

Human Papillomavirus Infections

Chapter 203 | Part 5: Infectious Diseases

KEY CLINICAL POINTS

- 1 HPV is an icosahedral, nonenveloped, 8000-base-pair, double-stranded DNA virus (diameter 55 nm).
- 2 Persistent HPV infection is the primary risk factor for cervical cancer; relative risks range from 10 to 20 and exceed 100 in case-control studies.
- 3 HPV types 16 and 18 cause $\geq 70\%$ of cervical squamous cell carcinomas and 85% of cervical adenocarcinomas worldwide.
- 4 Immune response is unique due to lack of viremia; CD4⁺ T cells are critical for controlling infection progression.
- 5 HIV infection significantly accelerates HPV disease progression, particularly in anal cancer (130/100,000 vs. 5/100,000 in MSM).
- 6 Imiquimod 5% cream is a standard treatment for genital warts (bedtime application, 3x/week for up to 16 weeks; $\approx 56\%$ clearance).
- 7 Vaccination options include Quadrivalent (types 6, 11, 16, 18) and Nine-valent (adds 31, 33, 45, 52, 58).
- 8 Cervical cancer screening is cost-effective; initiation at age 21 regardless of sexual debut.
- 9 Most HPV infections are cleared within 6–9 months.
- 10 Oropharyngeal cancers (linked to type 16) show a better prognosis than cervical cancer (5-year survival $\approx 80\%$).

DEFINITION & CLASSIFICATION

- **Structure:** Nonenveloped, double-stranded DNA virus
- **Morphology:** Icosahedral structure; diameter of 55 nm
- **Genome:** 8000-base-pair; contains early (E) genes, late (L) genes, and regulatory noncoding regions
- **Pathophysiology:** E6 and E7 proteins drive oncogenesis by inactivating p53 and Rb pathways
- **Infection Mechanism:** Occurs via microtrauma to mucosal surfaces; replication completes as keratinocytes differentiate
- **Classification:**
 - Low-risk: Types 6, 11 (cause genital warts; $\approx 10\%$ of low-grade cervical lesions)
 - High-risk: Types 16, 18 (cause dysplasia and 70–85% of cervical cancers)
 - Other oncogenic types: 31, 33, 45, 52, 58 (account for remaining 30% of cervical cancers)
- **Scope:** Over 200 HPV types identified; ≈ 40 infect the anogenital tract
- **Other Human Parvoviruses:**
 - HBoV1: Respiratory infections in children <5 years
 - HBoV2-4: Found in feces; role in gastroenteritis uncertain
 - Bufavirus/cutavirus: Detected in diarrheal stools; cutavirus linked to cutaneous T-cell lymphoma

- Parvovirus 4 (parv4): Found in plasma donations and injection drug users; apathogenic
 - Adeno-associated viruses (AAV): Require helper viruses for replication; used in gene therapy; linked to rare acute hepatitis
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EPIDEMIOLOGY

- **Prevalence:** ≈50% of young women infected within months of first intercourse
- **Clearance:** Most infections become undetectable in 6–9 months
- **Risk Factors:** Multiple sexual partners; immunosuppression (e.g., HIV)
- **Cervical Cancer Burden:** Peaks in low-income countries (>85% of cases occur there)
- **HIV Impact:** Accelerates progression; anal cancer rates reach 130/100,000 in HIV-infected MSM vs. 5/100,000 in HIV-negative MSM
- **Specific Types:**
 - HPV 1: Causes plantar warts but not genital infections

Epidemiology of HPV Types

- **Low-risk types:** 6, 11 (genital warts; ≈10% of low-grade cervical lesions)
 - **High-risk types:** 16, 18 (cause dysplasia and 70–85% of cervical cancers)
 - **Other oncogenic types:** 31, 33, 45, 52, 58 (account for remaining 30% of cervical cancers)
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ETIOLOGY & PATHOPHYSIOLOGY

- **Transmission:** Sexual contact (vaginal, anal, oral) or direct genital contact
 - **Immune Response Characteristics:**
 - No viremic phase
 - 60–70% of infected individuals develop detectable serum antibodies
 - Neutralizing antibodies provide partial protection against reinfection
 - **Cell-Mediated Immunity:** CD4+ T cells regulate infection control; HIV compromises this
 - **Oncogenic Prevention:** T cell responses to E2/E6 proteins associate with cervical cancer prevention
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CLINICAL FEATURES

- **Genital Warts:** Soft, sessile growths (types 6/11); penile lesions 2–5 mm in diameter; vulvar warts as whitish papules
 - **Cervical Cancer:** Early erosion with easy bleeding → advanced stages show ulceration or exophytic masses
 - **Anal Cancer:** Rectal bleeding, pain, or mass sensation (20% asymptomatic at diagnosis)
 - **Oropharyngeal Cancers:** Increasing incidence in men 40–50 years old; linked to HPV type 16
 - **Anatomic Distribution of Lesions:**
 - Male: urethra, penis, scrotum; keratotic plaques on penile lesions
 - Female: vulva, vagina, cervix; vaginal lesions as elongated papillae
 - Both: perianal/anal/oropharyngeal infections
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DIFFERENTIAL DIAGNOSIS

- **Genital warts:** Molluscum contagiosum, syphilis (condyloma lata)
 - **Cervical cancer:** Benign polyps, ectropion
 - **Anal cancer:** Hemorrhoids, fissures
 - **Oropharyngeal cancer:** Tonsillitis, abscesses
 - **Vulvar cancer:** Lichen sclerosus, planus
 - **Penile cancer:** Balanitis, other dermatoses
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DIAGNOSTIC APPROACH

1. Cervical Cancer Screening (General):

- Age 21–29: Pap smear every 3 years
- Age 30–65: Co-testing (Pap + HPV DNA) → if negative, repeat in 5 years
- High-risk HPV types (non-16/18): Follow with cytology

2. Cervical Cancer Screening (HIV-infected):

- Annual cytology starting within 1 year of diagnosis

3. Clinical Identification:

- Genital warts: Identified by morphology (e.g., cauliflower-like growths)
- Cervical cancer: Identified via cytology/biopsy

Screening Algorithms

- **Age 21–29:** Pap every 3 years; no co-testing
 - **Age 30–65:** Co-testing (Pap + HPV) every 5 years if negative
 - **Positive HPV 16/18:** Colposcopy required
 - **HIV-infected:** Annual cytology starting within 1 year of diagnosis
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MANAGEMENT & TREATMENT

1. Genital Warts (Topical):

- Imiquimod 5% cream: Apply at bedtime, 3 times per week for up to 16 weeks → ~56% clearance
- Other options: podophyllin, trichloroacetic acid

2. Cervical Dysplasia:

- Loop electrosurgical excision procedure (LEEP)
- Cryotherapy

3. Cervical Cancer Management:

- Colposcopy
- Biopsy
- Cone biopsy
- Surgery (e.g., radical hysterectomy)
- Radiation therapy
- Chemotherapy (cisplatin-based)

4. Vaccination:

- Quadrivalent: targets types 6, 11, 16, and 18

- **Nine-valent:** adds types 31, 33, 45, 52, and 58
- **Timing:** Recommended for adolescents (age 11–12); catch-up available up to age 45

Therapeutic Options

- **Genital warts:** Imiquimod 5% cream, podophyllin, trichloroacetic acid
- **Cervical dysplasia:** LEEP, cryotherapy
- **Cancer treatment:** Radical hysterectomy, radiation therapy, cisplatin-based chemotherapy

COMPLICATIONS & PROGNOSIS

- **Cervical cancer:** 5-year survival ≈66% in developed countries; <20% in low-income regions
- **Anal cancer:** 5-year survival ≈60–70%
- **Oropharyngeal cancer:** 5-year survival ≈80% (better than cervical)
- **Complications of HPV Infection:**
 - Cervical cancer: Metastasis to bladder/bowel, pelvic pain
 - Anal cancer: Bowel obstruction, bleeding
 - Oropharyngeal cancer: Dysphagia, airway obstruction
 - Genital warts: Recurrent lesions, psychological impact

SPECIAL POPULATIONS

- **HIV-infected individuals:**
 - Accelerated disease progression
 - Higher rates of persistent infection and cancer
 - Requirement for more frequent/earlier screening (annual cytology starting within 1 year)
- **Immunosuppressed patients:**
 - Management of warts requires more aggressive therapy
- **Adolescents:**
 - Vaccination recommended at age 11–12
- **Global disparities:** Limited screening access in low-income regions increases cervical cancer mortality

KEY PEARLS & HIGH-YIELD POINTS

- **High-Risk vs Low-Risk:** Types 16/18 (high) are the primary drivers of cervical cancer; types 6/11 (low) cause common genital warts.
- **Imiquimod Dosage:** 5% cream, 3x/week for up to 16 weeks.
- **Screening Thresholds:** Age 21 start; 3-year interval for young adults; 5-year interval for older adults with co-testing.
- **HIV Impact:** Significant acceleration of anal cancer (130/100,000 vs. 5/100,000).