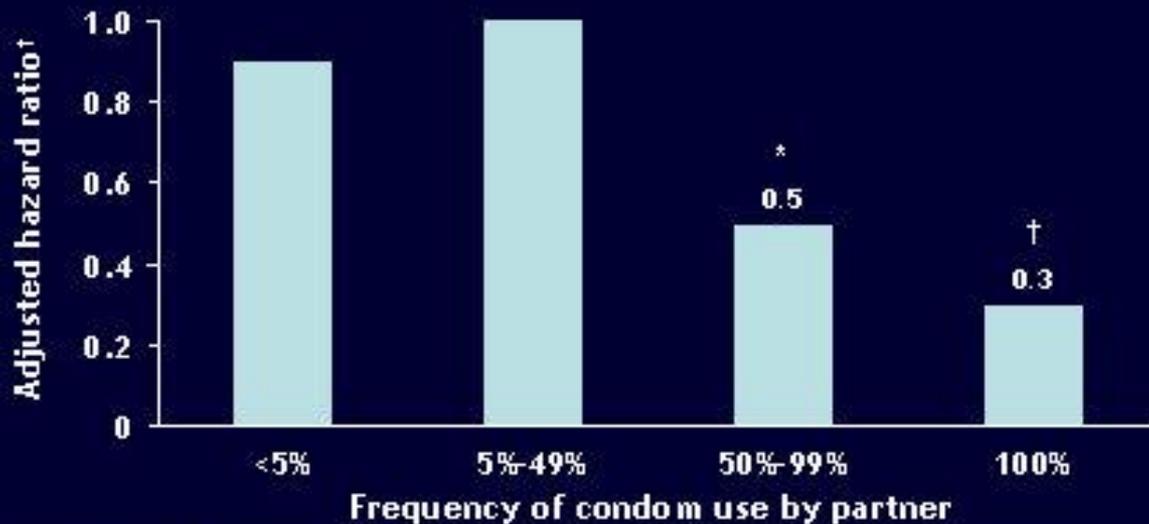
- Anal intraepithelial neoplasia (AIN), like its cervical counterpart, CIN, is a potential precursor lesion of squamous cell carcinoma of the anus
- AIN screening analogous to pap smear programs for CIN have been recommended in high-risk populations to reduce the incidence of anal carcinoma in certain 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

# 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



\*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



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# 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



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# 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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