
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)

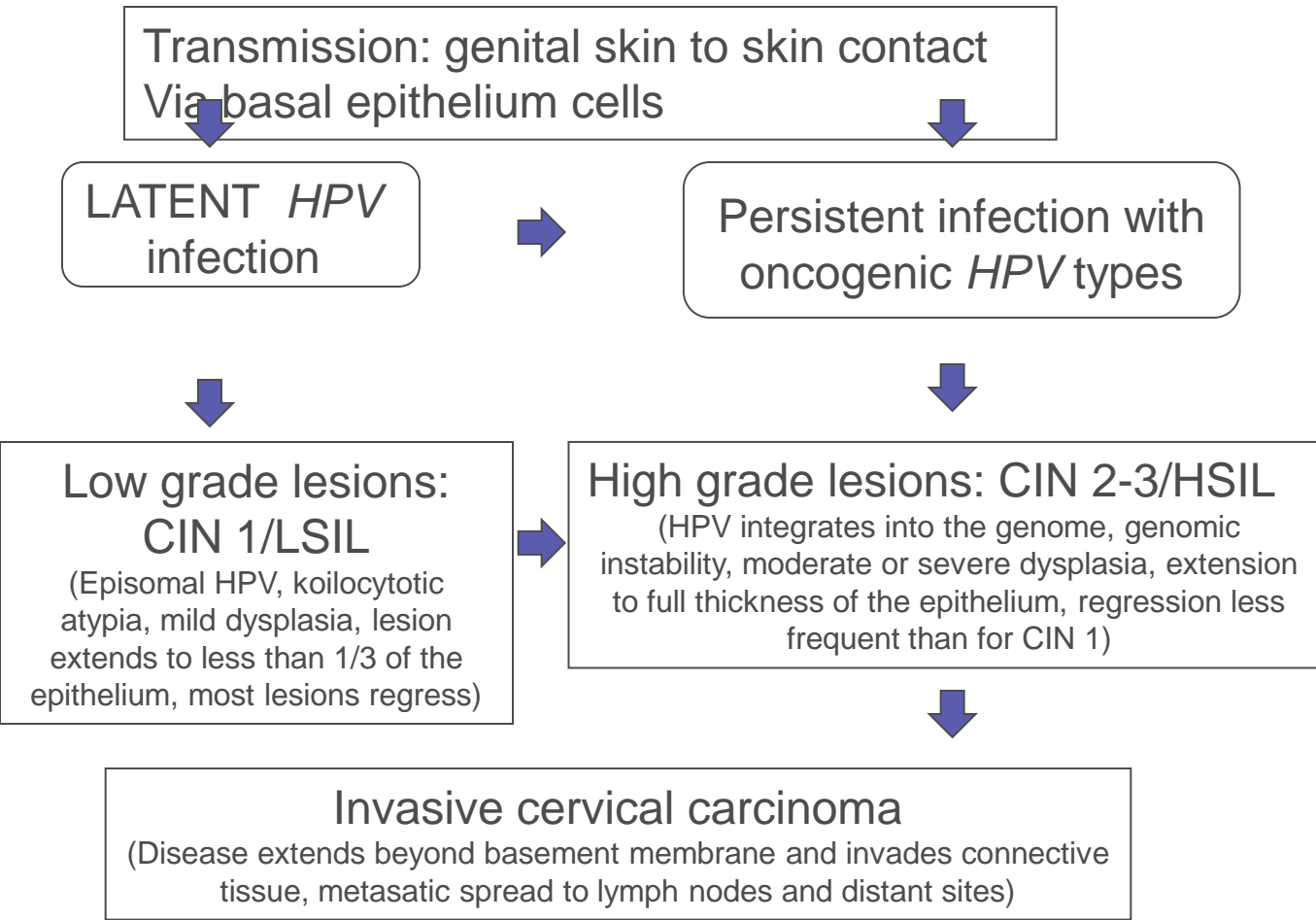
- Discuss the significance of persistent infection with high-risk HPV type
 - Identify the most common mode of HPV transmission
 - Identify additional impact of HPV for HIV positive individuals
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HPV Associated with Cancer and External Genital Warts

	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



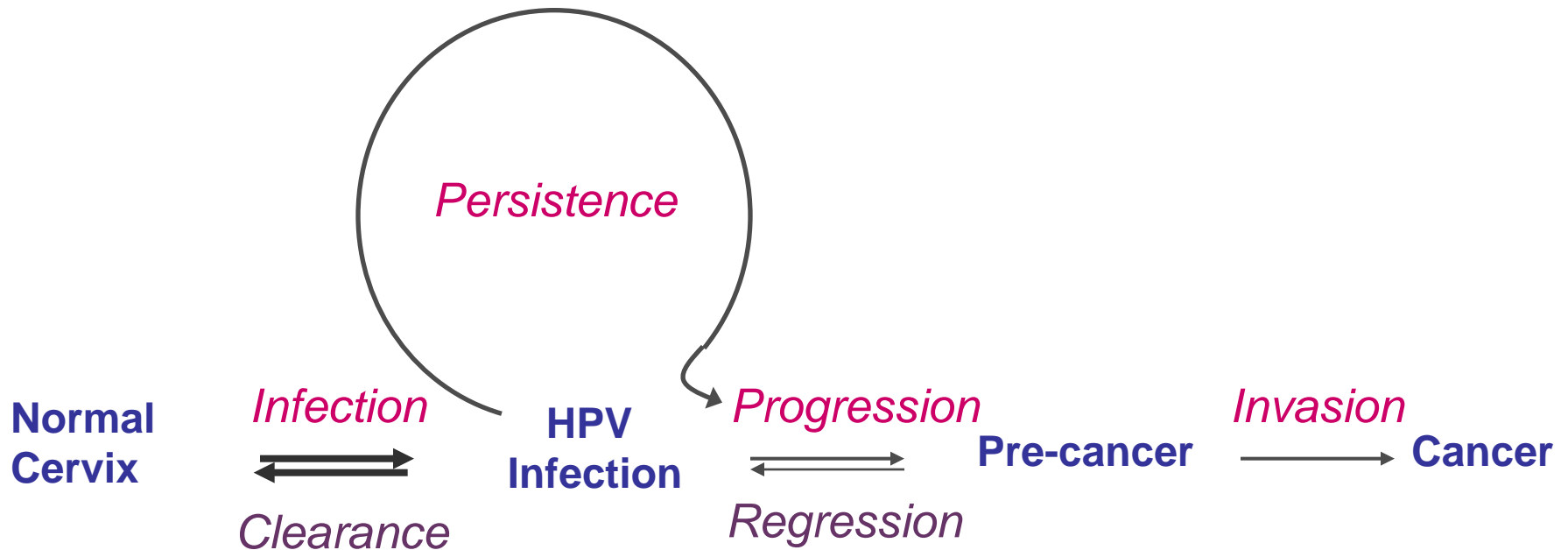
Cofactors:

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

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

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 prevalence of HPV

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

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

Prevalence of HPV in Men

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

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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.

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

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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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

HPV-Associated Disease

Anogenital cancers

- Cervical
- Anal
- Vulvar and vaginal

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HPV-Associated Disease (Continued)

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

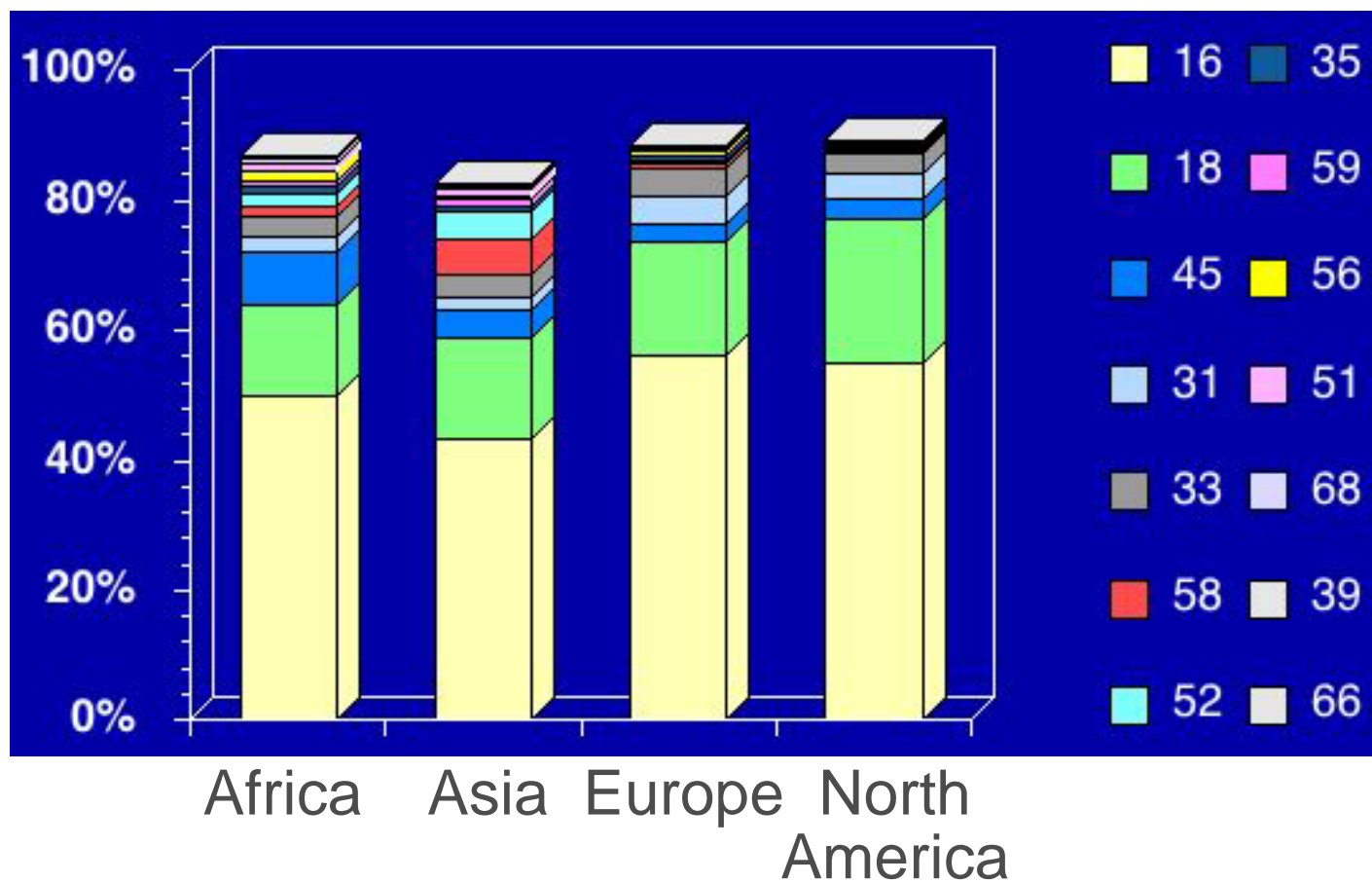
HPV and Cervical Cancer

- 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

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

HPV Types Associated with Cervical Cancer



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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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

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

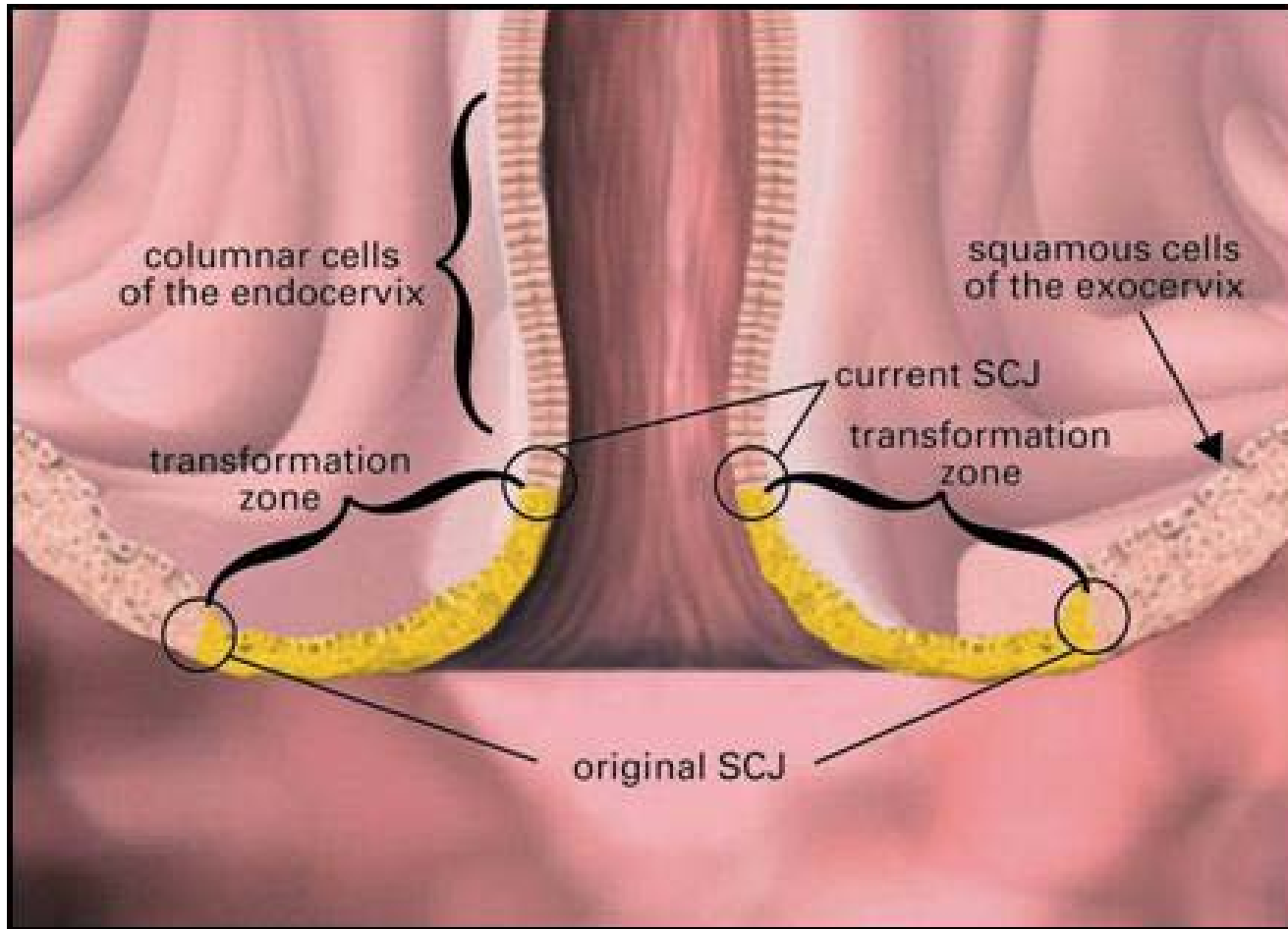
Impact: External Genital Warts

- 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

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

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
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Risk Factors for HPV Infection

Sexual
Activity

Multiple
Partners

Younger
age at
sexual
debut

Lack of
condom
use

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

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%

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

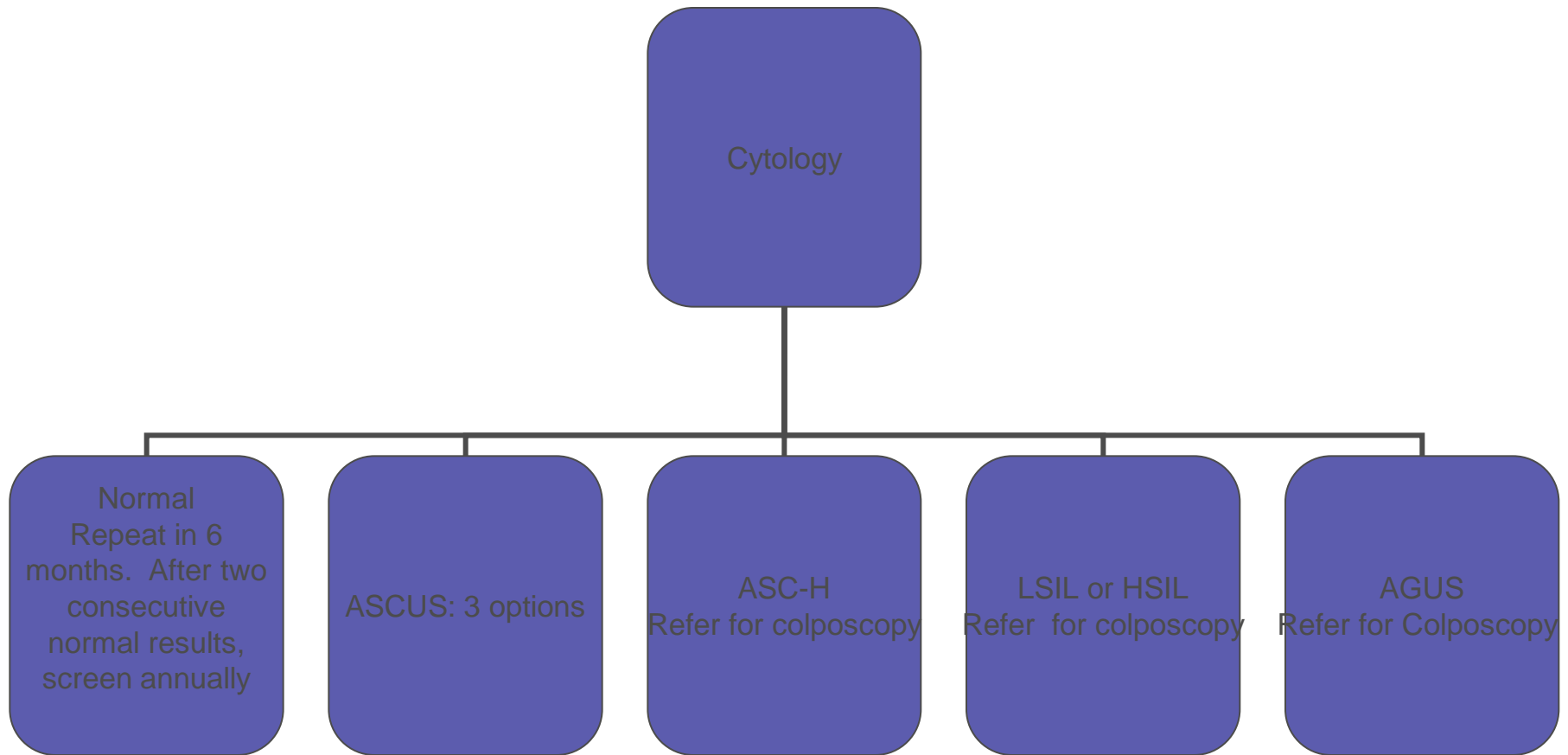
Guidelines: Cervical Cancer Screening Interval

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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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
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