Managing HPV for HIV-Positive Women

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Parallel Paths Project

- A series of training sessions on topics of reproductive health for HIV/AIDS social and medical service providers
- Find more and updated information at: http://mcrh-tn.org/outreach_parallel_paths.asp
- Funding for this project provided by the MAC AIDS Fund.

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Learning Objectives

- Discuss the epidemiology and natural history of HPV infection and cervical intraepithelial neoplasia
- Identify the most common genital HPV types in benign and malignant disease

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Learning Objectives (Continued)

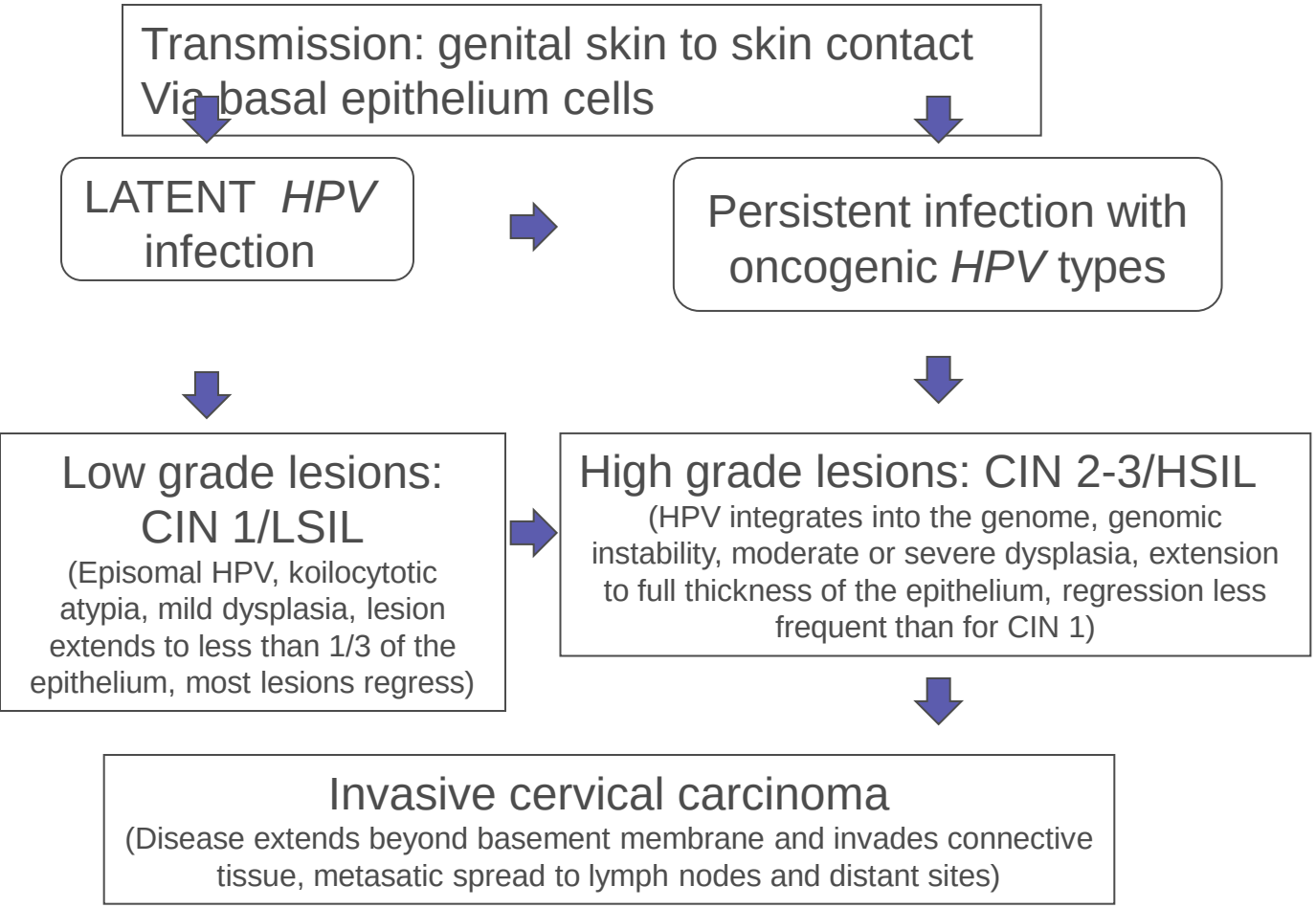
- Discuss the significance of persistent infection with high-risk HPV type
- Identify the most common mode of HPV transmission
- Identify additional impact of HPV for HIV positive individuals

HPV Associated with Cancer and External Genital Warts

	High-Risk Types	Low-Risk Types
Selected types	16,18,31,33,35, 39,45,51,52,56, 58,59,68,82	6,11,40,42,43, 44,54,61,72,81
Associated abnormalities	Low-grade cervical lesions	Low-grade cervical lesions
	High-grade cervical lesions	External genital warts
	Anogenital cancers	

Soper D. *Inf Dis Obstet Gynecol.* 2006; Munoz N. *N Engl J Med.* 2003; Munoz N. *Vaccine.* 2006; Wallboomers JM. *J Pathol.*1999; De Villiers EM. *Int J Cancer.* 2004; zur Hausen H. *J Nat Cancer Inst.* 2000.

HPV Necessary for Cervical Cancer



Cofactors:

- Oral contraceptive use, other hormonal influences
- Parity
- Other STIs
- Smoking
- Nutrition
- Host genetics: Polymorphisms in HLA and other genes
- Viral genetics: Genotype, molecular variants

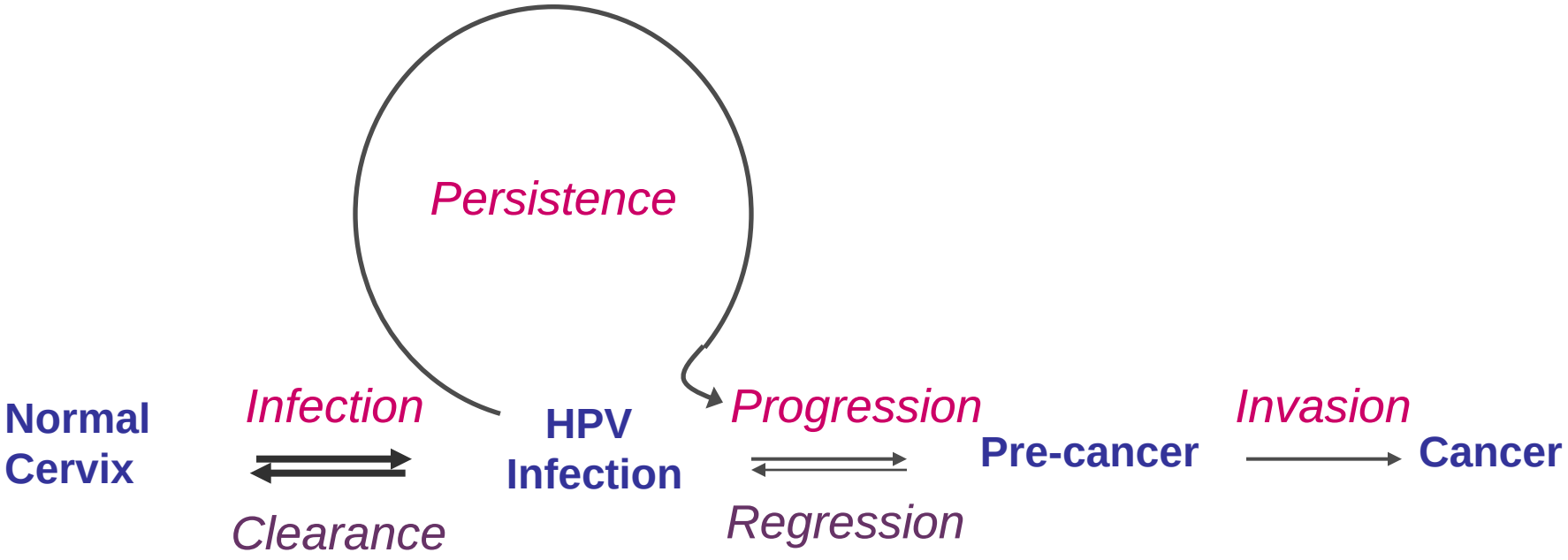
Trottier H. *Vaccine.* 2006; Ley C. *J Natl Cancer Inst.* 1991.

HPV Transmission

- Virus primarily transmitted via genital contact
- Primarily through sexual intercourse, including receptive anal intercourse
- Can also be transmitted by:
  - Non-penetrating sexual activities
  - Oral-genital contact
- Fomite transmission has never been proven

Burchell AN. *Vaccine.* 2006.

Natural History of HPV & Cervical Cancer



Courtesy of M. Schiffman, National Cancer Institute.

High Lifetime Risk of HPV Infection

- 6.2 million new infections
- NHANES 2003-2004 reports a prevalence rate of 26.8% in US females age 14 -59
- Approximately 75% lifetime risk for sexually active individuals
- Additional research for HIV positive individuals, show similar prevelance of HPV

Cates W. *Sex Transm Dis.* 1999; Weinstock H. *Perspect Sex Reprod Health*. 2004; Koutsky L Am J Med 1997; Dunne EF. *J Infect Dis.* 2006; Dunne EF. *JAMA.* 2007.

New HPV Infection is Common in Young Women

Study of 603 female college students

- About 20% were HPV positive at entry
- Almost 40% converted to positive within 24 months

Winer RL. *Am J Epidemiol.* 2003.

HPV Cumulative Incidence: Ho Study

Three-year study

- 608 college students in NJ
  - Mean age 20 years
- Cumulative 36-month incidence of high-risk HPV in women negative at baseline: 43%
- By 12 months after infection,70% had cleared the infection
- By 24 months, over 90% had cleared the infection

Ho GYF. *N Engl J Med.* 1998.

Prevalence of HPV in Men

- HPV prevalence in men ranged from 1.3% to 72.9%.
- Most studies (56%) showed ≥ 20% prevalence

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Dunne EF. *J Infect Dis.* 2006.

Prevalence of HPV in Men (Continued)

- Rates were influenced by:
  - Study population
  - Number of sites collected
  - Number of samples collected
  - Methods used to detect HPV DNA
- Multiple types were common (>50%) and HPV 16 was consistently among the most common anogenital types isolated.

Dunne EF. *J Infect Dis.* 2006.

HPV Cumulative Incidence: Brown Study

Two-year study

- 60 female adolescents 14-17 years old
- 80% had high-risk HPV at some point
- Only 3 had all specimens test negative
- All 3 denied any sexual exposure

Brown DR. *J Infect Dis.* 2005.

Role of Persistent Infection

- Persistent infection with high-risk types of HPV is necessary for the progression of high grade lesions to invasive cancer
- Only persistent infection with high-risk types of HPV progresses to high-grade precancerous lesions and invasive cancer

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Trottier H. *Vaccine.* 2006.

Role of Persistent Infection (Continued)

- Average episode lasts 4-20 months
- <50% of women have same type 1 year later
- Type 16 has a greater risk of persistence

Trottier H. *Vaccine.* 2006.

HPV-Associated Disease

Anogenital cancers

- Cervical
- Anal
- Vulvar and vaginal

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Munoz N. *Vaccine*. 2006; Lacey CJN. *Vaccine*.2006.

HPV-Associated Disease (Continued)

- Other cancers
  - Oral cavity, pharynx, larynx
  - Skin
  - Conjunctiva
- External genital warts
- Laryngeal papillomatosis

Munoz N. *Vaccine*. 2006; Lacey CJN. *Vaccine*.2006.

HPV and Cervical Cancer

- Virtually all cervical cancers are associated with persistent infection with high-risk HPV types
- Data from a variety of studies have confirmed that certain HPV types are associated with cervical cancer:
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
- Others are probably associated:
  - 26,53, 66, 68,73, 82

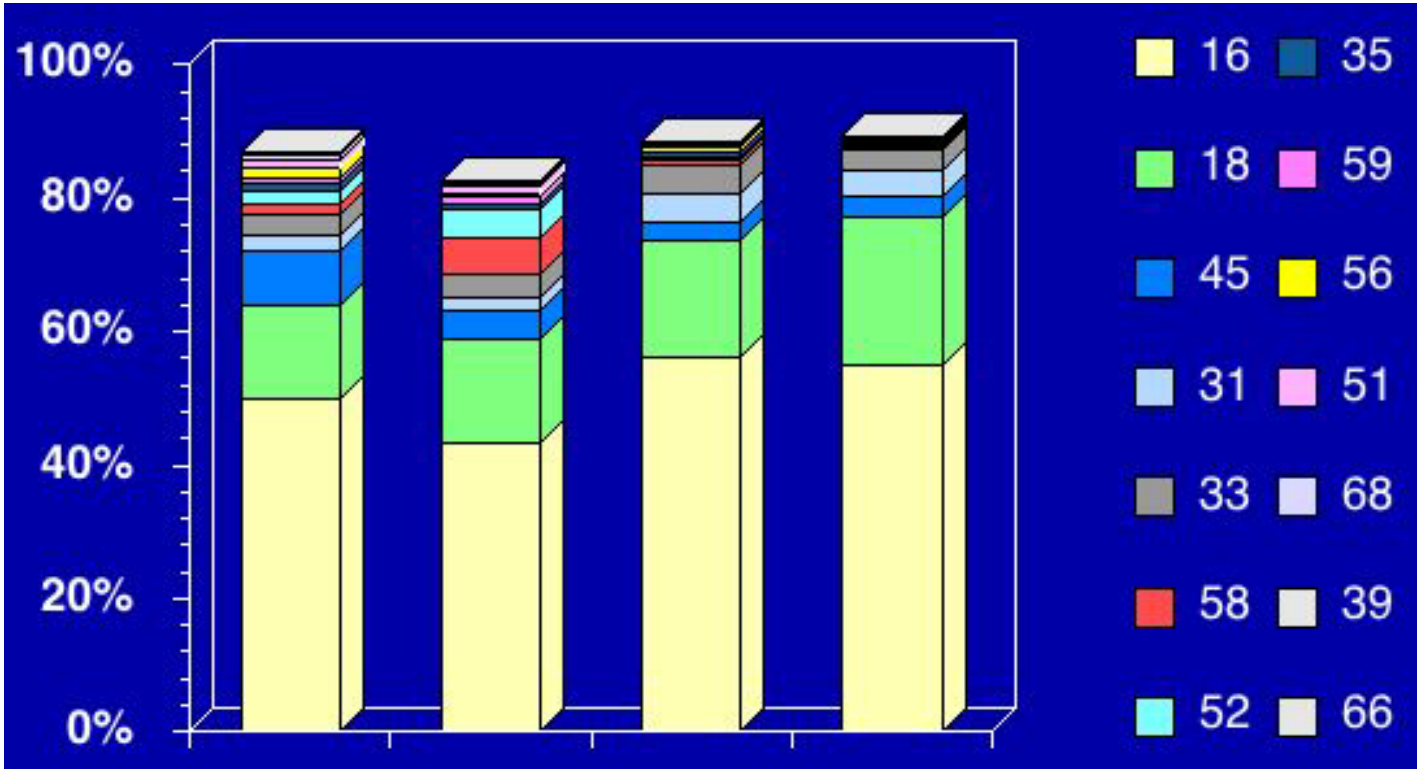
IARC. *Monographs on the Evaluation of Carcinogenic Risks to Humans.* (in press); Munoz N. *Vaccine.* 2006.

HPV Impact: Cervical Cancer

- In the US in 2007:
  - 11,150 cases
  - 3,670 deaths
- Worldwide (2005 estimate):
  - 288,000 deaths per year
  - 80% of deaths occur in developing countries
- Cervical cancer screening: costs $3.4 billion annually

American Cancer Society. *Cancer Facts and Figures*. 2007; IARC. *Cervical Cancer.* 2005; Insinga RP. *AJOG.* 2004.

HPV Types Associated with Cervical Cancer



Clifford GM. *Br Med J.* 2003.

HPV and Non-Cervical Cancers

- HPV 16 and 18
  - Evidence of causal role in cancer of vagina, vulva, penis, anus
- HPV 16
  - Evidence of carcinogenicity in oral cavity, oropharynx, periungual skin

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IARC. *Monographs on the Evaluation of Carcinogenic Risks to Humans* (in press).

HPV and Non-Cervical Cancers
(Continued)

- HPV 18
  - Some evidence of carcinogenicity in oral cavity
- HPV 6, 11, 16, and 18
  - Limited evidence for carcinogenicity in laryngx

IARC. *Monographs on the Evaluation of Carcinogenic Risks to Humans* (in press).

HPV Associated Cancer - US

Site	Total Cancers	# Cases Attributable to HPV (%)
Cervix	11,150	11,150 (100)
Penis	1,280	512 (40)
Vulva/Vagina	5,630	2,252 (40)
Anus	4,650	4,185 (90)
Airway	24,540	6,380 (26)
TOTAL	47,250	24,479 (12)

American Cancer Society. Cancer Facts and Figures. 2007;
Parkin DM. *Vaccine.* 2006.

HPV 16 and Abnormal Pap Tests

Category	Percentage		Total per Year
	Paps	16+	
ASC	5.1%	13.3%	399,000
LSIL	2.6%	23.6%	295,000
HSIL	0.7%	60.7%	182,100

Davey DD. *Arch Path Lab Med.* 2004.
CDC. *MMWR* (RR-2). 2007

Impact: External Genital Warts

- 90% caused by HPV types 6 and 11
- Affects 1% of sexually active women age 18 to 45
- 500,000 to 1 million cases annually
- 240,000 initial office visits
- 1/3 of all STI dollars
- $167 million annually

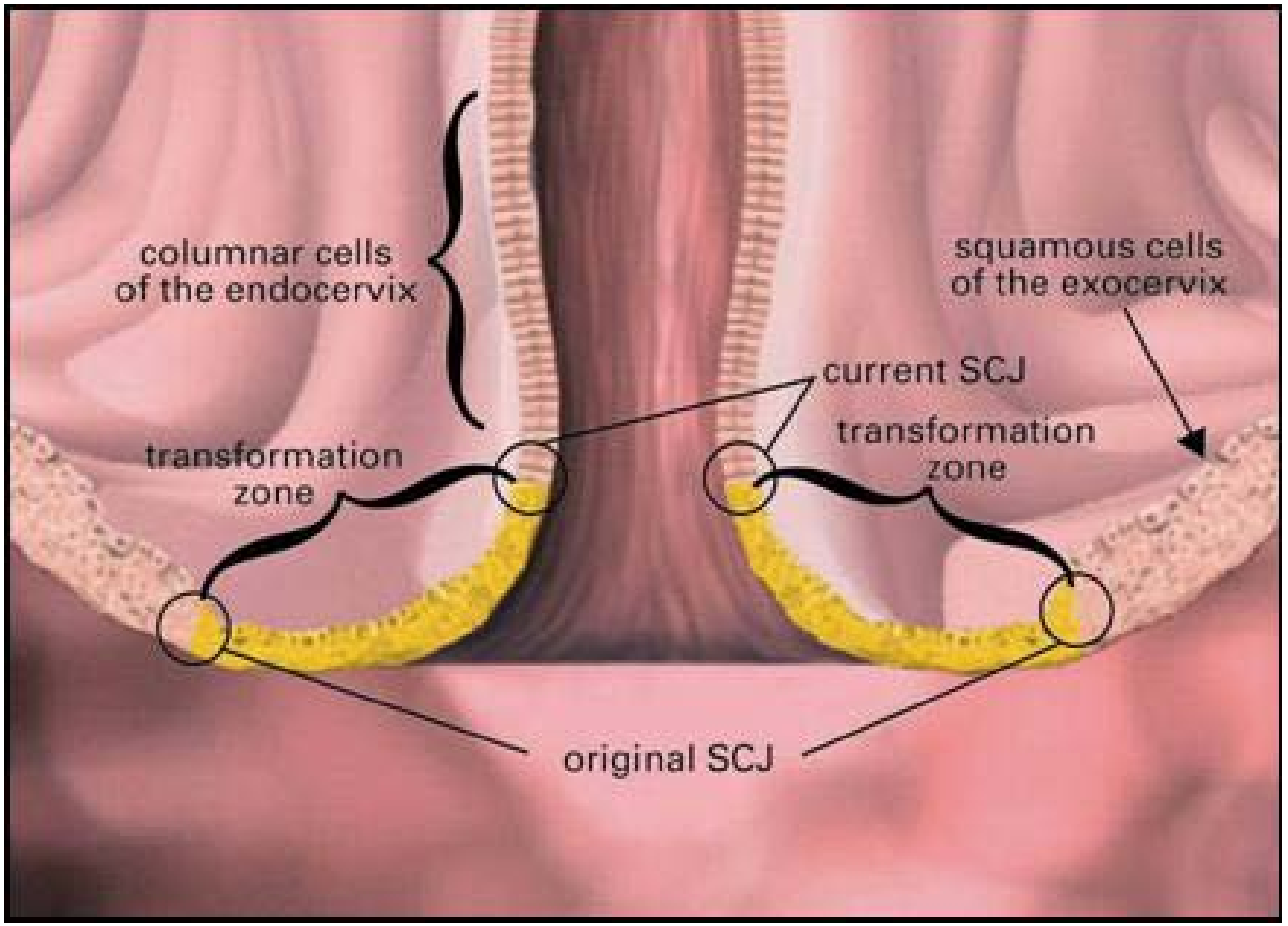
Chesson HW et al. *Perspect Sex Reprod Health.* 2004; CDC. *HPV Information for Clinicians.* 2006.

Transformation Zones and HPV Infection

- Area where one type of epithelium contacts and gradually replaces another through process of metaplasia
- Present in cervix, anus, tonsils
- Areas of HPV-related carcinogenesis

Moscicki AB. *Vaccine.* 2006.

Cervical Transformation Zone



Source:
http://www.merckmedicus.com/ppdocs/us/hcp/diseasemodules/hpvd/images/figure25.jpg

Human Immunity

Acquired

	Humoral Immunity	Cellular Immunity
Antigen	Bacteria, Parasite	Viruses, Tumors
Effectors	B Cells	T Cells
Result	Antibody Production	Cytotoxic T cell activation

T Lymphocytes

- Recognize peptide antigen presented in HLA
- T Helper Cells secrete cytokines
- Cytotoxic T lymphocytes attack tumor and HPV presenting cells

Risk Factors for HPV Infection

- Sexual Activity
- Multiple Partners
- Younger age at sexual debut
- Lack of condom use

Ley C. *J Natl Cancer Inst.* 1991; Winer RL. *N Engl J Med.* 2006; Ho GYF. *N Engl J Med.* 1998.

Risk Factors for *Persistent* HPV Infection &/or Neoplastic Progression

- Smoking
- HPV type
- Increasing age
- Lack of condom use
- Immunodeficiency (eg, HIV)
- Possibly OC use
- Possibly other STIs, such as chlamydia

Moscicki A-B. *Vaccine.* 2006; Moscicki A-B. *J Infect Dis.* 2004; Hogewoning CJ. *Int J Cancer*. 2003.

Risk of Progression

Degree of dysplasia	Regression	Persistence	Progression to invasive cancer
CIN 1	60%	30%	1%
CIN 2	40-50%	40%	5%
CIN 3	33%	55%	>12%

Ostor AG. *Int J Gynecol Pathol.* 1993.

Current Approach to Cervical Cancer Prevention

Requires 3 separate but linked components

- Screening
  - Cytology with or without HPV DNA testing
- Evaluation of screen positive women using colposcopy and cervical biopsy
- Treatment of women with biopsy-confirmed high-grade cervical cancer precursors

Wright T. *Obst Gynecol.* 2004.

Guidelines: Cervical Cancer Screening Interval

ACS

- Annually with conventional Pap test
- Every 2 years with liquid-based test
- At age 30 if 3 normal consecutive Pap tests, change to every 2 to 3 years

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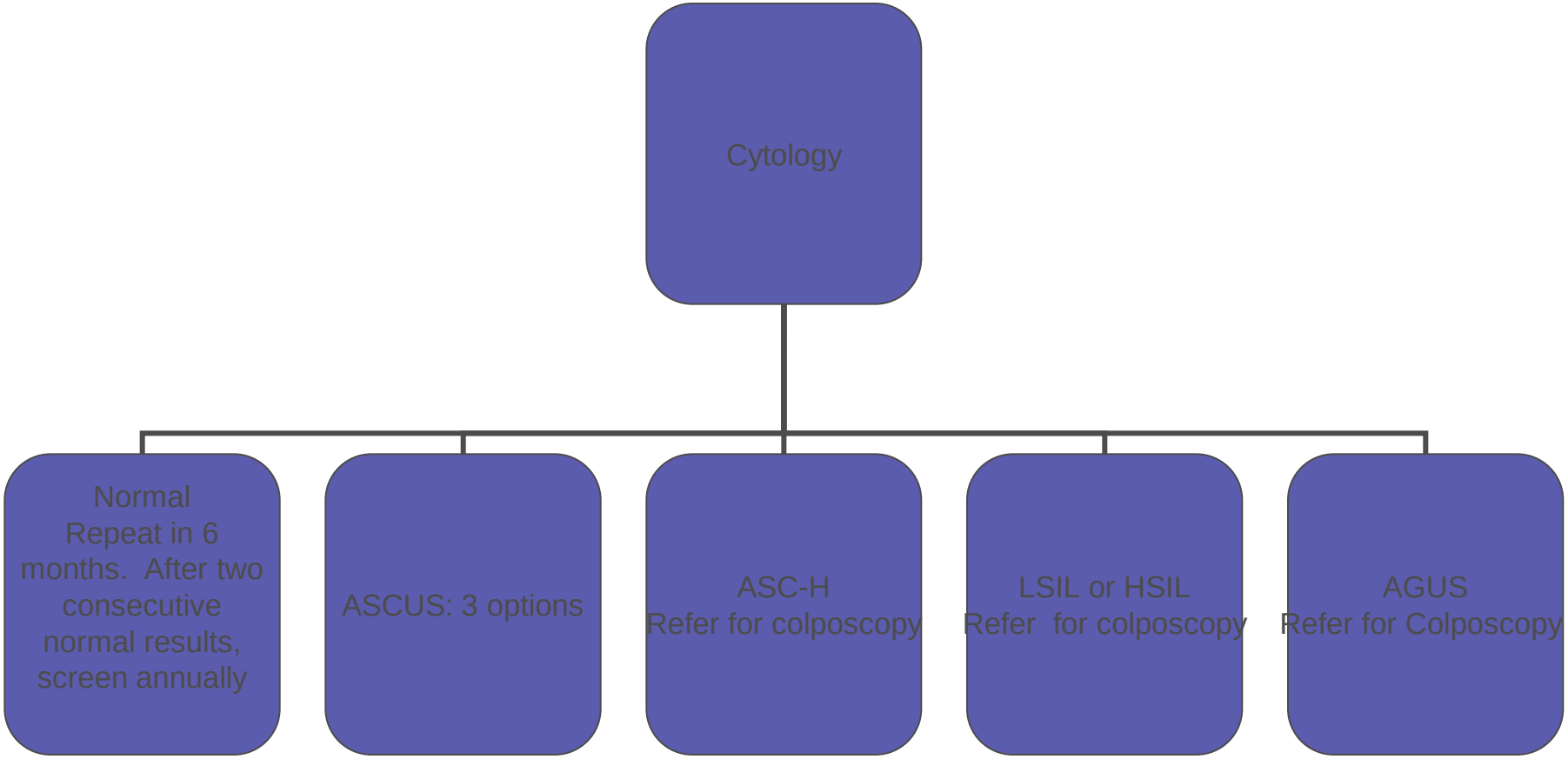
Saslow D. *CA Cancer J Clin.* 2002; ACOG Committee on Practice Bulletins. *Obstet Gynecol.* 2003; USPSTF. *Screening for Cervical Cancer: Recommendations and Rationale.* 2003.

Management of Abnormal Pap Results in HIV-infected Women



In Summary

- Most will get HPV at some time
- Most will clear high risk HPV, but some will not
- The time to clear HPV is variable
- Persistence of HIGH RISK HPV can lead to true pre-cancer
- LONG persistence of HPV and CIN 3 are necessary for the accumulations of random mutations that can lead to cancer