Northwest AIDS Education and Training Center

Cervical Cancer Screening in HIV

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Outline

- Epidemiology of HPV and cervical cancer in HIV
- Review of cervical anatomy and HPV pathophysiology
- Current cervical cancer screening guidelines
  - When to start
  - When to stop
  - What to order and how often
  - What to do after hysterectomy
  - Role of HPV testing
  - Special populations
- Follow-up of abnormal cytology
- Future directions in cervical cancer screening

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Epidemiology of HPV and Cervical Cancer in HIV

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HPV Epidemiology

- 5th most common cancer in humans
- 2nd most common cancer in women
- 190,000 women die each year world wide
  - 78% in resource poor settings, still the leading cause of death from cancer for women
- Up to 50% of sexually active women in the US HPV+ 36 months after coitarche
  - Prevalence of ~57% in sexually active adolescent women
  - Resolution of infection occurs in 90% of adolescents in 2y
- Women 50 years of age: 80% will have acquired genital HPV infection

1. Cates W, *Sex Transm Dis,* 1999.
2. Weinstock H, *Perspect Sex Reprod Health,* 2004.
3. *Am J Epi,* 2003;157:218.

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Human Papilloma Virus (HPV)

- Most common sexually acquired infection in the world
- DNA tumor virus
- Intraepithelial infection
- > 100 types
  - 40 infect cervix
  - 13 oncogenic (16, 18, 31, 33…) → cancer
  - 6, 11 → genital warts
- Recurrent infections common
- Available prevention: HPV vaccine and CONDOMS!

CDC Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected adults and adolescents, *MMWR*, 2009.

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HPV and HIV

- HPV is more persistent in HIV positive women
- Higher levels of HPV are detected in HIV positive women
- Multiple HPV infections are more common
- The incidence rate of cervical cancer is still up to 9 times more likely in women with HIV
- Cervical cancer→ AIDS-defining condition
- Cervical dysplasia→ "B" condition

Sun XW, *NEJM*, 1997.
Jamieson DJ, *AJOG*, 2012.
Mbulaiteye SM, *J Acquir Immune Defic Syndr*, 2003.

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HPV Manifestations

- Persistent HPV infection can lead to:
  - Warts
    - Genital
    - Anal
    - Oral
  - Cancer precursors
    - CIN
    - VIN
    - VAIN
    - AIN
  - Cancer (squamous and adenocarcinoma)
    - Cervix
    - Vulva
    - Vagina
    - Oral cavity
    - Penis
    - Oropharynx

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HPV and Cancer, US Rates 2004-2008

Site	Average #/yr	% HPV related	Range
Cervix	11967	96	95-97
Vulva	3136	51	37-65
Vagina	729	51	37-65
Anus-female	3089	93	86-97
Anus-male	1678	93	86-97
Oral-female	2370	63	50-75
Oral-male	9356	63	50-75

Gillison, Cancer 2008; 113: 3036-46

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Review of Cervical Anatomy and HPV Pathophysiology

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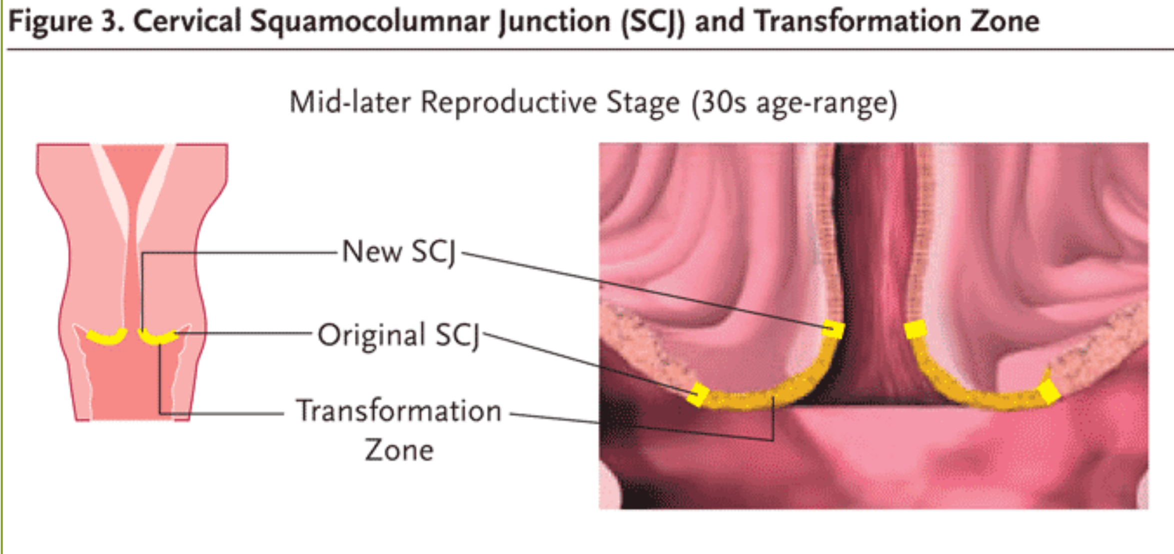
Definitions and Anatomy

- Pre-pubescent cervix covered with columnar epithelium
- Columnar cells gradually replaced by squamous epithelium (squamous metaplasia)
- Squamocolumnar junction: intersection between columnar and squamous epithelium
- Transformation Zone: the area of squamous metaplasia
  - Most common location of neoplastic change
  - Important landmark for colposcopy



http://www.prn.org/index.php/coinfections/article/anogenital_hpv_neoplasia_hiv_positive_502

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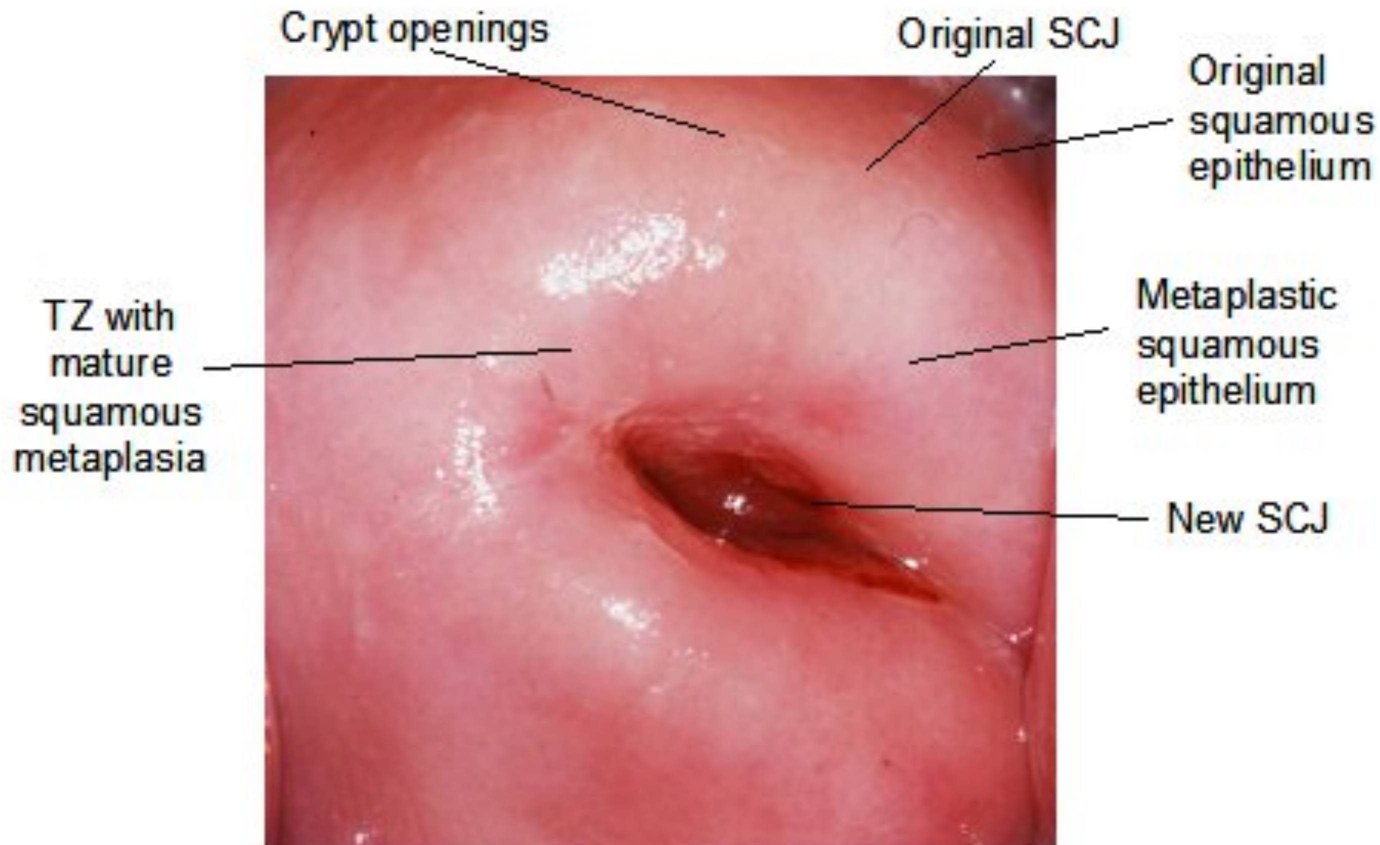
Normal Cervix



http://screening.iarc.fr/colpo.php

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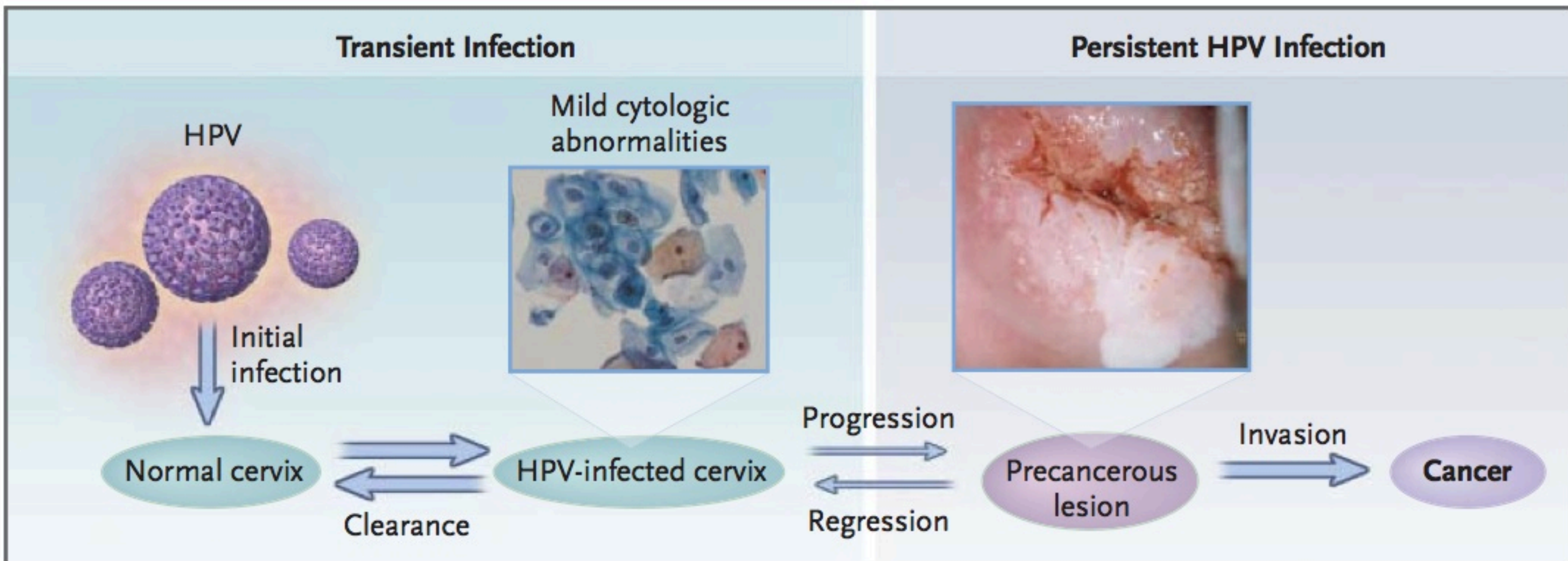
HPV Natural History



Wright, NEJM 2003; 348(6):489-490.

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Current Cervical Cancer Screening Guidelines

Different Guidelines: Different Functions

- USPSTF/ACS/ASCCP/ASCP→ age, interval and frequency of screening (updated March 2012)
- ASCCP Consensus Guidelines→ interpretation and management of screening and colposcopy results (updated 2006, minor changes March 2012)
- IDSA/CDC/HHS OI Guidelines→ both (updated 2009)

- Ultimate goal of all guidelines is cervical cancer prevention via:
  - Screening (cytology with or without HPV DNA testing)
  - Evaluation of screen positive women using colposcopy and biopsy
  - Treatment of women with biopsy-confirmed high-grade cancer precursors

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Frequency of Screening in HIV

- Pap smear twice in the first year after diagnosis or entry into care
  - If both Pap smears are normal, then annual screening with Pap
  - If abnormal, follow-up will depend on the abnormality

- Refer to colposcopy if:
  - ASCUS (Atypical squamous cells of undetermined significance)
  - ASC-H (Atypical squamous cells – cannot exclude high grade)
  - AGC (Atypical glandular cells)
  - LSIL (Low grade squamous intraepithelial lesion)
  - HSIL (High grade squamous intraepithelial lesion)

CDC Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected adults and adolescents, *MMWR*, 2009.

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Cervical Cancer Screening Guidelines

	USPSTF/ACS/ASCCP (WOMEN WITHOUT HIV)	WOMEN WITH HIV
AGE AT INITIATION	21 regardless of risk factors	Onset of sexual activity
FREQUENCY		
Age 21-29	Pap every 3 years	Annually
Age ≥30	Pap every 3 years OR Pap + HPV every 5 years	Annually
DISCONTINUATION	Age 65	?????? Never ??????
s/p HYSTERECTOMY	D/C if for benign reasons and no history of CIN 2+ for 20 years, otherwise screen for 20 years after	?????? Same ??????
HPV VACCINATED	No change	No change

Moyer VA, *Ann Intern Med*, 2012.
CDC Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected adults and adolescents, *MMWR*, 2009.

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Screening of Adolescents with HIV

- Symposium sponsored by NIH/ACS/ASCCP in 2009 to address adolescents
- Less is more approach
  - Start screening at age 21 regardless of risk factors
  - Never use HPV testing in adolescents
  - Rarely intervene with colposcopy or LEEP/CONE except HSIL, CIN3
    - Rationale: increased risk of pre-term delivery and LBW infants, psycho-sexual dysfunction, high rates of regression even with CIN 2,3
- But in HIV, regression rates are lower, more CIN
  - Start screening right away at onset of sexual activity
  - Any abnormality, ASCUS+→ colposcopy
  - Reserve treatment for CIN3
  - No role for HPV testing

J Low Genit Tract Dis. 2010 January; 14(1): 73–80.

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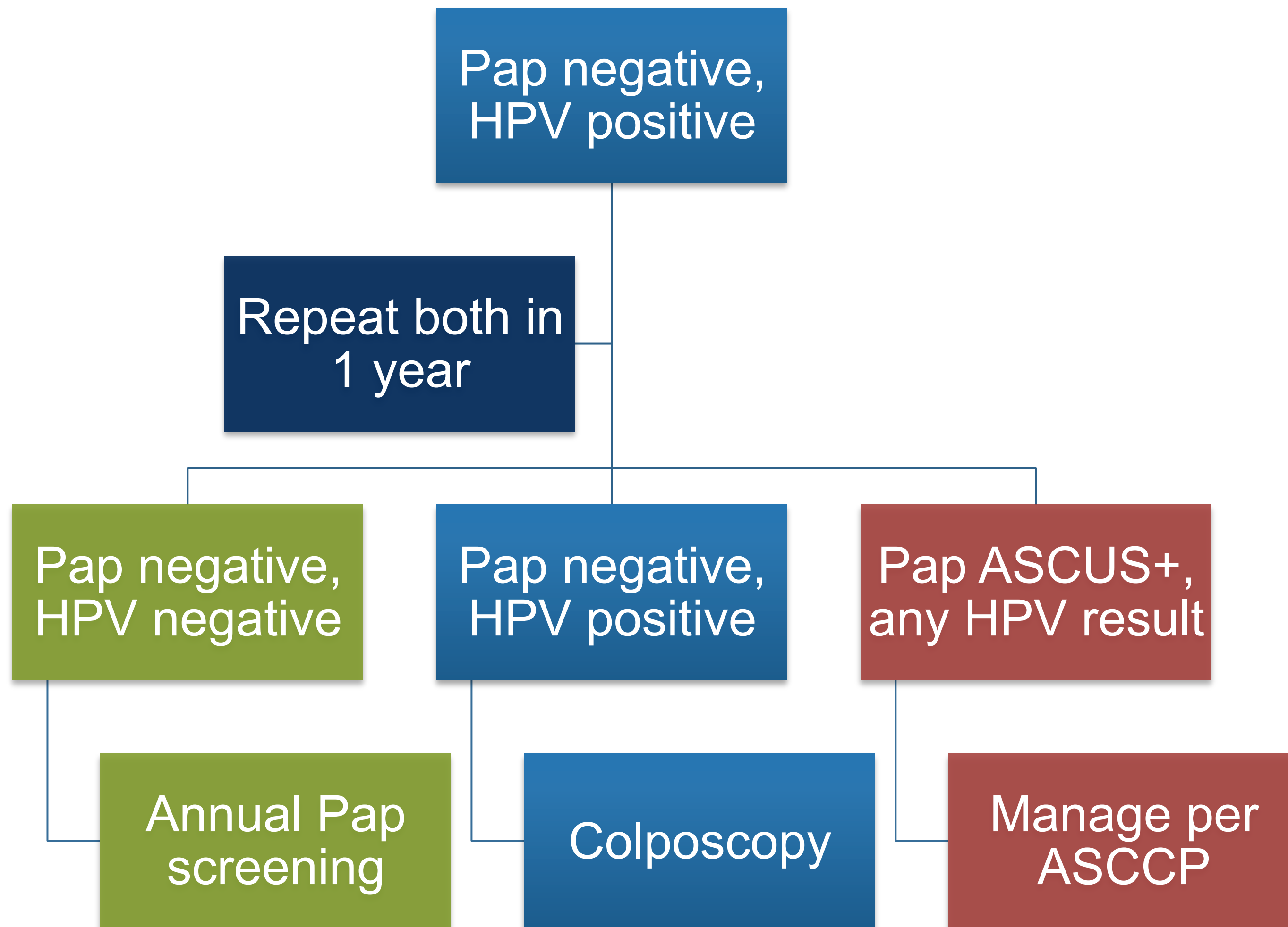
Oops, I ordered HPV and it's Positive



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Role for HPV Testing

General Population

- Triage ASCUS result
- Co-test with Pap ≥ 30 y
- Post-menopausal women LSIL
- Follow-up after colpo or treatment procedure (LEEP/CONE) per guidelines

HIV Population

- Triage ASCUS result?
- ~~Co-test with Pap ≥ 30 y~~
- ~~Post-menopausal women LSIL~~
- Follow-up after colpo or treatment procedure (LEEP/CONE) per ASCCP guidelines?
- Per CDC OI Guidelines: NEVER!

Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. MMWR 2009;58 (No. RR-4) April 10, 2009

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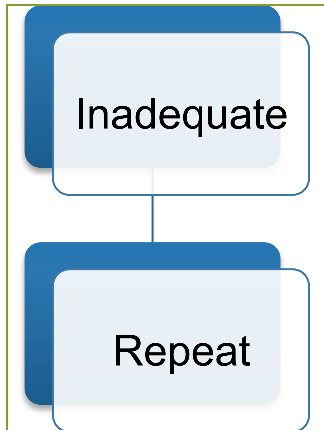
Pap Smear Results



Negative

Trichomonas

Treat

Other non-neoplastic

Atrophy

Intravaginal Estrogen and repeat in 3 months

Glandular Cells

Gynecologic Exam

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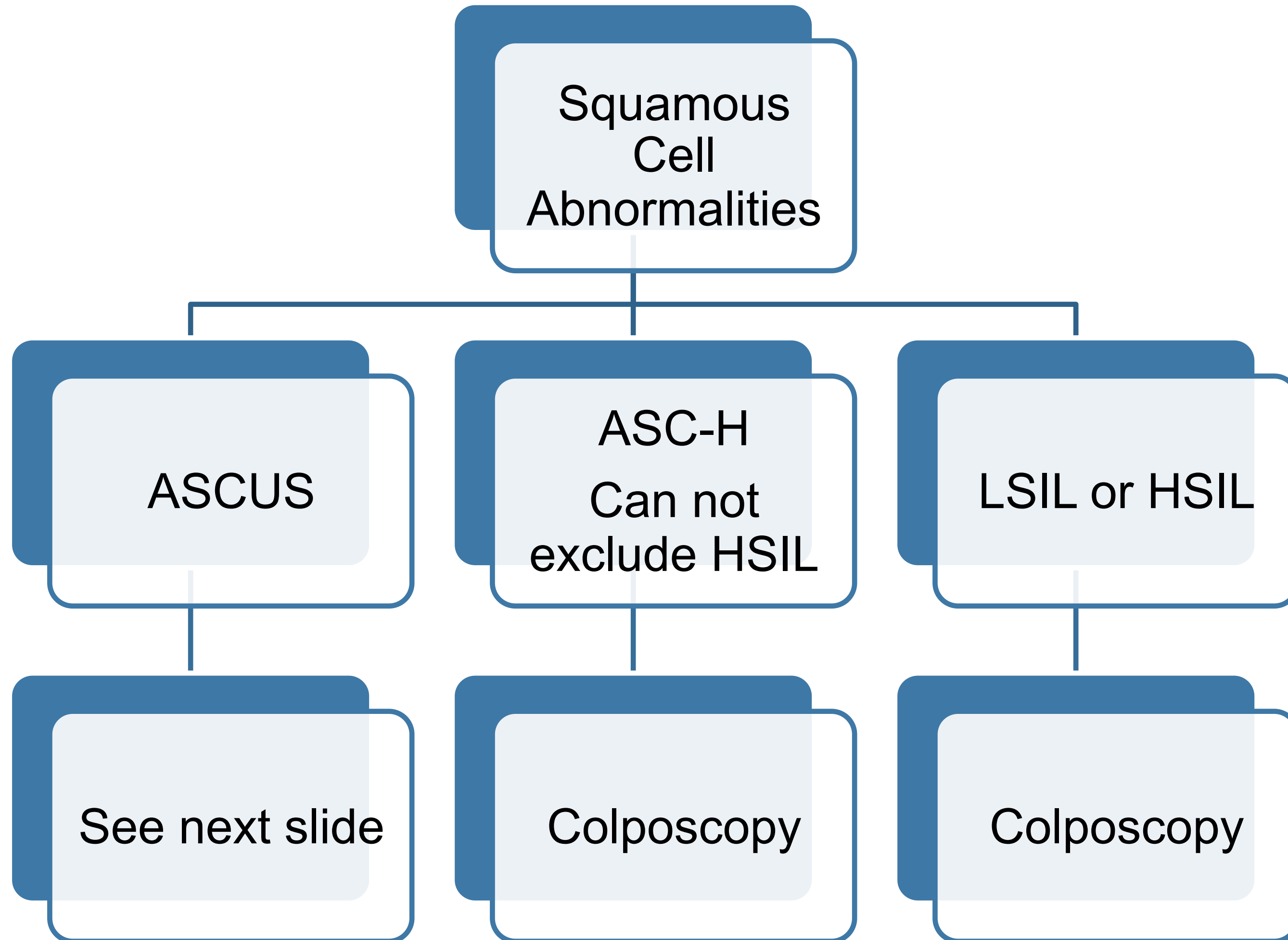
2006 Consensus Guidelines www.asccp.org

Pap Smear Results



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Triage of ASCUS Results

- Conflicting guidelines
  - 2006 ASCCP Guidelines
  - CDC OI Guidelines
- ASCUS common in HIV, up to 78% in 4-5 year follow-up
- ASCCP: HIV infected women with ASCUS can be triaged as uninfected women
  - UNLESS severely immunocompromised?
- CDC: Never use HPV, data insufficient in this population

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ASCCP Algorithm for ASCUS Management

Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US)

- **Repeat Cytology** @ 6 & 12 mos
  - **Both Tests Negative** → **Routine Screening**
  - **≥ ASC** *(on either result)* → **Colposcopy**
- **Colposcopy** — *Endocervical sampling preferred in women with no lesions, and those with unsatisfactory colposcopy*
  - **NO CIN**
    - **HPV Unknown** → **Repeat Cytology** @ 12 mos
    - **HPV Positive*** → **Cytology** @ 6 & 12 mos OR **HPV DNA Testing** @ 12 mos
      - → **≥ ASC or HPV (+)** → **Repeat Colposcopy**
      - → **Negative** → **Routine Screening**
  - **CIN** → **Manage per ASCCP Guideline**
- **HPV DNA Testing*** — *Preferred if liquid-based cytology or co-collection available*
  - **HPV Positive*** *(managed in same manner as women with LSIL)* → **Colposcopy**
  - **HPV Negative** → **Repeat Cytology** @ 12 mos

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* *Test only for high-risk (oncogenic) types of HPV*

http://www.asccp.org/ConsensusGuidelines/ConsensusGuidelinesOverview/tabid/5956/Default.aspx

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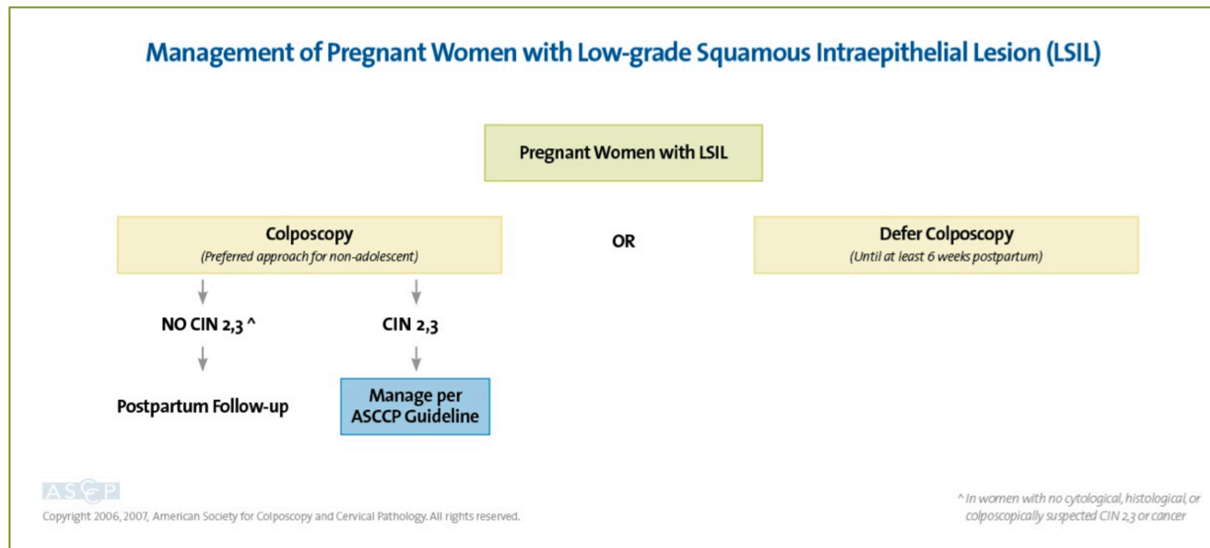
Management of the Pregnant Woman

- Want to avoid invasive intervention in pregnant women
- Only finding that would affect management, timing, route of delivery is invasive cancer
- Can defer colposcopy for ASCUS and LSIL until 6 weeks post-partum
- Immediate colposcopy for HSIL or AGC



www.asccp.org

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Follow-up of Abnormal Screening

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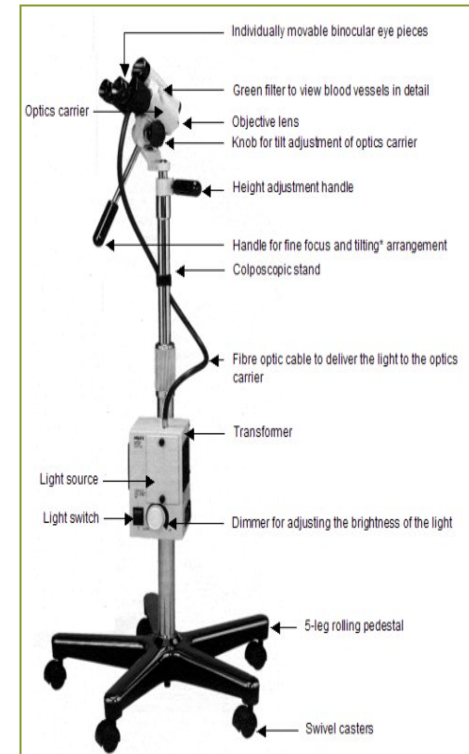
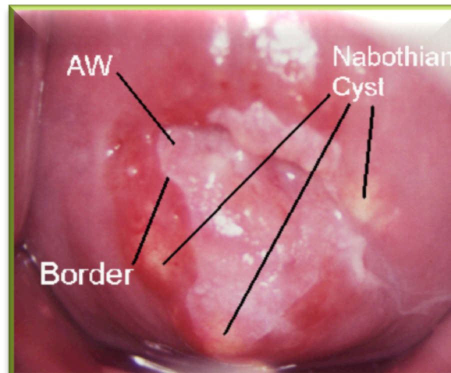
Goal of Colposcopy

- Localize the Transitional Zone (squamo-columnar junction)
- Evaluate the extent of the disease with application of acetic acid
- Locate the area most suspicious for biopsy
- Determine if invasive cancer is present





http://screening.iarc.fr/colpo.php

Vazquez E. General Principles of Colposcopy, Residents Academic Day 7/22/2010 #7

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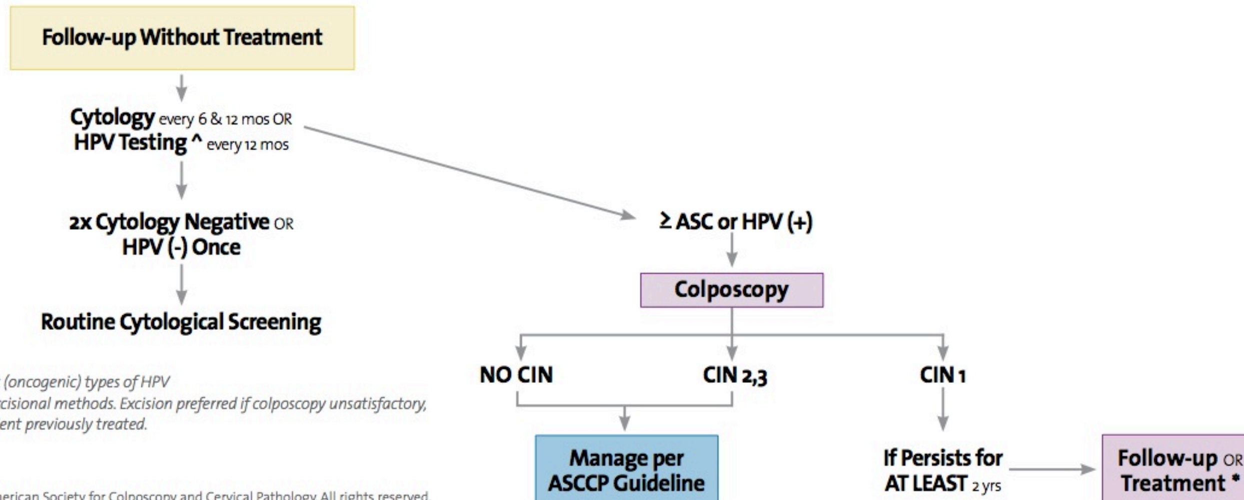
ASCCP Algorithms

- Available at ASCCP website
  - http://www.asccp.org/LinkClick.aspx?fileticket=FRKDC1RPF7A%3d&tabid=5965
- Not specifically for women with HIV, but very similar to the OI Guidelines with the exception of HPV testing



www.asccp.org

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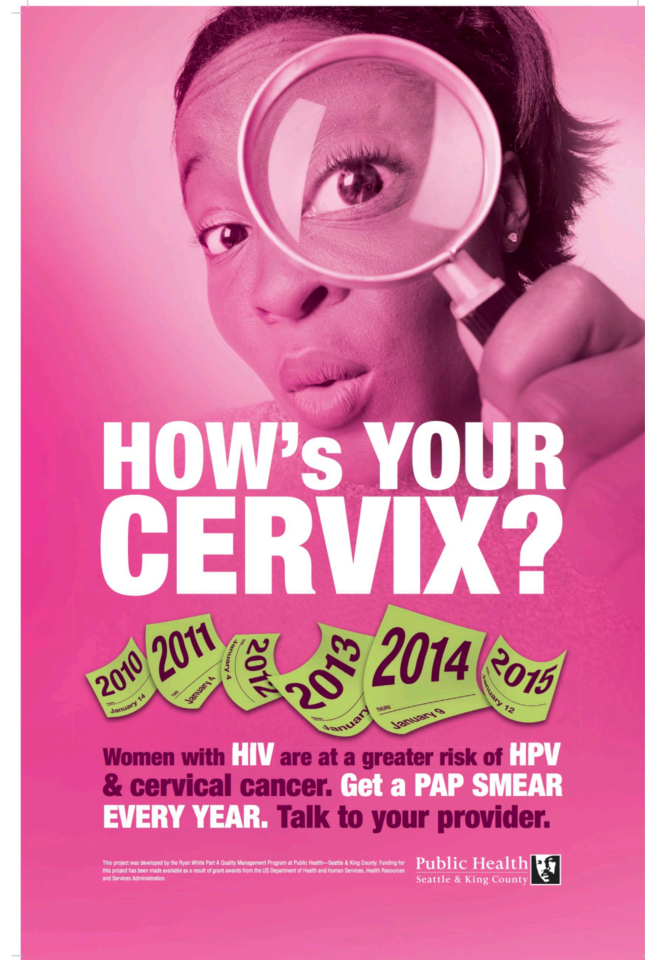
Strategies for Improving Screening Rates

- Patient education addressing rationale and importance of Pap smears for women living with HIV
  - Face-to-face
  - Public Health materials in multiple languages
- Ask about specific concerns and normalize fear and embarrassment
- Offer options for a female clinician if patient uncomfortable with male provider, if possible
- Reminder notices, systemic ticklers
- Coordination of care with GYN



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Possible Future Directions

- Role for HPV testing in women with HIV?
  - Increase interval for testing
- HPV Vaccine efficacy data in women with HIV
- New HPV vaccines
  - 9 valent, predicted to cover 85% of HPV infections (current 70%)
- More specific HPV tests for infection (DNA methylation)
- Anal Pap guidelines
  - Women with HIV, CIN3 likely candidates for screening
- Better financial coverage for HPV co-testing
  - Again not currently recommended in HIV

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Take-Home Points

- Abnormal cervical cytology is more common among HIV-infected women
- Early diagnosis and treatment can be achieved only by routine screening, ideally as part of primary care
- Complete pelvic exam needed to evaluate for uterine, vaginal, and vulvar abnormalities, as well as vaginitis, condyloma, HSV and other STDs
- At this time, annual Pap smears are the standard of care
- Role of HPV testing is limited in women with HIV
  - Triage of women with ASCUS?
  - Follow-up after colposcopy?
- Be aware of and address cultural/individual factors that may be interfering with screening
- Refer to colposcopy for results of ASCUS (+/- HPV?) or worse

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Resources

- ACS/ASCCP/ASCP Screening Guidelines
  - http://onlinelibrary.wiley.com/doi/10.3322/caac.21139/abstract
- USPSTF Screening Guidelines
  - http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm
- Adult and Adolescent OI Guidelines, pages 68-75
  - http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi_041009.pdf
- American Society for Colposcopy and Cervical Pathology (ASCCP) Guidelines
  - www.asccp.org
- HRSA A Guide to the Clinical Care of Women with HIV/AIDS
  - www.hab.hrsa.gov
- Adolescent Guidelines and Rationale
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058950/