# Cervical cancer and HPV Associated disease in HIV positive women

Lynette Denny

Department Obstetrics & Gynaecology, University of Cape Town and Groote Schuur Hospital and Institute of Infectious Diseases and Molecular Medicine, University of Cape Town

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SA HIV Clinicians 2012

# 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)

*Smith-McCune, K.K. et al. PLoS One, 2010. **5**(4): p. e10094, Averbach, S.H. et al. AIDS, 2010. **24**(7): p. 1035-42. Low, A.J. et al. BMC Infect Dis. **11**: 20 – 26, Veldhuijzen, N.J. et al. AIDS, 2010. **24**(14): p. 2289-92, Auvert, B. et al. Infect Dis Obstet Gynecol, 2011: p. 692012

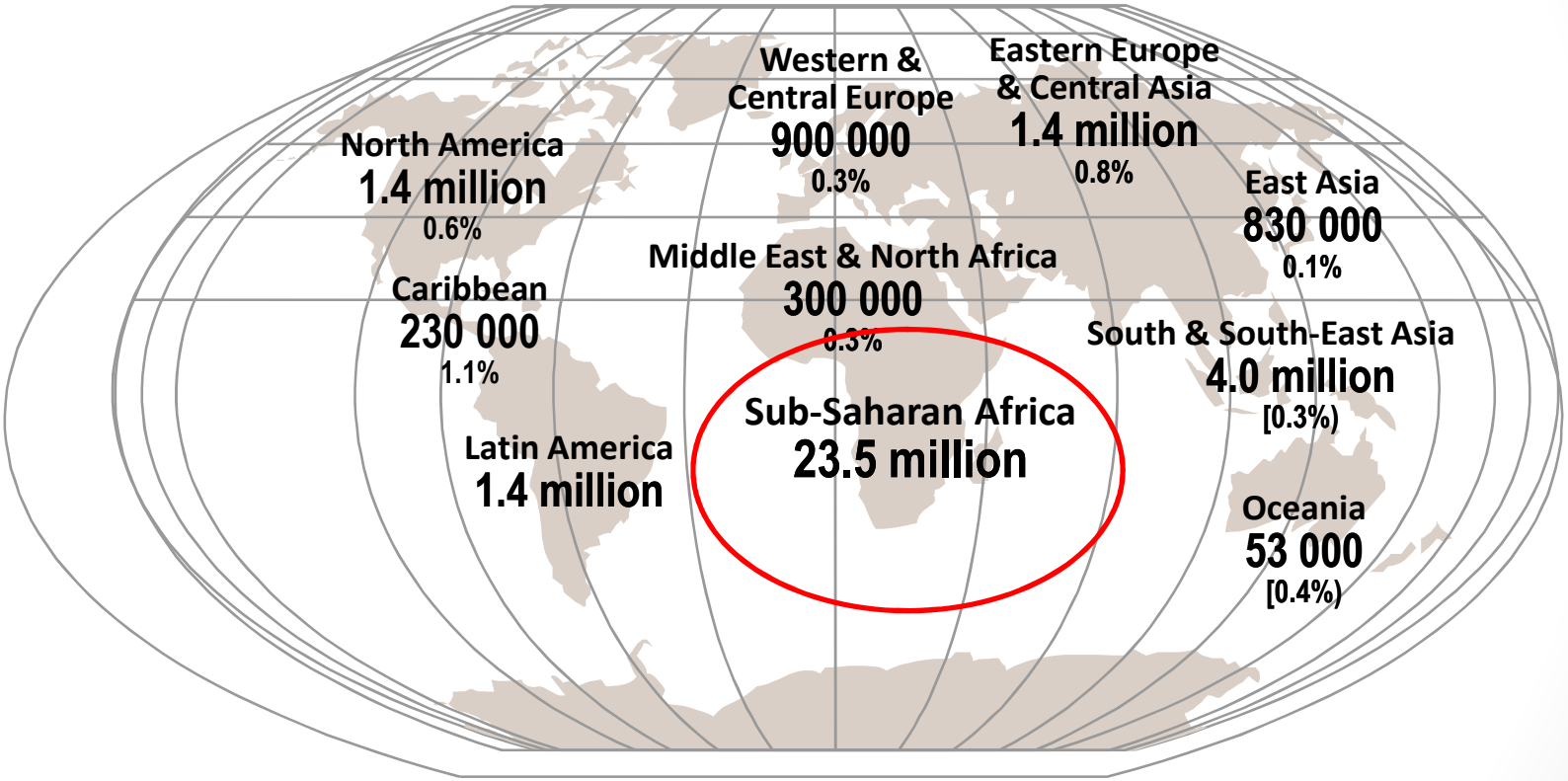
# Global Estimates of HIV for Adults and Children 2009 and New Infections and Deaths in 2011*

- 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

* Source: www.unaids.org UNAIDS Report on the Global AIDS Epidemic, 2010

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




**Total: 34 million (31.4 – 35.9 million)**

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

World Health Organization

*UNAIDS Global Report 2012

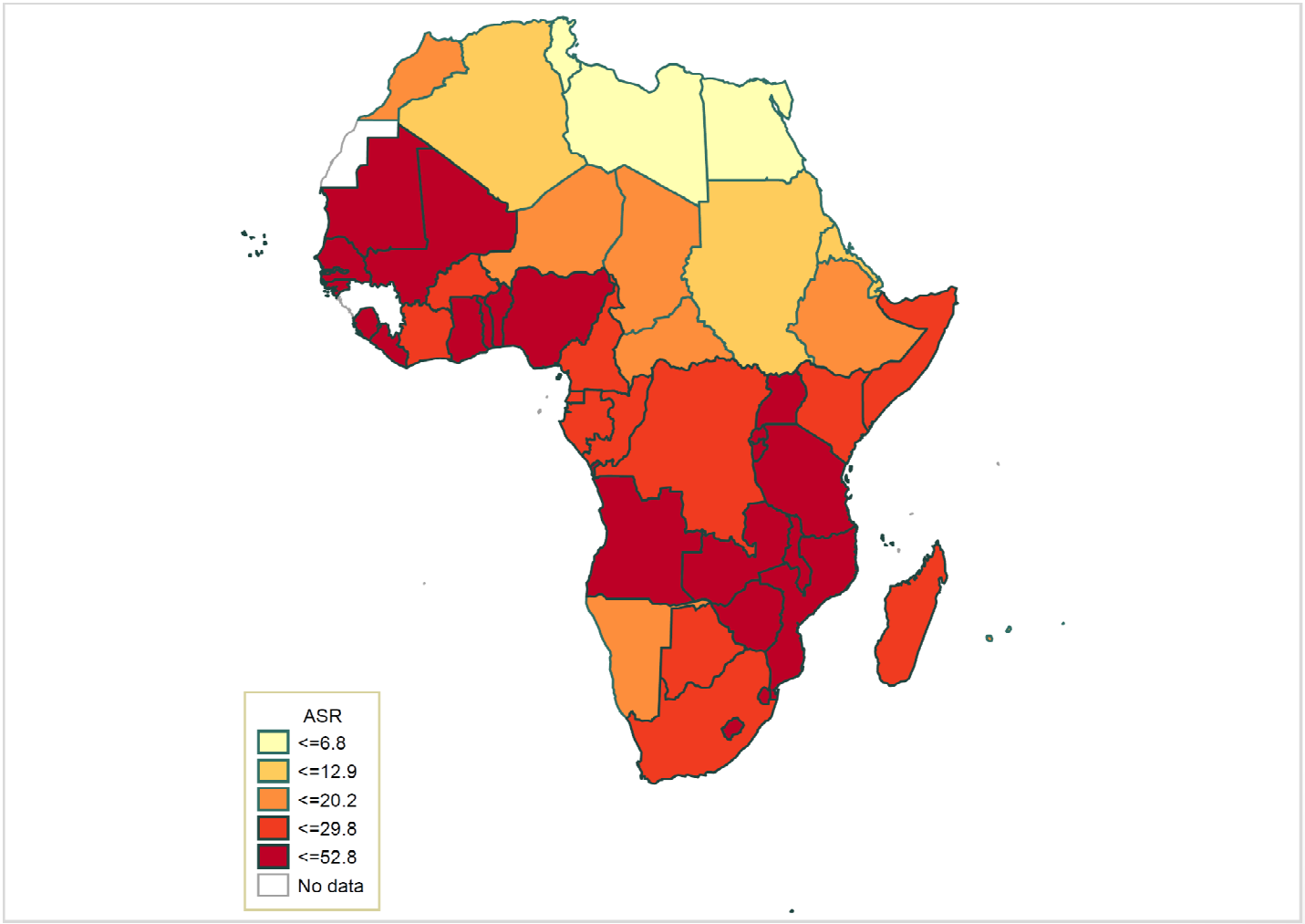
# Sub-Saharan Africa AIDS statistics

- 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

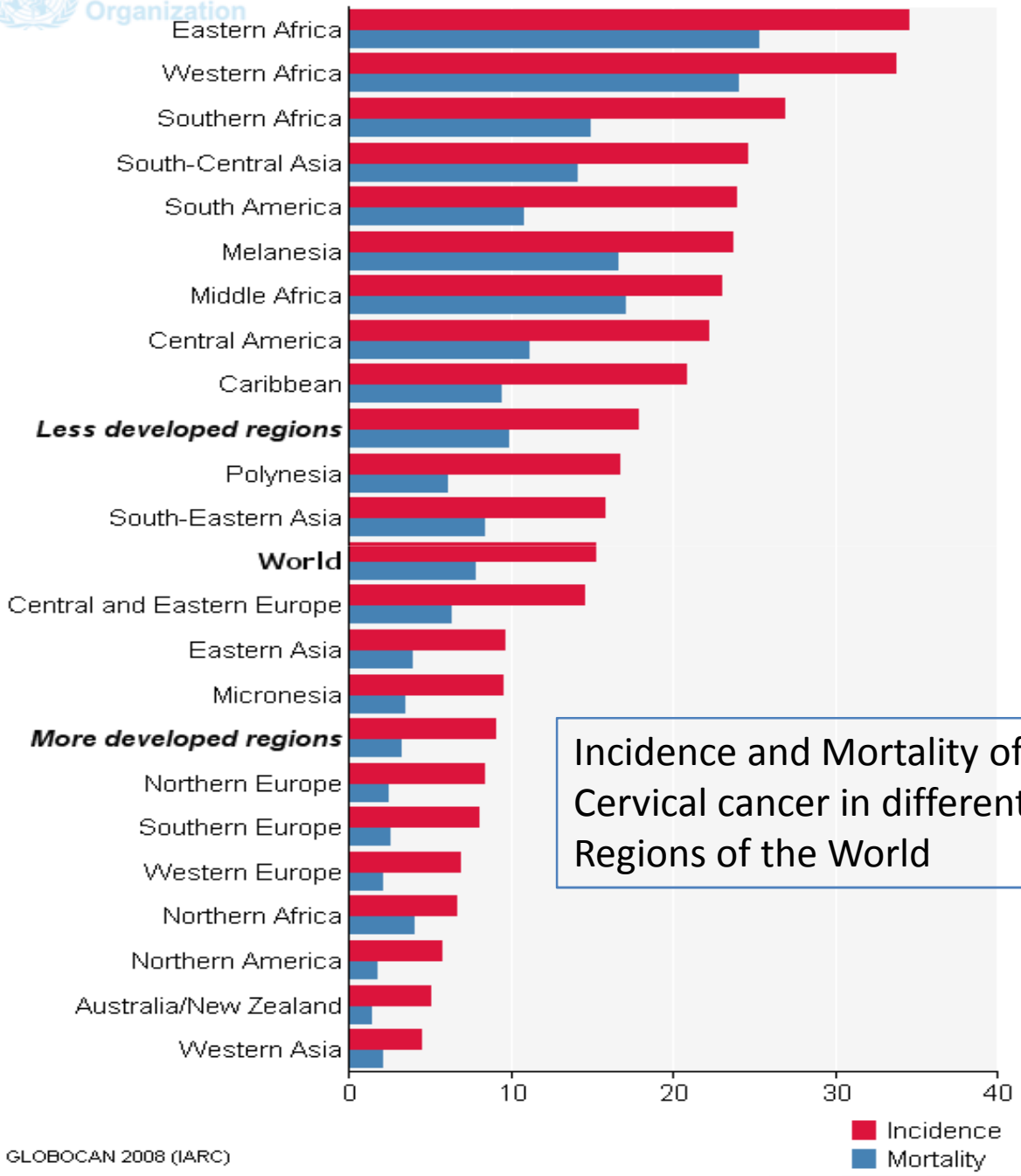
# Cervical Cancer

- 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*



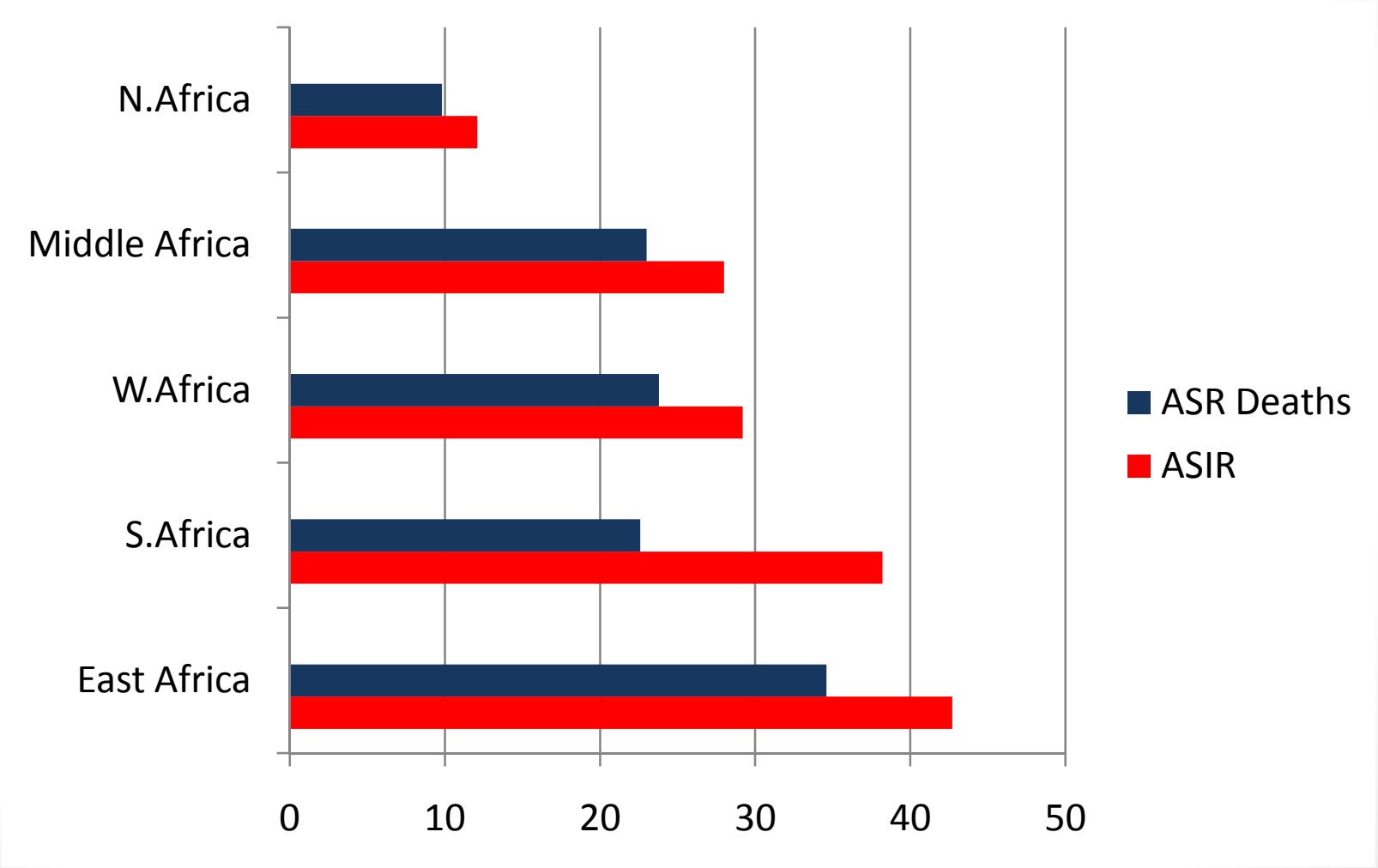

*Globocan 2008




GLOBOCAN 2008 (IARC)

Incidence and Mortality of Cervical cancer in different Regions of the World

# ASIR and ASR of Deaths from Cervical cancer per 100 000 in different regions of Africa



# Cervical cancer in HIV positive women

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

*Frisch et al, J Natl Cancer Institute, 2000;92 (18):1500 -10; ^ Tanon et al PLOS one2012;7(10)e48108
+ Odida et al Infectious Agents and Cancer 2011;6:8-13; # Adjorlolo- Johnson et al BMC Infectious diseases 2010;10:242
@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%

*Sanjose et al. Lancet Infect Dis 2007;7:453- 59

# HPV Prevalence In HIV positive Women with Normal cytology*

| Region | Number of Women | HPV prevalence (%) |
|---|---|---|
| Africa | 489 | 56.6 |
| Asia | 238 | 31.1 |
| Europe | 340 | 32.4 |
| North America | 2039 | 31.4 |
| South/Central America | 124 | 57.3 |
| All regions | 3230 | 36.3 |

*Clifford et al AIDS 2006;20:2337- 44

# HPV type distribution in SCC in women in Africa

| | SCC n = 570 (%)* | SCC N = 2402 (%) ^ | SCC N = 544 (%)+ | SCC N = 410 (%) # |
|---|---|---|---|---|
| **HPV 16** | **51.2** | **53.1** | **48.0** | **49.0** |
| HPV 18 | 15.0 | 19.8 | 23.0 | 23.0 |
| HPV 45 | 7.1 | 11 | 10.0 | 13.0 |
| HPV 35 | 8.7 | 4.1 | 5.0 | 5.0 |

*Schmidt et al IPV Sept 2011 Abstract P32, ^ Guan et al. Int J Cancer 2012
+ 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%

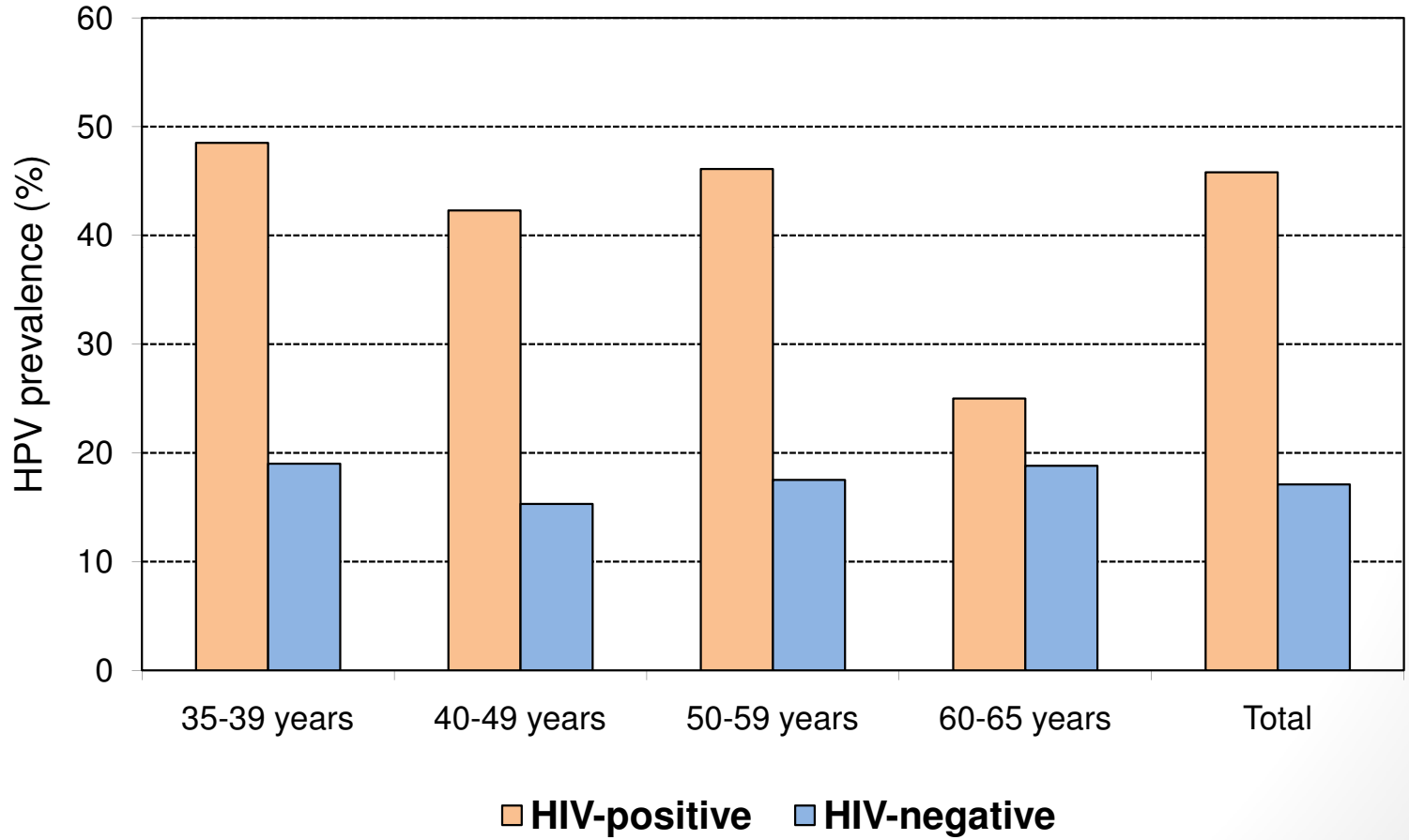
Strongly associated with Low CD4 count and high viral loads ($p < 0.001$)

# Cape Town Screen and Treat Study

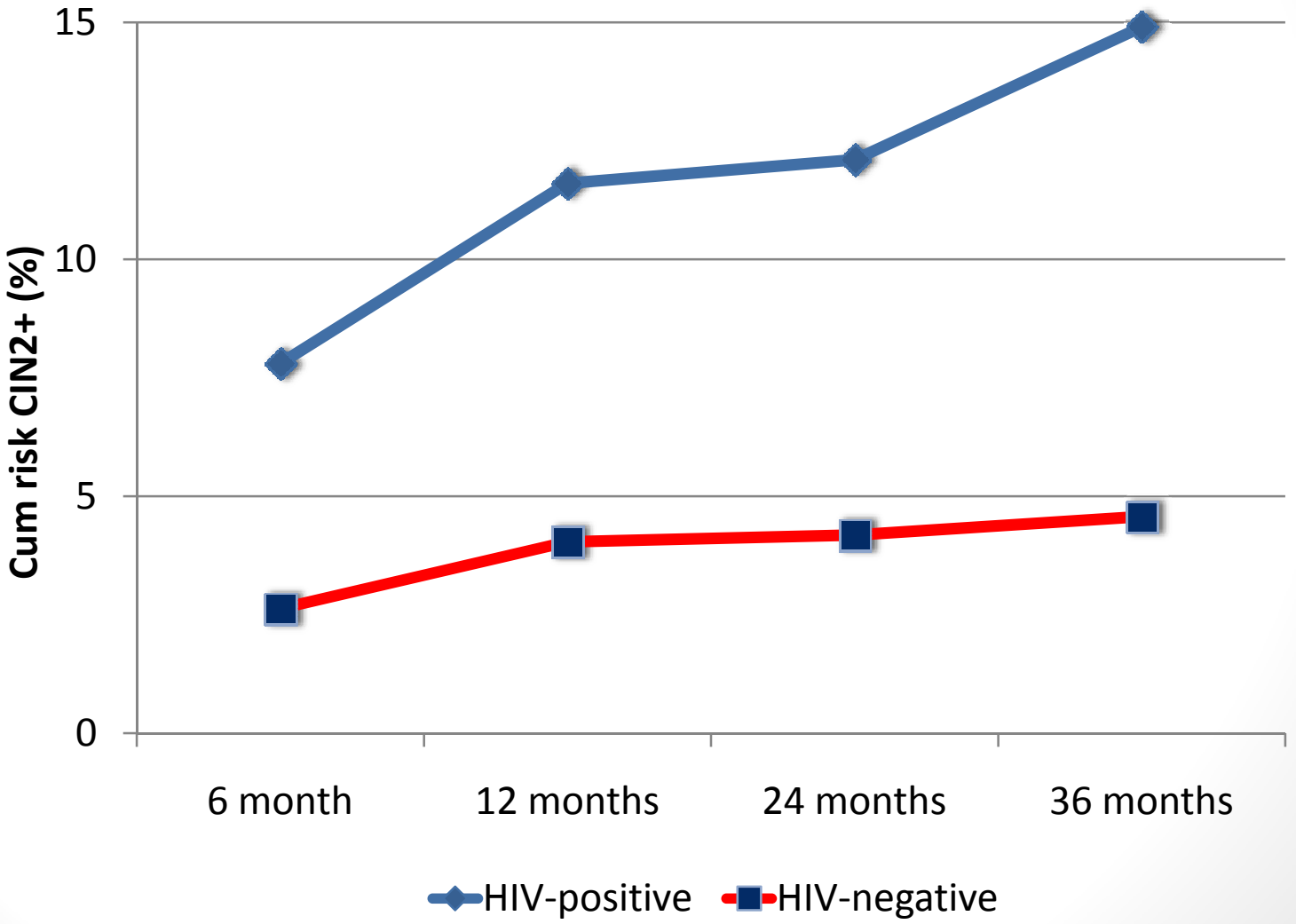
- Randomized clinical trial
- 6553 unscreened women 35-65 years in Cape Town, South Africa*
- 14% HIV-positive at baseline
- Comparison of HPV prevalence and CIN
  - 956 HIV-positive vs. 5596 negative women +

*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



# HPV infection attributable cancer in 2008 in Women and Men*

| Site | No. of new cases 2008 | Attributable to HPV (%) | No. attributable to HPV | Less Developed regions | More Developed regions |
|---|---|---|---|---|---|
| Cervix | 530 000 | 100% | 530 000 | 470 000 | 180 000 |
| Vulva | 27 000 | 43% | 12 000 | 4 100 | 7 500 |
| Vagina | 13 000 | 70% | 9 000 | 5 700 | 3 400 |
| Anus | 27 000 | 88% | 24 000 | 12 000 | 12 000 |
| Naso-pharynx | 84 000 | 86% | 72 000 | 66 000 | 5 900 |
| Oro-pharynx | 85 000 | 26% | 22 000 | 6 400 | 15 000 |
| Total | | | 669 000 | 564 200 | 223 800 |

*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[1]
- Incidence of anal cancer increasing by 2% per year among men and women in general population[2]
- Incidence highest in MSM and in HIV positive women/men[3]
- 7 fold increase in Penile cancer in HIV infected men[4]
- 60 fold increase in anal cancer in HIV infected men[5]
- High rates of genital warts in both men and women, often resistant to conventional therapies [5,6]

[1]Hoots BE, et al. Int J Cancer 20009;124:2375-83, [2]Scholefield JH, et al Br J Surg 2005;92:1133- 36, Johnson et al, Cancer 2004;101:281 – 8, [3] Palefsky J, Curr Opin HIV AIDS 2009;4:52-6, [4]Frisch M et al J Natl Cancer Instit 200;92:1500 – 10; [5]Dolev et al AIDS 2008; 22:1213 – 19; [6]De Panfilis et al Sex Trans Dis 2002; 29:121-25

# 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**