



HPV and HIV Co-infection

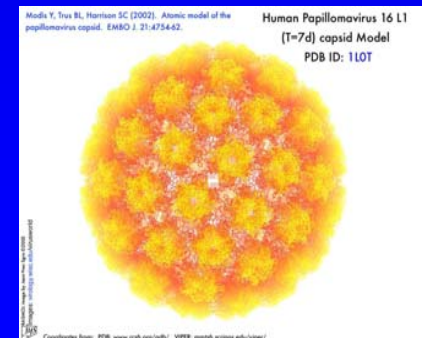
**Women and HIV International Clinical
Conference**

Dallas, Texas

April 30th 2008

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Brown University

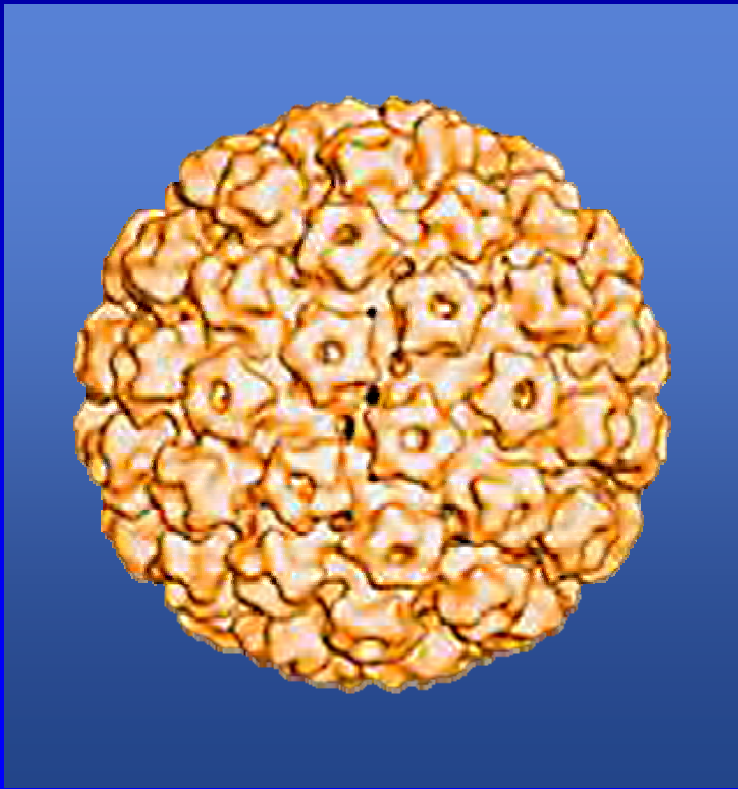


Objectives

- **Review HPV in HIV infected women**
 - Difference in prevalence compared with HIV un-infected women
 - Difference in HPV related diseases compared with HIV un-infected women
 - What has changed with the introduction of highly active antiretroviral therapy (HAART)
- **Review the Quadrivalent HPV vaccine**
 - Efficacy in preventing anogenital disease
 - Limitations
 - Guidelines
 - Vaccinating HIV-infected women

Human Papilloma Virus

Nonenveloped double-stranded DNA virus
(Papovaviridae family)



- **>100 types identified**
- **30–40 anogenital**
 - 15–20 oncogenic types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58
 - HPV 16 (54%) and HPV 18 (13%) account for the majority of worldwide cervical cancers.
 - Nononcogenic types include: 6, 11, 40, 42, 43, 44, 54
 - HPV 6 and 11 are most often associated with external genital warts

HPV Clinical Manifestation

- **Plantar warts, types 1, 2**
- **Common warts, types 1, 2**
- **Flat warts types 10, 3**
- **Epidermodysplasia verruciformis (autos recessive)**
- **Condyloma accuminata or anogenital warts, types 6 and 11**
- **Intraepithelial neoplasia, types 6, 11, 16, and 18**
- **Cervical and anal carcinoma, types 16 and 18**
- **Recurrent respiratory papillomatosis (juvenile and adult forms), types 6 and 11**
- **Focal epithelial hyperplasia of Heck, types 13 and 32**
- **Conjunctival papillomas and carcinomas**
- **Oropharyngeal cancers**

HPV and HIV



HPV and cancer

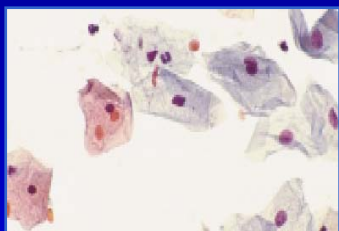
- Infection with oncogenic HPV types is the most significant risk factor in cervical cancer etiology
- Analysis of 932 specimens from women in 22 countries indicated prevalence of HPV DNA in cervical cancers worldwide = 99.7% (Walboomers JM, et al. *J Pathol.* 1999;189:12–19)
- Specific oncogenic HPV types (16, 18, 31, 33, and 45) have been detected in 63%–97% of invasive cervical cancer cases worldwide (Clifford GM et al. *Br J Cancer.* 2003;88:63–73)
- HPV infection is strongly associated with oropharyngeal cancer (OR 12.3), particularly HPV-16 (OR 14.6), regardless of tobacco and alcohol use

HPV Persistence

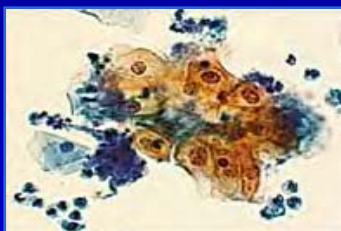
- **Widely accepted that persistence of high-risk types of HPV is crucial for development of cervical precancer and cancer**
- **Other associated factors**
 - Age (≥ 30 years)
 - Infection with multiple HPV types
 - Immune suppression

Terminology for Cervical Cytology (Bethesda)

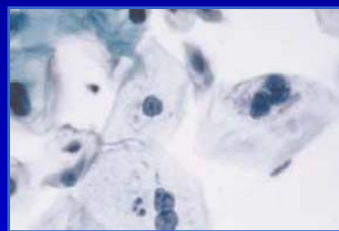
Normal



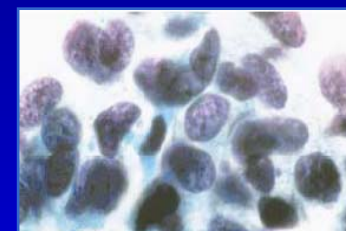
ASCUS



LSIL

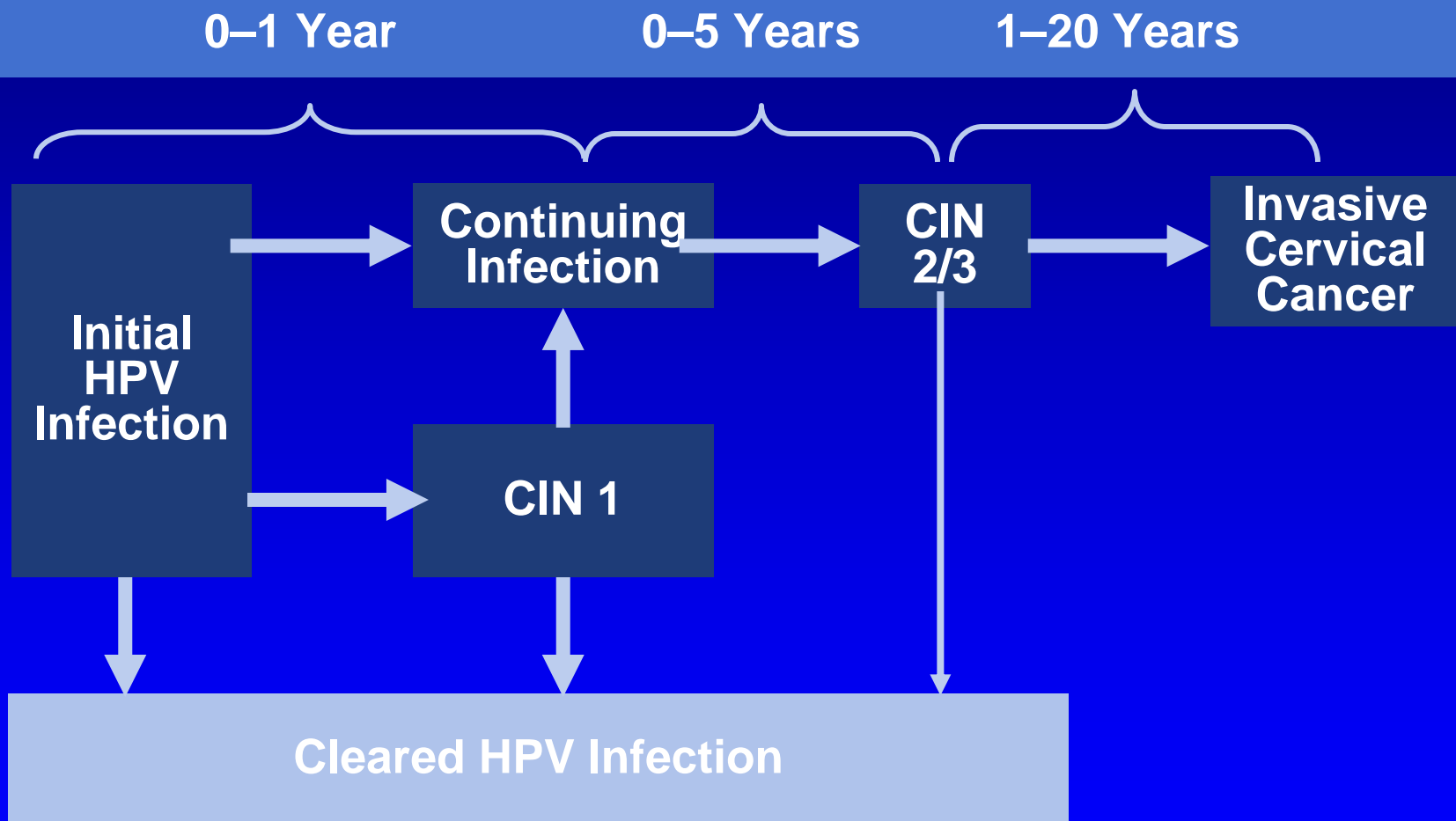


HSIL



- Two types of atypical squamous cells (ASC)⁴
 - Atypical squamous cells of undetermined significance (ASCUS)
 - Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (ASC-H)
- Squamous intraepithelial lesions (SIL)⁴
 - Low-grade SIL (LSIL): Mild dysplasia, cervical intraepithelial neoplasia 1 (CIN 1)
 - High-grade SIL (HSIL): Moderate and severe dysplasia, CIN 2/3, carcinoma in situ (CIS)

Natural History of HPV Infection and Potential Progression to Cervical Cancer



(Merck). Pinto AP, Crum CP. Natural history of cervical neoplasia: Defining progression and its consequence. *Clin Obstet Gynecol.* 2000;43:352–362.

HPV Prevalence in HIV-infected vs. HIV-negative individuals

- HERS (Am J Obgyn,2002), all high risk for HPV acquisition

| | HIV (+) 767 women | HIV (-) 390 women |
|----------------------|----------------------|--------------------------|
| Any HPV | 64% | 27% |
| ≥2 HPV types | 37.8% | 19.6% |
| Association with age | No 68.5% to 61.9% | Inverse 48.7% to 7.7% |

HPV Persistence in HIV-infected vs. HIV-negative individuals

- **HERS: Same HPV DNA types 6 to 36 months apart.**
 - All HPV risk types more likely to persist in HIV (+) than (-) women (OR 2.5)
 - Persistence was 1.9x greater with CD4 counts <200 cells/ μ L than >500 cells/ μ L
- **Two other studies on HIV (-) women found that**
 - cancer-associated HPV types more likely to persist than low risk types (NEJM, 1998;338:423 and JID 1994;169:235)

Cervical dysplasia and cancer

- **15-40% with evidence of dysplasia; 10-11 x greater than HIV(-) women**
 - declining CD4 counts
- **Dysplasia and cancer is associated with more extensive cervical involvement and to involve other sites (vagina,vulva,perianal region)**
- **Overall, HIV infected women have a higher burden of HPV related diseases compared with HIV negative women**

HPV/HIV Coinfection in the Era of HAART

- **Mixed results re impact of HAART on anogenital neoplasia**
 - Effect of time and contribution of poor survival in data.
 - Once high grade lesion develop, the progression from high grade to cancer may not be CD4 dependant
 - Importance of identifying precancerous lesions

HPV/HIV Coinfection in the Era of HAART

- **International Collaboration on HIV and Cancer year 2000 publication included cancer data from 23 studies (about 50.000 subjects) for the period 1992-1999**
 - No significant change in the incidence rate of invasive cervical cancer
 - Longer follow-up time is needed
- **WIHS, Minkoff et al. AIDS 2001 compared PAP results between women on and off HAART who had documented cervical HPV infection**
 - Women on HAART had slower progression and increased regression of CIN



Human Papilloma Virus (HPV) Infection of the Anus is More Prevalent and Diverse than HPV Infection of the Cervix among HIV-Infected Women in the SUN Study

E. Milu Kojic, Susan Cu-Uvin, Lois Conley, Tim Bush, Elizabeth Unger, Keith Henry, John Hammer, E. Turner Overton, Joel Palefsky, John T. Brooks

The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy

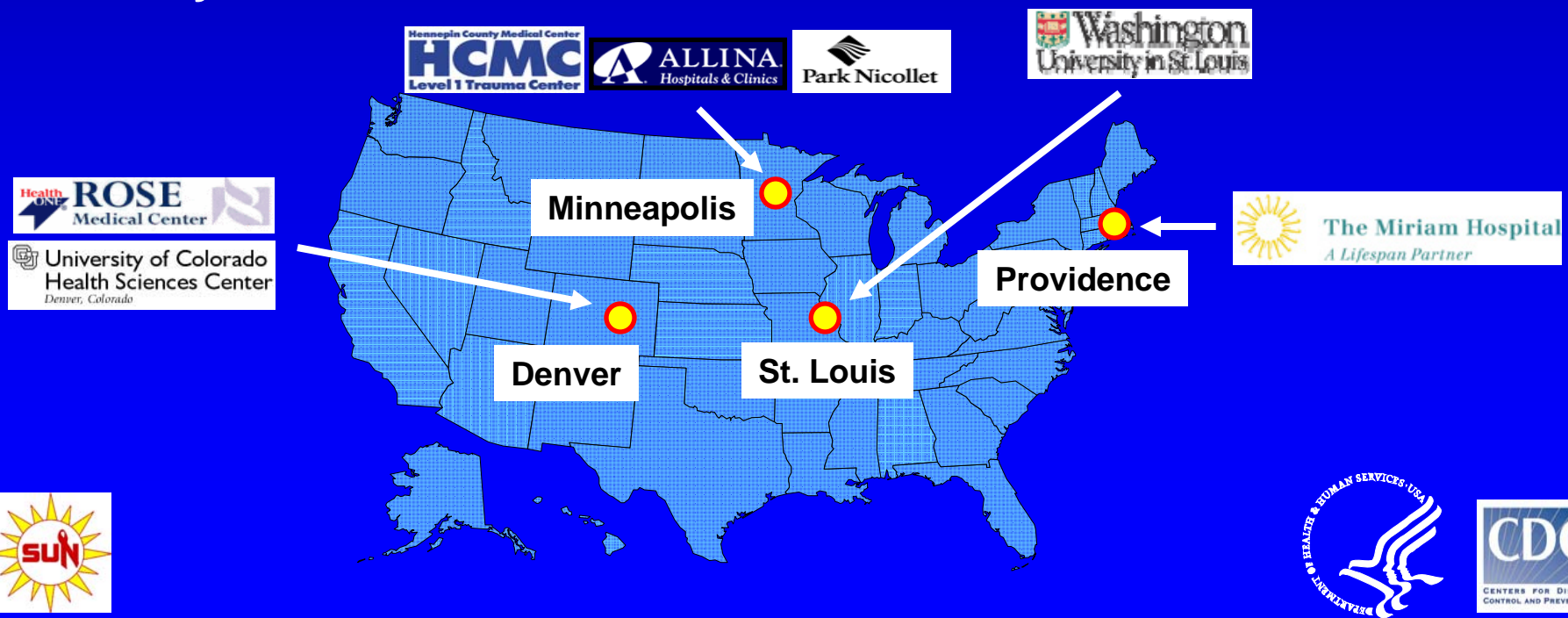




Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN)



- 5-year prospective observational cohort study
- 685 adults at 7 clinics in 4 U.S. cities
- HAART only or no treatment for HIV
- Followed during routine care with additional testing at baseline and every six months





Objectives

- **Monitor incidence of and risk factors for complications related to treatment and prolonged survival**
- **Monitor changes in morbidity and mortality related to HIV infection**

At baseline, all patients completed a behavioral questionnaire and provided, among other specimens, cervical and anal swabs for cytopathologic examination (Pap smears) and HPV detection and genotyping





Demographics

Baseline visit (n=122)

Age

Mean and median

40 years

Range

21 - 64 years

Race/Ethnicity:

White, non-Hispanic

34%

Black, non-Hispanic

53%

Hispanic

10%

Other

3%





Laboratory Results

**Nadir CD4 cell count
(cells/ μ l)
(n=113)**

**Mean: 224
Median: 216
Range: 4 - 725**

**Current CD4 cell count
(cells/ μ l)
(n=119)**

**Mean: 482
Median: 419
Range: 108 - 1748**

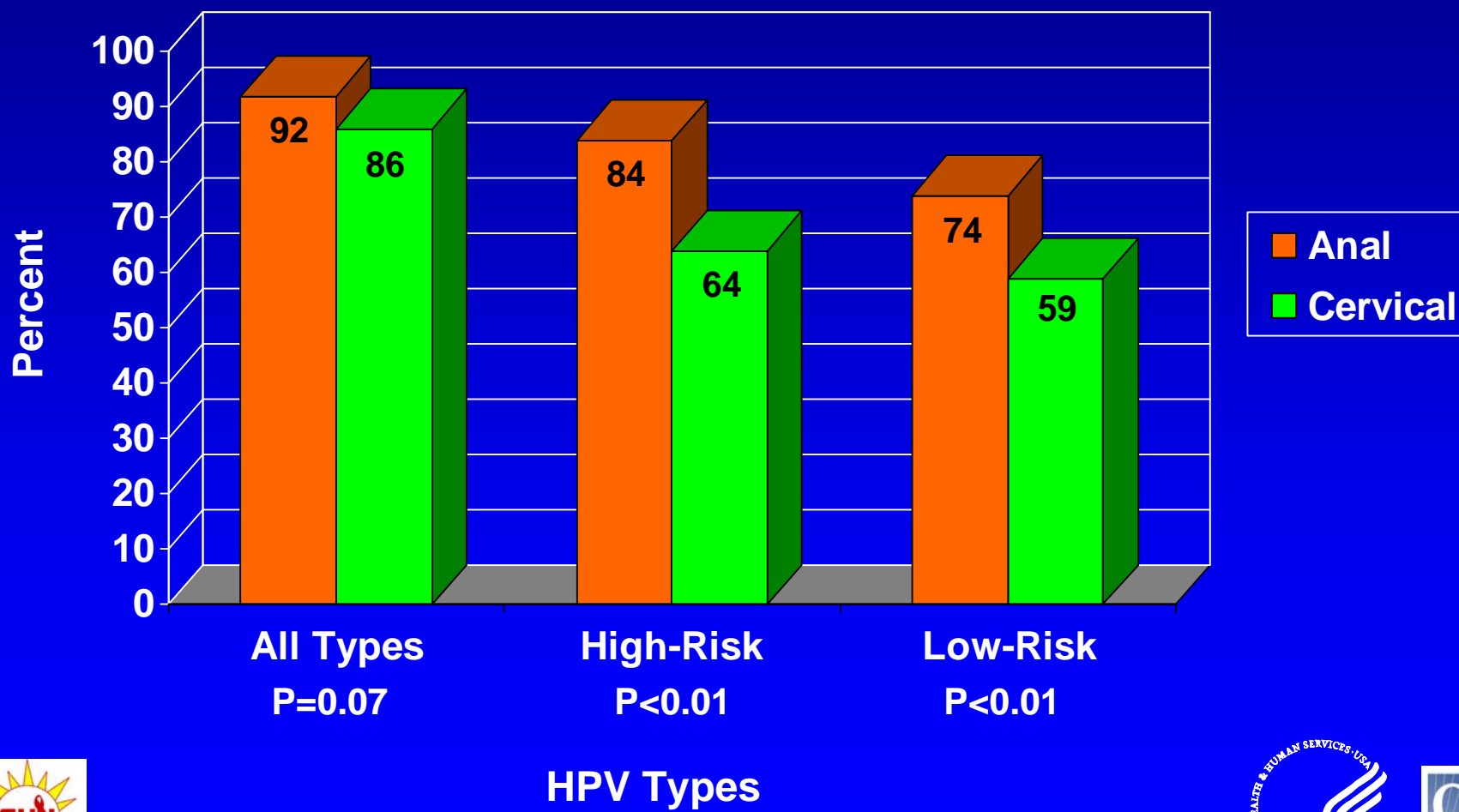
**HIV viral load (\log_{10})
(n=121)**

**Mean: 2.1
Median: 1.7
Range: Und - 5.7**



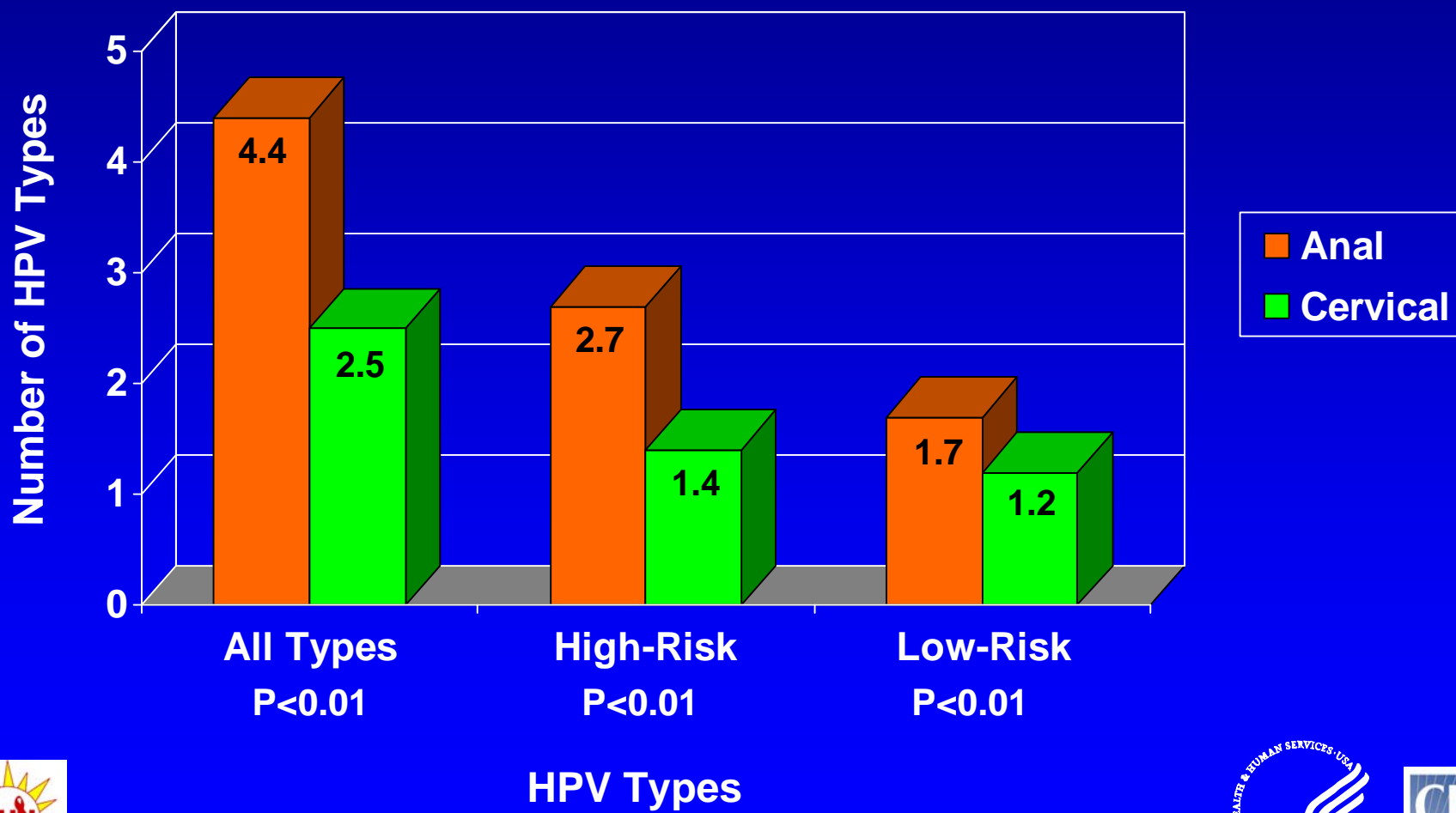


Prevalence of HPV in the Cervix and the Anus





Mean Number of HPV Types in the Cervix and the Anus





HPV and Anal Sex



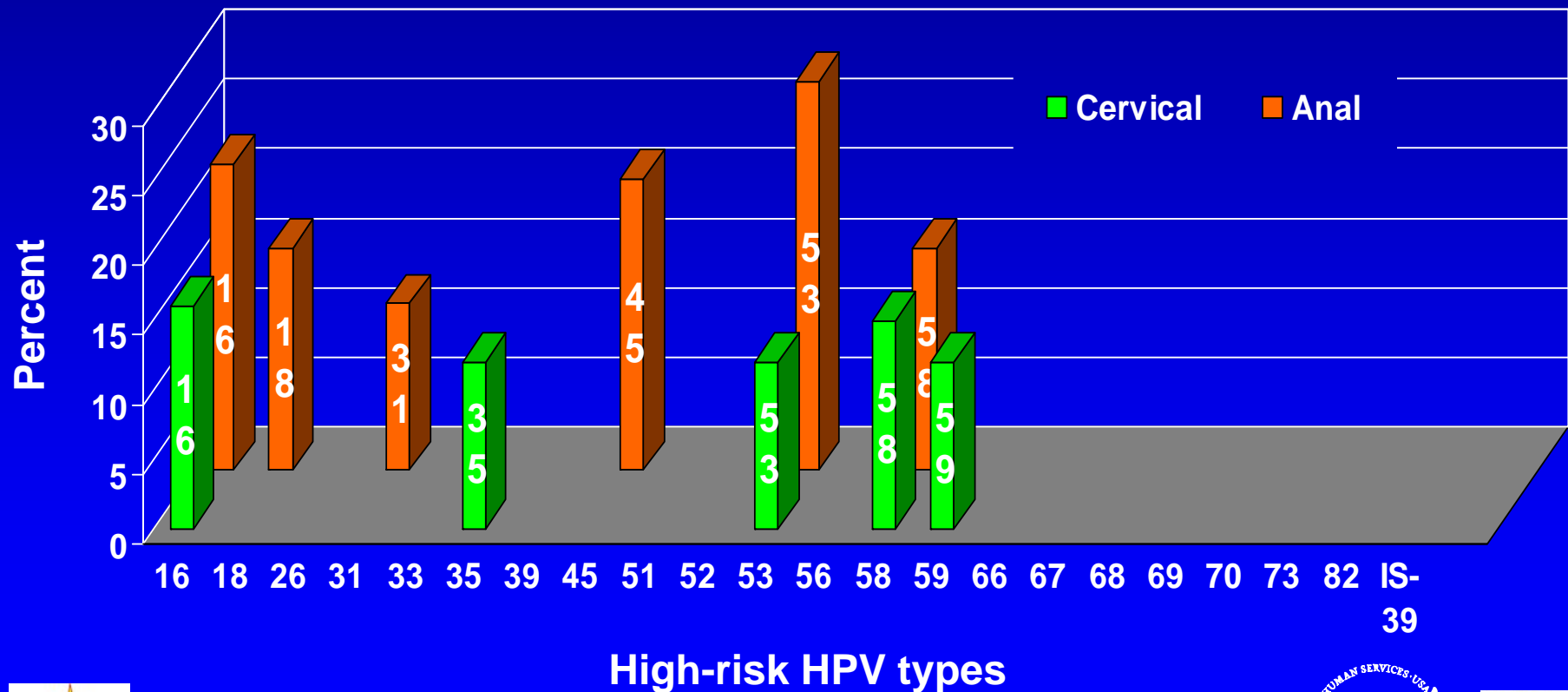
- History of any anal sex was reported by 40% of women
- No significant difference between women reporting a history of anal sex compared with women who did not

| | Self – reported anal sex | | P value |
|---------------|--------------------------|-----|---------|
| | Yes | No | |
| Anal HPV+ | 93% | 89% | 0.53 |
| Cervical HPV+ | 85% | 86% | 0.91 |



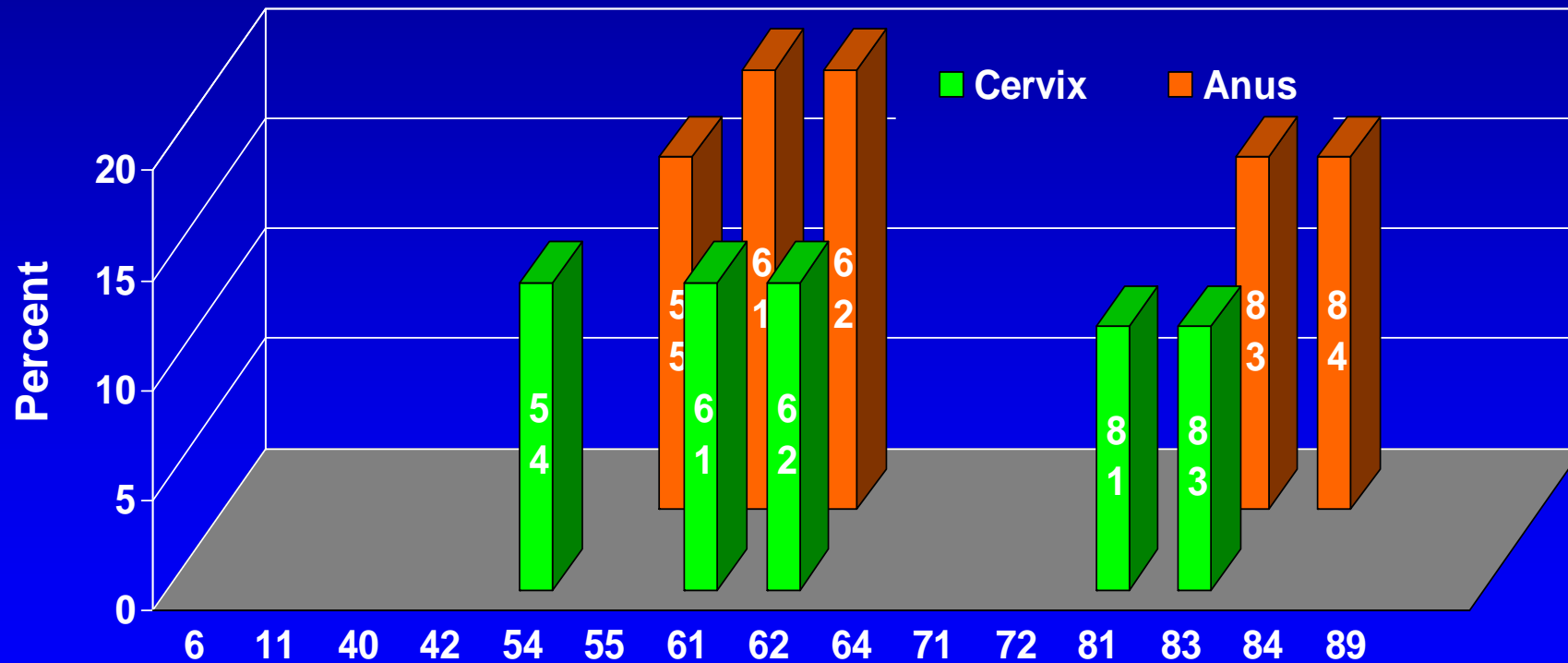


Five Most Prevalent High-Risk HPV Types in Anus and Cervix





Five Most Prevalent Low-Risk HPV Types in Anus and Cervix

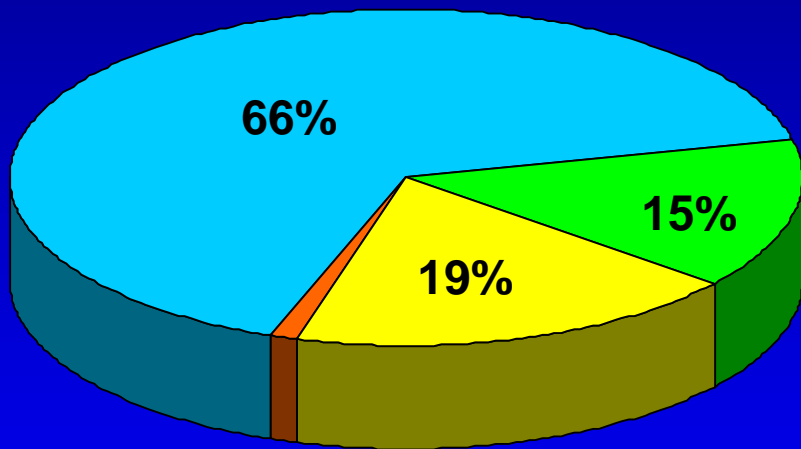


Low-risk HPV types



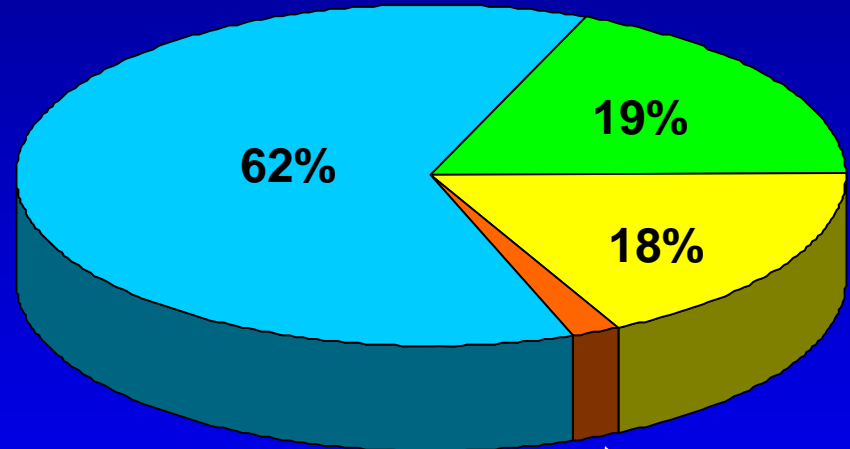
Cervical and Anal Cytology Results

Cervical

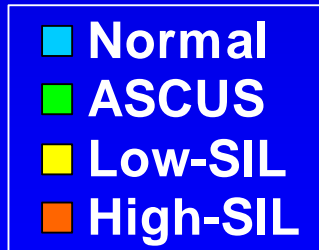


1%

Anal

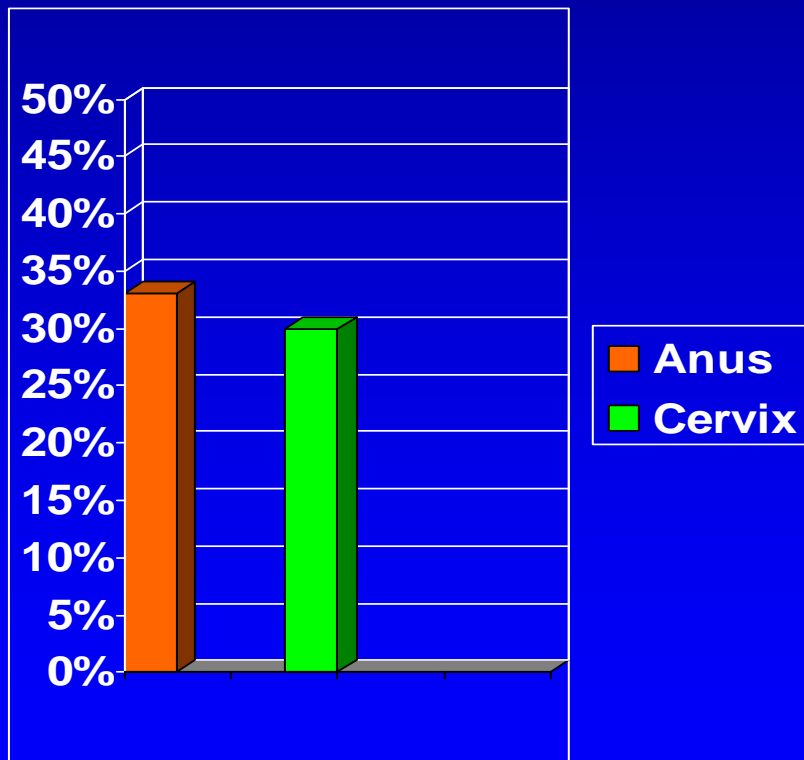


2%



Anogenital Cytological Abnormalities (PAP)

Overall Prevalence of Abnormal PAP smears:



- **49% of women: Normal both sites**
- **12% of women: Abnormal both sites**
- **21% of women: Abnormal anal only**
- **18% of women: Abnormal cervical only**

History of anal sex was not predictive of an abnormal anal PAP:

- **42% of women with a hx of anal sex had an abnormal anal PAP**
- **30% of women with no hx of anal sex had an abnormal anal PAP**



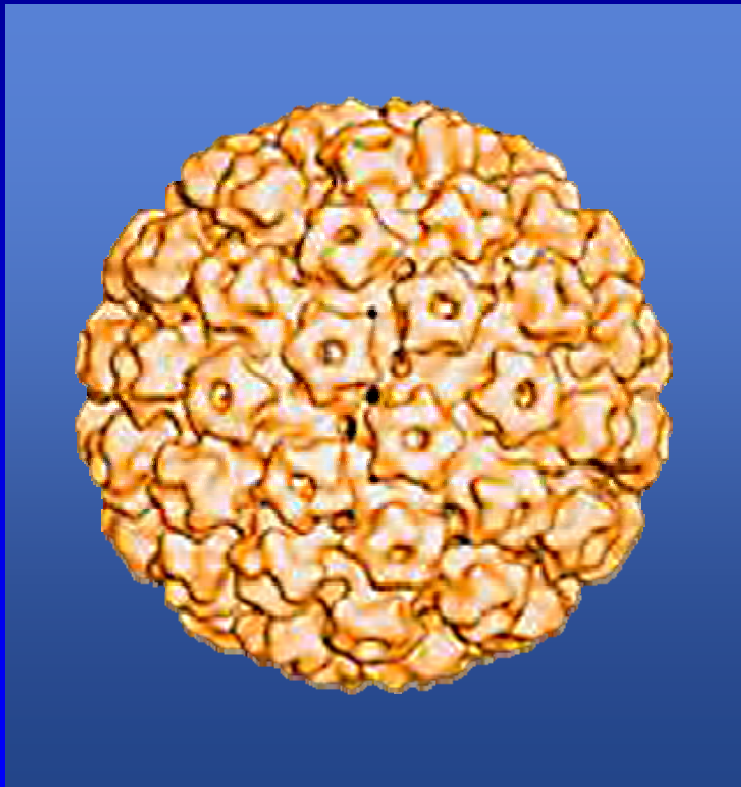
Conclusion



- In the era of HAART, HIV-infected women have a high prevalence of HPV infections
- HPV prevalence is higher in the anus than in the cervix
- HPV diversity is greater in the anus than the cervix
- No correlation between finding abnormal cytology in anus and cervix
- There is no difference in HPV prevalence or abnormal cytology between women who reported a history of anal sex and those who did not



HPV Vaccine



- **Capsid with major and minor capsid proteins**
- **Capsid enclosing the DNA genome**
 - ORFs divided into early (E) and late (L) regions
 - L1 and L2 ORFs in the regulatory part of the genome encode capsid proteins

HPV Vaccine

- **Candidate vaccines consist of virus like particles (VLP) generated by recombinant expression of the major capsid protein L1**
- **L1 VLP is an empty capsid that seems to have identical morphology to the native virion**
- **L1 VLP give type specific protection**

Two candidates:

1. **Bivalent HPV 16/18 vaccine from GSK:
Cerverix ®**
2. **Quadrivalent HPV 6/11/16/18 from Merck:
Gardasil®**

HPV Vaccine

Lancet Oncology May 2005;6:271-78

- **FDA approved June 8, 2006**
- **Recommended for females ages 9 to 26**
- **All women in the vaccine arm developed detectable antibody responses to the vaccine types – substantially higher titers than in those assigned placebo that had a prior history of natural HPV infection**
- **HPV 16 titers a log higher than other**
- **Combined incidence of persistent infection or disease due to HPV 6, 11, 16, and 18 fell by 90% in vaccine vs. placebo group**
 - **0.7 vs. 6.7 incidence per 100 women-years at risk**

FUTURE I – NEJM May 2007

- **Randomized double-blind, placebo-controlled study assessing the efficacy of the vaccine in preventing anogenital disease related to the four vaccine HPV types**
- **Compared 2723 vaccinated women to 2732 women receiving placebo**
 - Age 16-24, mean age 20 years
 - Not pregnant
 - No history of abnormal PAP or anogenital warts
 - Followed for 48 months

FUTURE I – External lesions

NEJM May 2007

| | Vaccine group | | Placebo | | Vaccine efficacy |
|---------------------------------------|----------------------|-------------|---------|-------------|------------------|
| | Total | No of cases | Total | No of cases | % |
| External lesions due to vaccine types | 2261 Per protocol | 0 | 2279 | 60 | 100 |
| | 2723 Int to treat | 28 | 2732 | 102 | 73 |
| External lesions due to any HPV types | 2732 | 104 | 2732 | 157 | 34 |

FUTURE II – High Grade Cervical Lesions

NEJM May 2007

- **Randomized double-blind, phase III study assessing the efficacy of the vaccine, compared 6087 vaccinated women to 6080 women receiving placebo**
 - Age 15-26, mean age 20 years
 - Not pregnant
 - No history of abnormal PAP or anogenital warts
 - No more than four sex partners
 - Followed for 48 months

Subj in per protocol population

| Lesion type | Vaccine group | | Placebo | | Vaccine efficacy |
|-------------------|---------------|-------------|-------------|-------------|------------------|
| | Total | No of cases | Total | No of cases | % |
| HPV 16, 18 | 6305 | 1 | 5260 | 42 | 98 |
| CIN grade 2 | | 0 | | 28 | 100 |
| CIN grade 3 | | 1* | | 29 | 97 |
| Adenocarc | | 0 | | 1 | 100 |

*Also positive for HPV 58

Intention to treat

| Lesion type | Vaccine group | | Placebo | | Vaccine efficacy |
|-------------------|---------------|-------------|-------------|-------------|------------------|
| | Total | No of cases | Total | No of cases | % |
| HPV 16, 18 | 6087 | 83 | 6080 | 148 | 44 |
| CIN grade 2 | | 41 | | 96 | 57 |
| CIN grade 3 | | 57 | | 104 | 45 |
| Adenocarc | | 5 | | 7 | 28 |
| HPV any | 6087 | 219 | 6080 | 266 | 17 |
| CIN grade 2 | | 149 | | 192 | 22 |
| CIN grade 2 | | 127 | | 161 | 21 |
| Adenocarc | | 5 | | 8 | 37 |

Comparison of ACIP and ACS Recommendations for HPV Vaccination

| Advisory Committee on Immunization Practices | American Cancer Society |
|---|---|
| <p>Routine HPV vaccination with three doses of the quadrivalent vaccine (Gardasil) is recommended for girls 11 and 12 years of age 9,10</p> | <p>Routine HPV vaccination is recommended for girls 11 and 12 years of age 8</p> |
| <p>Girls as young as nine years can be vaccinated</p> | <p>Girls as young as nine years can be vaccinated</p> |
| <p>HPV vaccination is recommended for all females 13 through 26 years of age</p> | <p>HPV vaccination is recommended for all females 13 through 18 years of age</p> |
| <p>The vaccine is not licensed for use in females younger than nine years or older than 26 years 9</p> | <p>HPV vaccination is not recommended for women older than 26 years 8</p> |
| | <p>Data are insufficient to recommend for or against universal vaccination of women 19 to 26 years of age</p> |


Limitations

- **Overall vaccine efficacy is modest in preventing disease among women with previous HPV exposure**
 - Vaccination before the onset of sexual activity is preferable
- **Only two oncogenic types are included in the vaccine**
 - Sizable contribution of other HPV types to overall high grade lesions (44 vs 17% vaccine efficacy)
- **Overall incidence of high grade lesions due to any HPV types continued to increase at end of obs period whereas the incidence due to 16 and 18 had reached a plateau**
 - Does eliminating 16 and 18 allow other oncogenic types to “fill the biologic niche”
- **Interim analysis (FDA) showed a disproportionate number of CIN 2 and 3 related to non-vaccine HPV types among vaccinated women (not statistically significant)**
 - Need updated analyses from these ongoing trials

Limitations

- **COST \$360 for the series**
- **In women with no evidence of previous HPV 16 and 18 exposure before vaccinations (per protocol group), 98% efficacy in preventing disease – what about efficacy in this group in preventing disease due to any HPV**
- **FUTURE did not enroll girls <15 years old**
- **Politics and parents:**
 - “Vaccination will have a disinhibiting effect and thus encourage sexual activity among teens” “Invitation to teenage promiscuity”
 - Mandating vaccine (with opt out) “Intrusion on parental discretion”
- **Boys / men**
- **HIV infected**

Prevalence of vaccine HPV types in HIV-infected individuals

| | HERS | Sun  |
|----------------------------|---------------|---|
| HPV types 6, 11, 16, 18 | 15.9% | |
| 6 and 11 | 3.1% and 0.9% | 13 and 3% anal 5 and 3% cervical |
| 16 and 18 | 5.7% and 6.1% | 14 and 21% anal 4 and 15% cervical |



Prevalence of HPV Types Present in Quadrivalent HPV Vaccine (6, 11, 16, 18)



| | Anus | Cervix | Either anus or cervix |
|------------------|------|--------|--------------------------|
| HPV 16 and/or 18 | 32% | 19% | 38% |
| HPV 6 and/or 11 | 16% | 9% | 19% |

| | Number of women | Percent of women |
|---------------------|-----------------|------------------|
| All 4 vaccine types | 0 | 0 |
| 3 vaccine types | 2 | 2 |
| 2 vaccine types | 13 | 11 |
| 1 vaccine type | 19 | 17 |



Prevalence of vaccine HPV types in HIV-infected individuals

Although HIV-infected women have a higher prevalence of vaccine HPV subtypes 6, 11, 16, and 18, the majority of them do not

Unlikely to have all the vaccine types

- benefit at least from some of the vaccine types
- ?significance of the higher titers induced by the vaccine

HPV vaccine needs to be tested in HIV infected individuals

A Phase II Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Human Papillomavirus Vaccine in HIV-Infected Women

**E. M. Kojic, S. Cu-Uvin, M. Cespedes, J. Aberg, L. G. Naini, M. Kang for the
*ACTG A5240 Study Team***

A5240 Hypothesis

- **Vaccination with the quadrivalent HPV vaccine (Gardasil®) will result in titers to types 6, 11, 16, and 18 above a level of type specific seropositivity in HIV- infected women.**
- **The HPV vaccine is safe and well tolerated among HIV-infected women.**

Study Schema: ACTG A5240

- **Design:**
 - A phase II, open-label single-arm study
- **Stratification:**
 - Cohort 1 (N=134):
 - 67 participants with $200 < CD4+ \leq 350$ and HIV-1 RNA $\leq 10,000$
 - 67 participants with $200 < CD4+ \leq 350$ and HIV-1 RNA $> 10,000$
 - Cohort 2 (N=134):
 - 67 participants with $200 < CD4+ \leq 350$ and HIV-1 RNA $\leq 10,000$
 - 67 participants with $200 < CD4+ \leq 350$ and HIV-1 RNA $> 10,000$
 - Cohort 3 (N=134):
 - 67 participants with $CD4+ \leq 200$ and HIV-1 RNA $\leq 10,000$
 - 67 participants with $CD4+ \leq 200$ and HIV-1 RNA $> 10,000$

Study Schema: A5240

- **Population**

- HIV infected women, 13 to 45 years of age
- CD4 counts and HIV viral load as per prior enrolment cohorts

- **Exclusions**

- Anal, cervical and or vulvar cancer
- Pregnancy or breast-feeding
- Use of immunomodulatory agents
- Serious illness requiring hospitalization
- Hemophilia, thrombocytopenia
- Hysterectomy

THANK YOU