HPV and Genital Dermatology

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Disclosures

- Gilead-own stock

Objectives

- Describe epidemiology of genital HPV infection in the US
- Discuss the clinical manifestations and differential diagnosis of genital HPV
- Identify methods used to diagnose genital warts and cervical cellular abnormalities
- Discuss CDC-recommended treatment regimens for genital warts
- Discuss HPV prevention

Human Papilloma Virus (HPV)

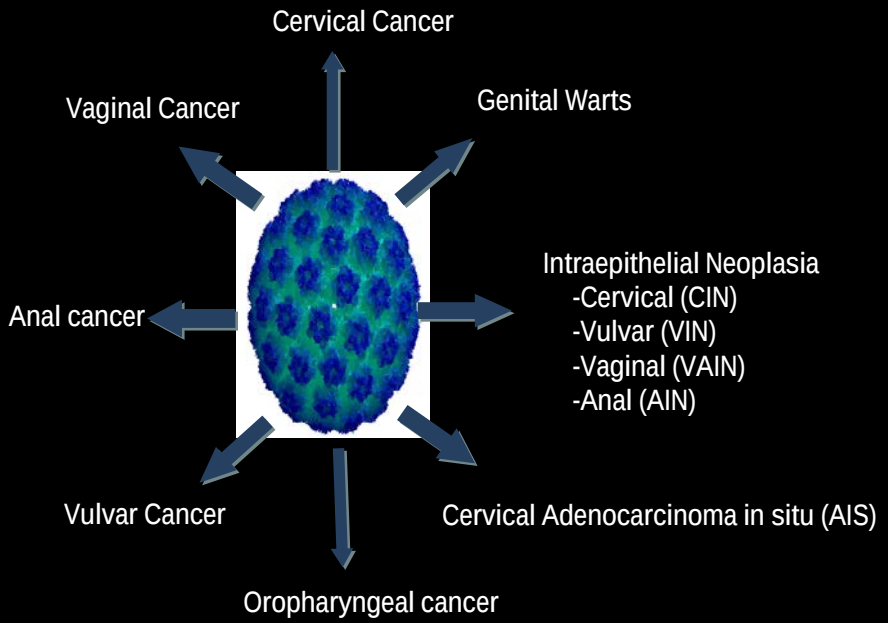
- Over 150 types identified: 40 infect the genital area
  - 15 oncogenic types
    - ❖ 99.7% of all cervical cancer cases
      - » 16 & 18 → 70% of cases
    - ❖ 70% of vaginal and vulvar cancers

Carcinogenic Risk	***Genotype***	***Pathology***
Low Risk	**6, 11**, 40, 42, 43, 44,54,61,70,72,81	Genital warts, low-grade cervical dysplasia
Intermediate Risk	26,53,*66*	
High Risk	***16, 18, 31, 33***, *35, 39,* ***45****, 51,* ***52****, 56,* ***58****, 59, 68,* 73, 82, 83	Low- and high-grade cervical dysplasia, squamous cell carcinoma, adenocarcinoma

Genotypes: found in vaccines; *genotypes*: detected with commercial tests

Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion. CDC.HPV Vaccination. Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR vol 63 (5); August 29, 2014; Walboomers JM. J Pathol (1999);189(1):12

HPV Transmission and Diseases



- Most common STI in the U.S.
  - 79 million prevalent cases
  - 14 million incident cases/year among 15 - 59 yr olds
  - Genital warts: incid up to 100/100,000; 1.4 mil affected at any one time
- Sexually transmitted
  - Condom use reduces the risk, but it is not fully protective

Most HPV infections are transient and asymptomatic

- 70% will clear in 1yr, 90% in 2yrs
- Risk of persistence varies by HPV type and host factors

CDC. HPV Vaccination. Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR vol 63 (5); August 29, 2014

HPV-associated cancers United States, 2004-2008

Anatomic Area	Average annual number of cases*	Estimated+ HPV attributable	Estimated+ HPV 16/18 attributable
Cervix	11,967	11,500	9,100
Vagina	729	500	400
Vulva	3,136	1,600	1,400
Anus (F)	3,089	2,900	2,700
Oropharynx (F)	2,370	1,500	1,400
Total (Females)	**21,291**	**18,000**	**15,000**
Penis	1,046	400	300
Anus (M)	1,678	1,600	1,500
Oropharynx (M)	9,356	5,900	5,600
Total (Males)	**12,080**	**7,900**	**7,400**

* Defined by histology and anatomic site; Watson M et al. Cancer 2008. Data source: National Program of Cancer Registries and SEER, covering 100% coverage of US population. + Gillison ML, et al. Cancer 2008 . Ref: Human Papillomavirus-Associated Cancers MMWR 2012;61(15):258-261.

Genital Warts-Appearance

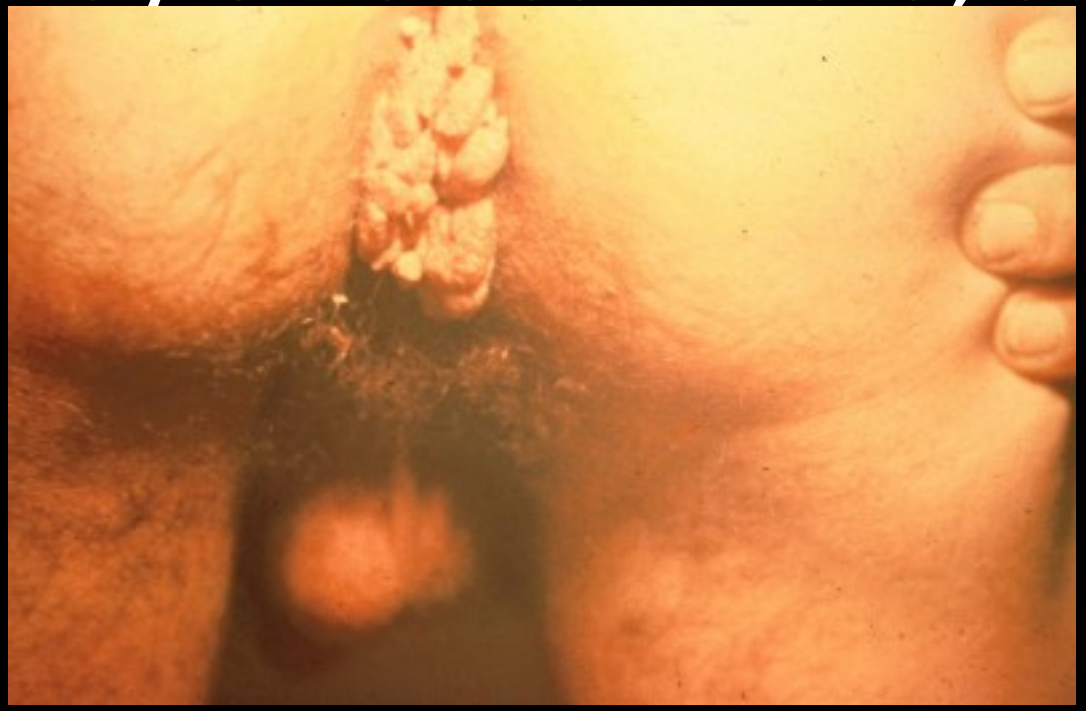
- Condylomata acuminata
  - Cauliflower-like appearance
  - Skin-colored, pink, or hyperpigmented
  - May be keratotic on skin; generally nonkeratinized on mucosal surfaces
- Smooth papules
  - Usually dome-shaped and skin-colored
- Flat papules
  - Macular to slightly raised
  - Flesh-colored, with smooth surface
  - More commonly found on internal structures (i.e., cervix), but also occur on external genitalia
- Keratotic warts
  - Thick horny layer that can resemble common warts or seborrheic keratosis

Genital Warts-Location

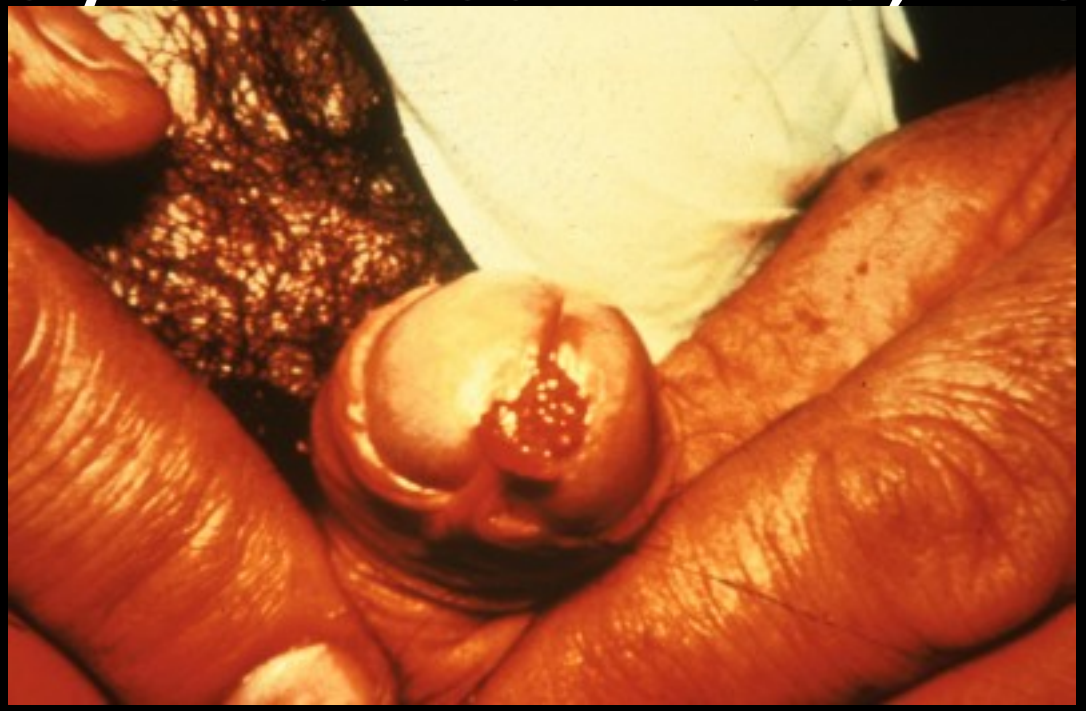
- Most commonly occur in areas of coital friction
- Perianal warts do not necessarily imply anal intercourse.
  - May be secondary to autoinoculation, sexual activity other than intercourse, or spread from nearby genital wart site
- Intra-anal warts are seen predominantly in patients who have had receptive anal intercourse.
- HPV types causing genital warts can occasionally cause lesions on oral, upper respiratory, upper GI, and ocular locations.
- Patients with visible warts are frequently simultaneously infected with multiple HPV types.

Condyloma acuminata, penile

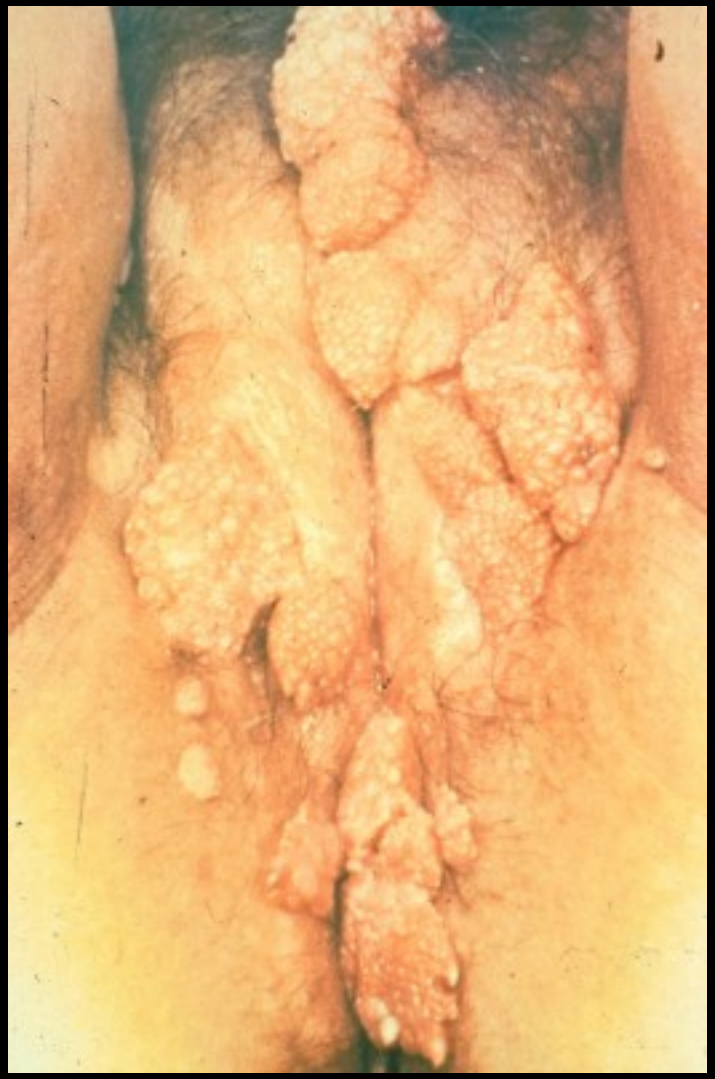
Condyloma acuminata, anal



Condyloma acuminata, meatal



Condyloma acuminata, vulva



Genital Warts-Symptoms

- Genital warts usually cause no symptoms. Symptoms that can occur include:
  - Vulvar warts-dyspareunia, pruritis, burning discomfort;
  - Penile warts-occasional itching;
  - Urethral meatal warts-hematuria or impairment of urinary stream;
  - Vaginal warts-discharge/bleeding, obstruction of birth canal (secondary to increased wart growth during pregnancy); and
  - Perianal and intra-anal warts-pain, bleeding on defecation, itching

- Most patients have fewer than ten genital warts, with total wart area of 0.5–1.0 cm^2.

Genital Warts-Duration and Transmission

- May regress spontaneously, or persist with or without proliferation.
  - Frequency of spontaneous regression is unclear, but estimated at 10–30% within three months.
  - Persistence of infection occurs, but frequency and duration are unknown.
  - Recurrences after treatment are common.

Diagnosis of Genital Warts

- Diagnosis is usually made by visual inspection with bright light.
- Consider biopsy when
  - Diagnosis is uncertain;
  - Patient is immunocompromised;
  - Warts are pigmented, indurated, or fixed;
  - Lesions do not respond or worsen with standard treatment; or
  - There is persistent ulceration or bleeding.

Differential Diagnosis of Genital Warts

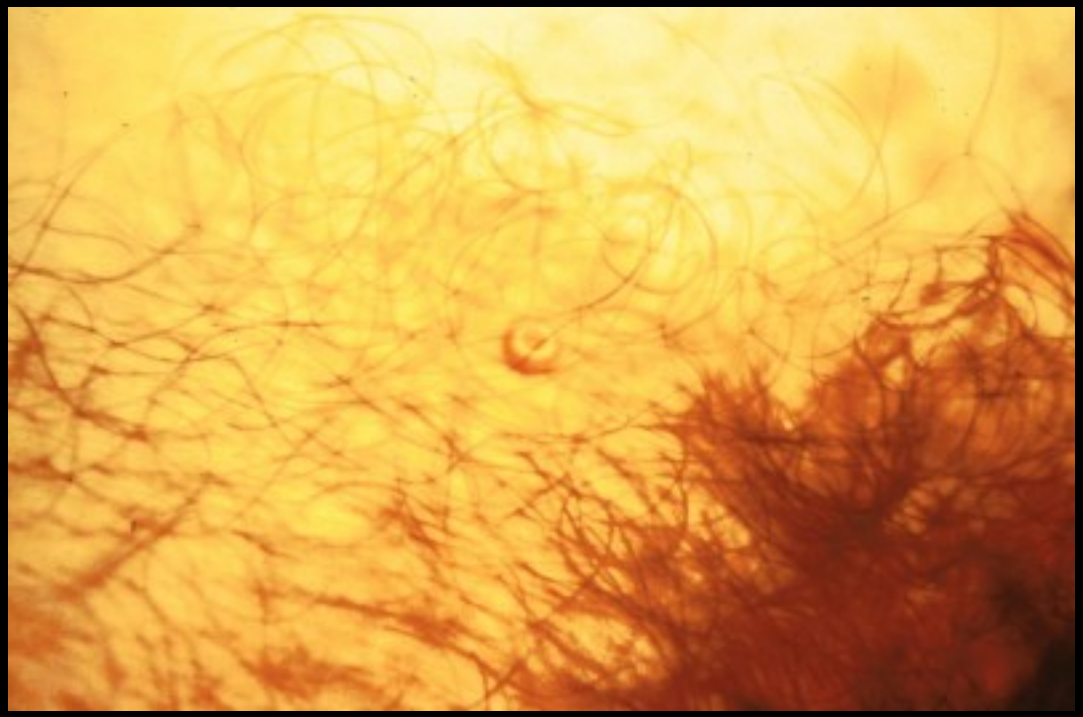
- Other infections
  - Condylomata lata
    - Tend to be smoother, moist, more rounded, and darkfield-positive for *Treponema pallidum*
  - Molluscum contagiosum
    - Papules with central dimple, caused by a pox virus; rarely involves mucosal surfaces
- Acquired dermatologic conditions
  - Seborrheic keratosis
  - Lichen planus
  - Fibroepithelial polyp, adenoma
  - Melanocytic nevus
  - Neoplastic lesions

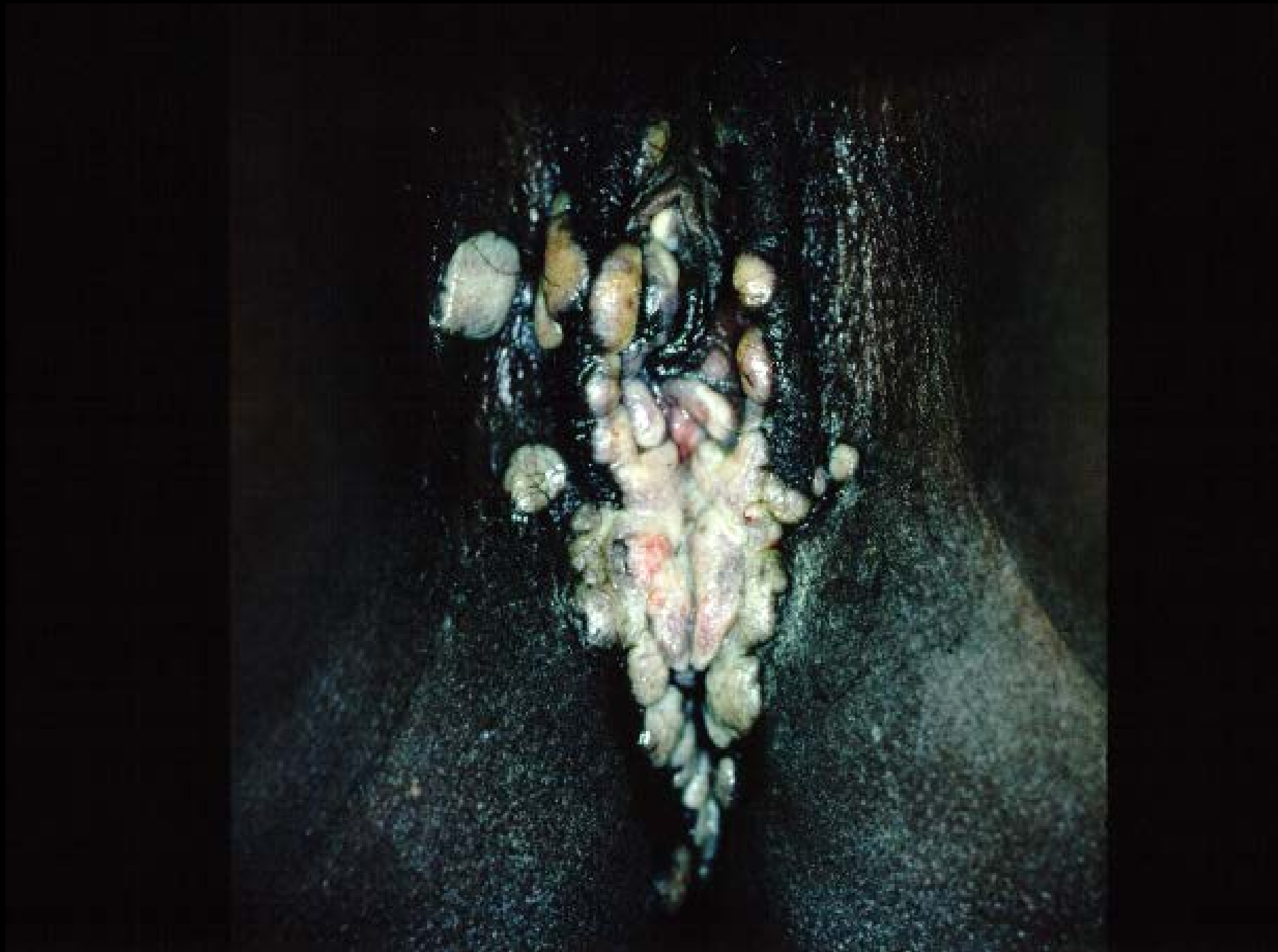
Differential Diagnosis of Genital Warts-continued

- Normal anatomic variants
  - "Pink pearly penile papules"
  - Vestibular papillae (micropapillomatosis labialis)
  - Skin tags (acrochordons)

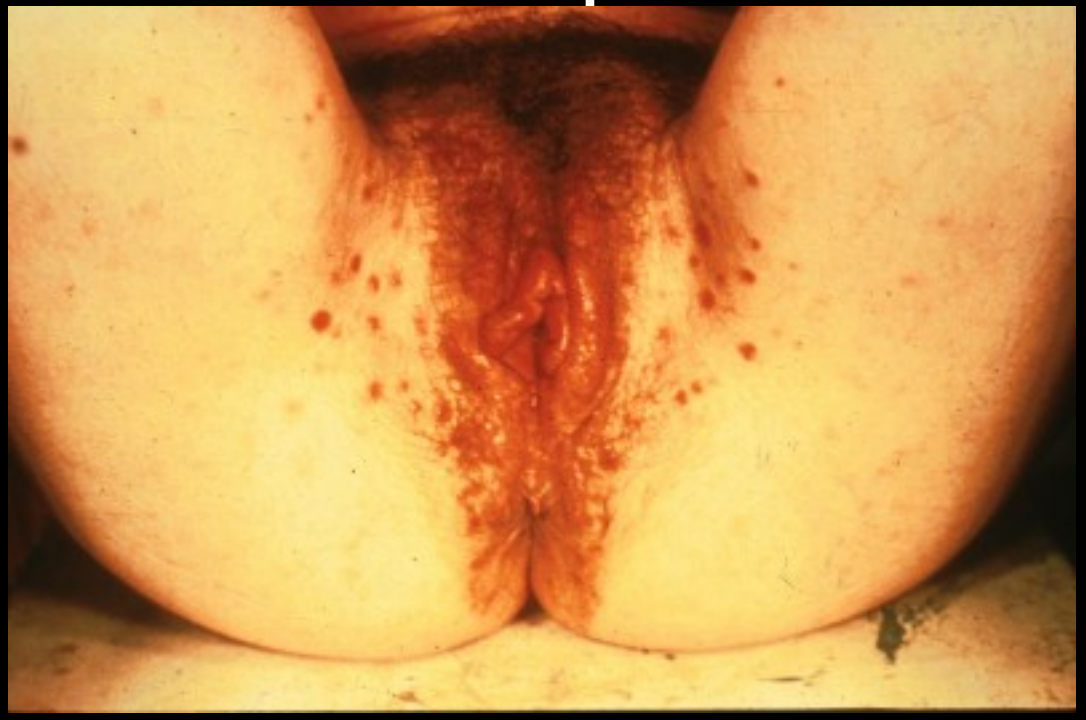
- External genital squamous intraepithelial lesions (SIL)
  - Squamous cell carcinoma *in situ*
  - Bowenoid papulosis
  - Erythroplasia of Queyrat
  - Bowen's disease of the genitalia

Molluscum contagiosum





Secondary syphilis - papulo-pustular



Treatment Regimens

- Factors influencing treatment selection include
  - Wart size,
  - Number of warts,
  - Anatomic site of wart,
  - Wart morphology,
  - Patient preference,
  - Cost of treatment,
  - Convenience, and
  - Adverse effects.

Treatment Response

- Affected by
  - Number, size, duration, and location of warts, and immune status
  - In general, warts located on moist surfaces and in intertriginous areas respond better to topical treatment than do warts on drier surfaces.
- Many patients require a course of therapy over several weeks or months rather than a single treatment.
  - Evaluate the risk-benefit ratio of treatment throughout the course of therapy to avoid over-treatment.
- There is no evidence that any specific treatment is superior to any of the others.
  - The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes

CDC-Recommended Regimens For External Genital Warts (Patient-Applied)

- Podofilox 0.5% solution or gel*
  - Apply solution with cotton swab or gel with a finger to visible warts twice a day for 3 days, followed by 4 days of no therapy.
  - Cycle may be repeated as needed up to 4 cycles

or

- Imiquimod 3.75% or 5% cream*
  - Apply cream once daily at bedtime, 3 times a week for up to 16 weeks.
  - Treatment area should be washed with soap and water 6–10 hours after application

or

- Sinecatechins 15% ointment*,**
  - Apply ointment 3 times daily for up to 16 weeks.
  - ***Do not wash off*** post-application

**Safety not established in pregnancy*

***Safety not established in HIV- or HSV-co-infected individuals*

CDC-Recommended Regimens For External Genital Warts (Provider-Administered)

- Cryotherapy with liquid nitrogen or cryoprobe
  - Repeat applications every 1–2 weeks, or
- Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90%
  - Apply small amount only to warts and allow to dry
  - Treatment may be repeated weekly if needed, or
- Surgical removal - tangential scissor excision, tangential shave excision, curettage, or electrosurgery

**Safety not established in pregnancy*

Recurrence After Treatment

- As many as two-thirds of patients will experience recurrences of warts within 6–12 weeks of therapy; after 6 months most patients have clearance.
  - If persistent after 3 months, or if there is poor response to treatment, consider biopsy to exclude a premalignant or neoplastic condition, especially in an immunocompromised person.
- Treatment modality should be changed if patient has not improved substantially after 3 provider-administered treatments or if warts do not completely clear after 6 treatments

Genital Warts in HIV-Infected Patients

- No data that treatment should be different
- Larger, more numerous warts
- Might not respond as well to therapy
- More frequent recurrence of lesions after treatment
- Squamous cell carcinomas arising in or resembling genital warts might occur more frequently among immunosuppressed persons, therefore, requiring biopsy for confirmation of diagnosis for suspicious cases, and referral to a specialist.

Transmission Issues

- Usually sexually transmitted
- Infection is often shared between partners
- Determining source of infection is usually difficult (incubation period variable)
- Recurrences usually are not reinfection
- Transmission risk to current and future partners after treatment is unclear.
- Likelihood of transmission and duration of infectivity with or without treatment are unknown.
- Value of disclosing a past diagnosis of genital HPV infection to future partners is unclear, although candid discussions about past STD should be encouraged.

HPV DNA Testing

- HPV DNA tests
  - FDA-approved:
    - To triage women with ASC-US Pap test results, and
    - As an adjunct to Pap test screening for cervical cancer in women 30 years or older.
    - Use of type-specific HPV DNA tests for routine diagnosis and management of genital warts is not recommended
- HPV DNA tests should not be used
  - In men,
  - In adolescents <21 years,
  - To screen partners of women with Pap test abnormalities,
  - To determine who will receive HPV vaccine, or
  - STD screening for HPV.

Pap and HPV Testing Guidelines, 2015

	HIV (-)	HIV (+)
Age at initiation	21yrs	Within 1 year of coitarche or at time of HIV diagnosis if ≥21yrs
Frequency Age 21-29 Age ≥ 30	 Every 3yrs Every 3yrs OR every 5yrs if Pap & hrHPV(-)	 Every yr; 3 consecutive nl Pap→ 3yrs Every 3yrs if cytology & hrHPV(-)
hrHPV	Primary hrHPV screening (≥ 26yrs) Co-testing w/ pap (≥ 30yrs) Triage ASCUS result	No primary hrHPV screening Co-testing w/ Pap (≥ 30yrs) Triage ASCUS result
Age at discontinuation	65yrs	No age cut-off
Prior hysterectomy	No screening, unless prior dysplasia ≥ CIN 2 or cancer w/i past 20 yrs	No screening, unless prior dysplasia ≥ CIN 2 or cancer
Prior HPV vaccination	Same as unvaccinated women	

https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv

Table 1. Use and Efficacy of the Bivalent, Quadrivalent, and 9-valent Human Papillomavirus Vaccines

Vaccine	HPV Types	Disease Reduction	Efficacy*
Bivalent	16 and 18	HPV genotypes 16- and 18-related cervical cancer, CIN 1, CIN 2/3, and adenocarcinoma in situ	HPV disease related to genotypes 16 and 18; 98.1%[†,‡]
Quadrivalent	6, 11, 16, and 18	HPV genotypes 6, 11, 16, and 18-related cervical, vulvar, and vaginal cancer; CIN 1; CIN 2/3; adenocarcinoma in situ; VIN 2/3; and vaginal intraepithelial neoplasia 2/3 in females Penile intraepithelial neoplasia 1/2/3 and penile cancer in males Warts, anal intraepithelial neoplasia, and anal cancer in males and females	HPV disease related to genotypes 6, 11, 16, and 18; up to 100%[§,‖] External genital disease in men; 90.4%[‖]
9-valent	6, 11, 16, 18, 31, 33, 45, 52, and 58	HPV genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58-related cervical, vulvar, and vaginal cancer; CIN 2/3; adenocarcinoma in situ; VIN 2/3; and vaginal intraepithelial neoplasia 2/3 in females Penile intraepithelial neoplasia 1/2/3 and penile cancer in males[¶] Warts, anal intraepithelial neoplasia, and anal cancer in males and females	HPV disease related to genotypes 6, 11, 16, 18; greater than 99% HPV related to genotypes 31, 33, 45, 52, and 58; 96.7%[¶]

HPV Vaccine Indications

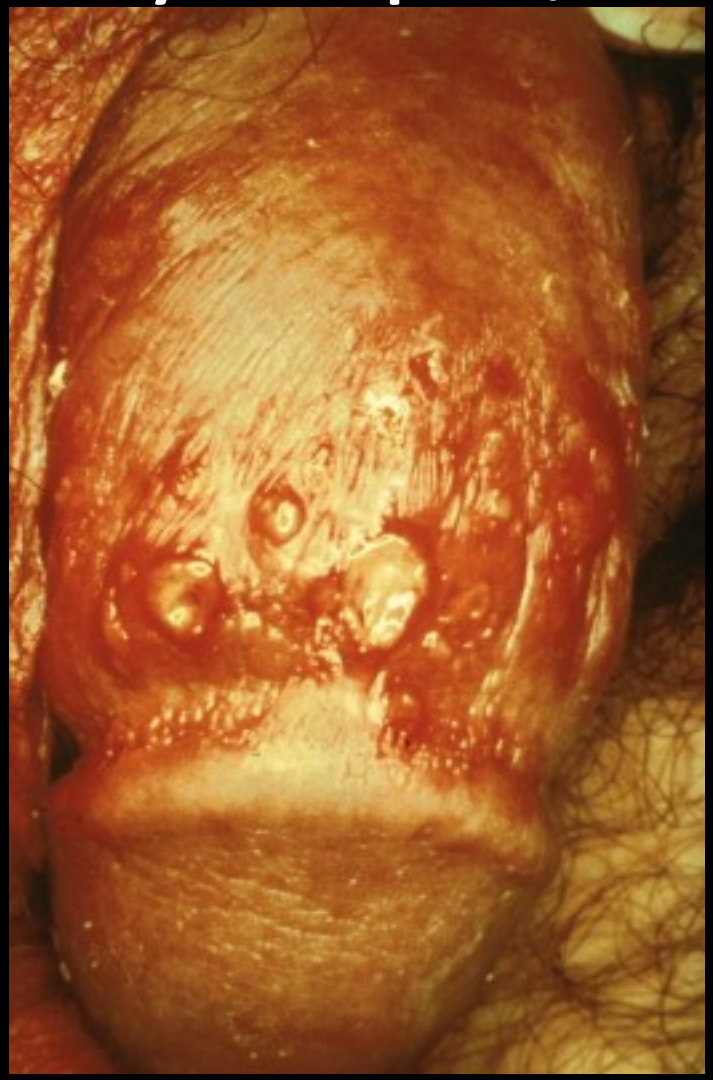
- Indicated for the prevention of cervical, vaginal, and vulvar cancers; precancerous or dysplastic lesions; and genital warts (Gardasil)
- Vaccinate all women and men age 9-26 regardless of sexual activity, history of cervical dysplasia, or genital warts
  - Rationale: some cross-reactivity or patient might not have been exposed to vaccine types
- U.S. ACIP guidelines: 3 doses (0, 2, 6 months)
  - If 1st dose <15 yr, only 2 doses need (0,6-12 mo)
- Immunocompromised persons
  - Vaccines are well tolerated and immunogenic in HIV(+) women
  - Unclear if there are vaccine differences in effectiveness
  - Vaccination is recommended
- Testing for HPV DNA is not recommended before vaccination. Vaccination is recommended even if the patient is tested for HPV DNA and the results are positive.
- Women who have received HPV vaccine should continue routine cervical cancer screening

Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR vol 63 (5); August 29, 2014

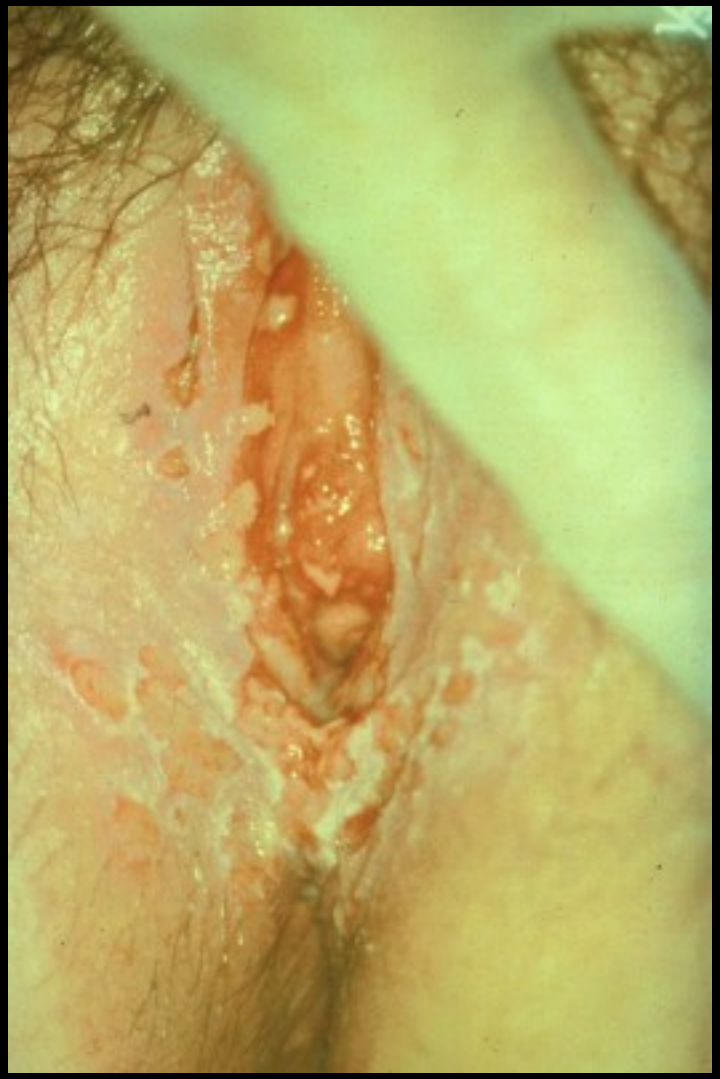
Other Genital Lesions

- Ulcerative
  - HSV
  - Syphilis
  - Chancroid
  - LGV
  - Granuloma inguinale
- Ectoparasitic infections
  - Lice
  - Scabies
- Other skin conditions
  - Lichen sclerosus
  - Irritative/allergic reactions
  - Psoriasis

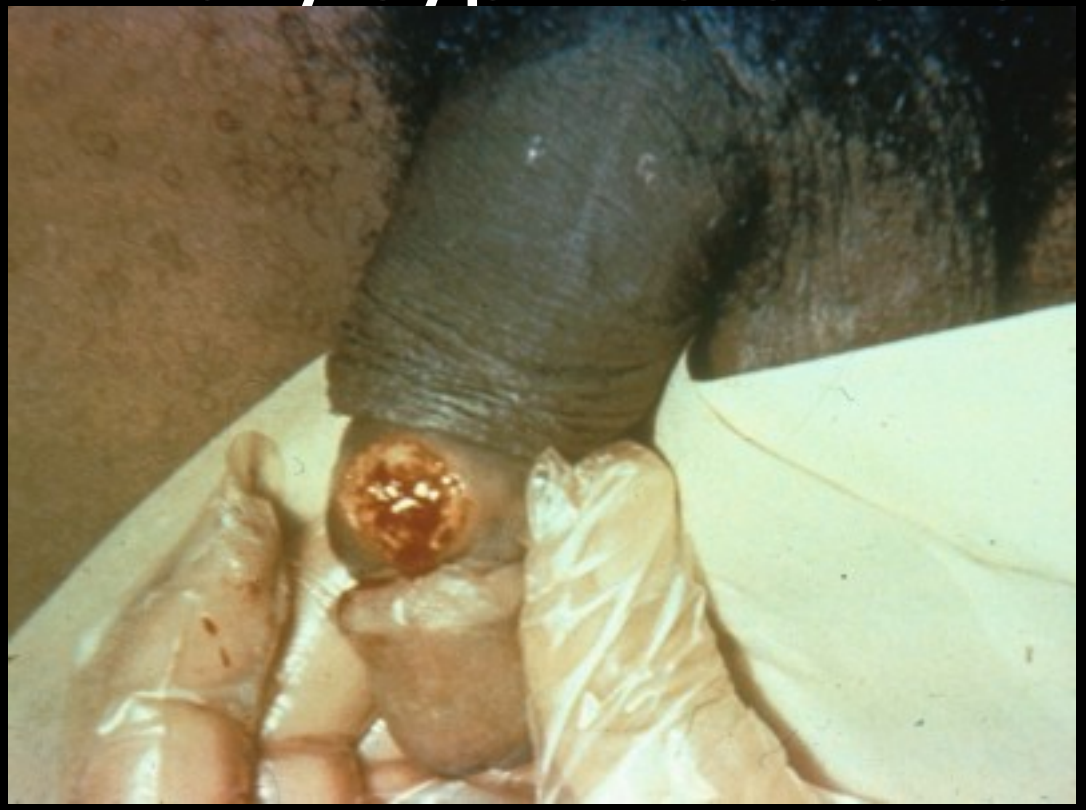
Primary herpes, male



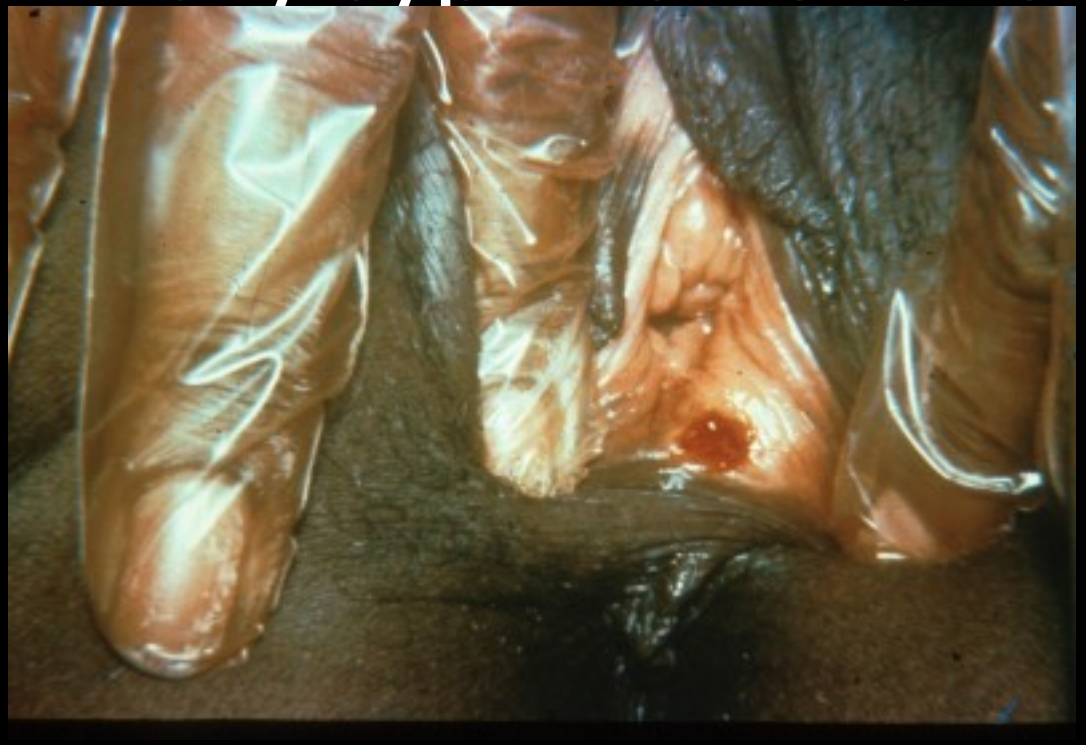
Primary herpes, female



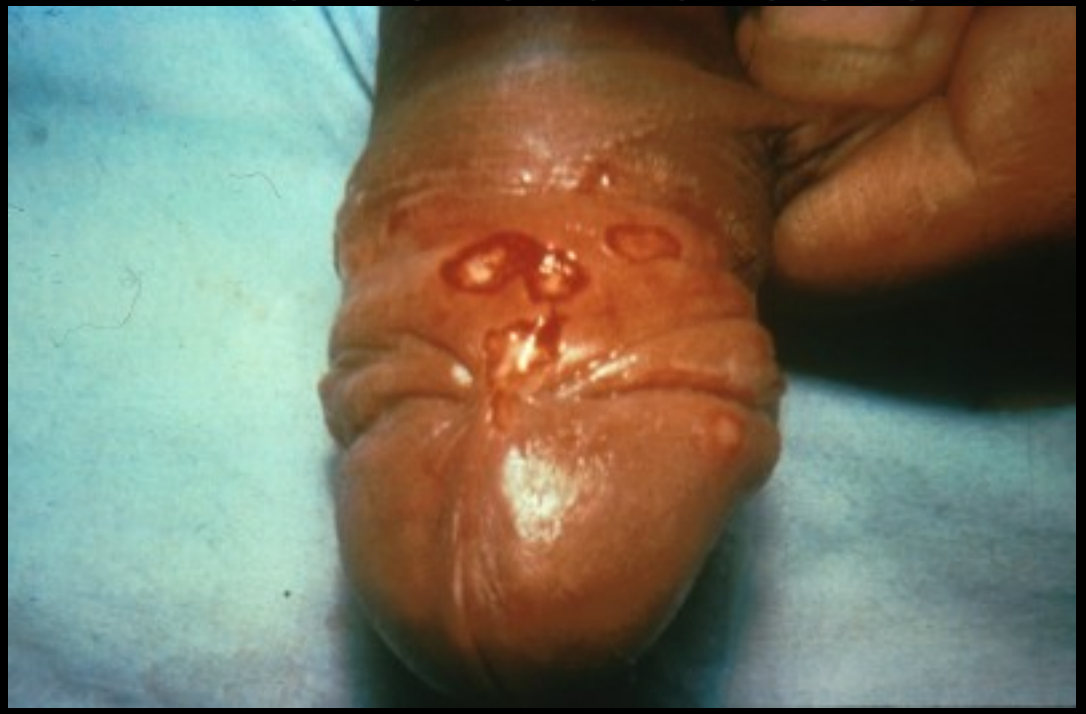
Primary syphilis-chancre



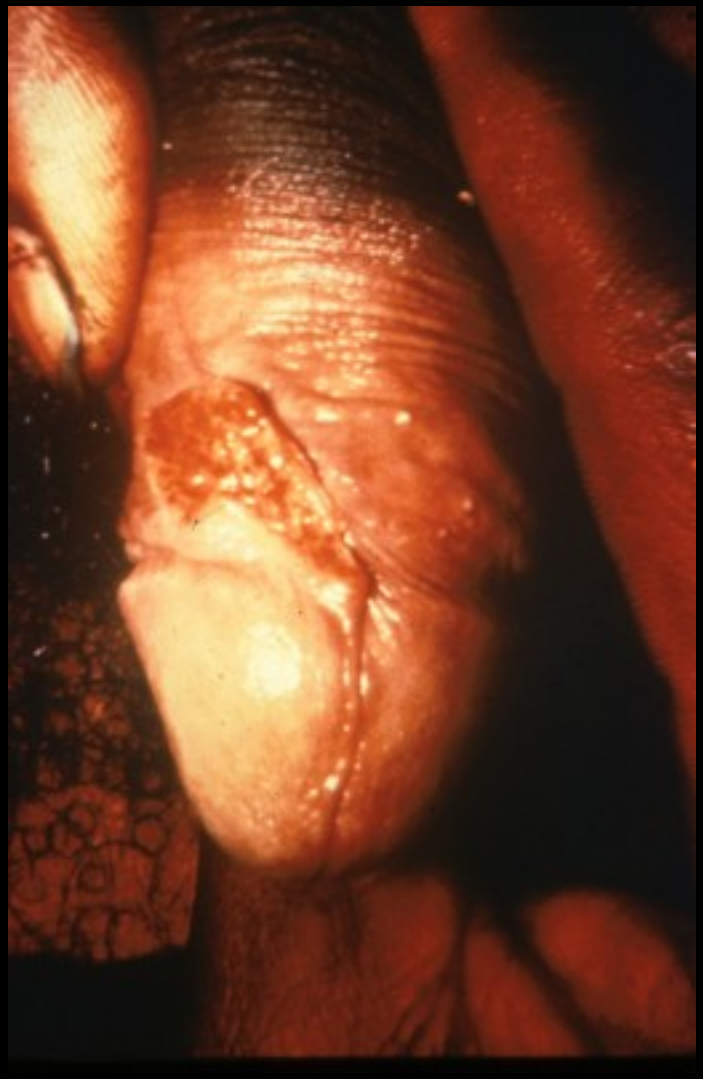
Primary syphilis - chancre



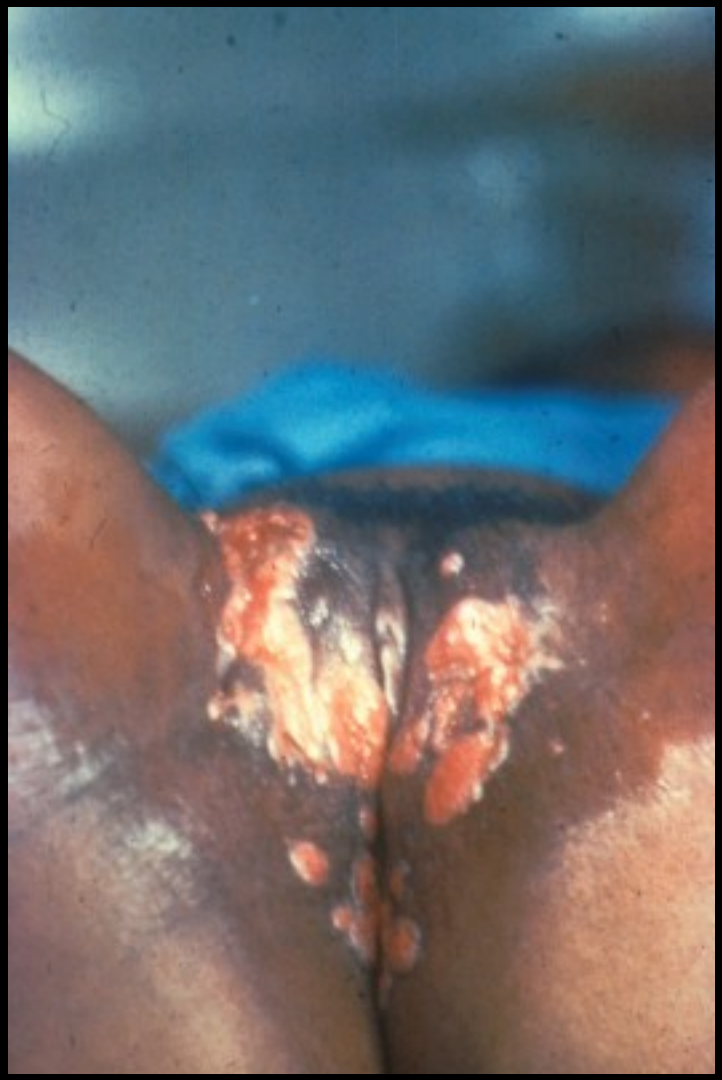
Chancroid ulcers



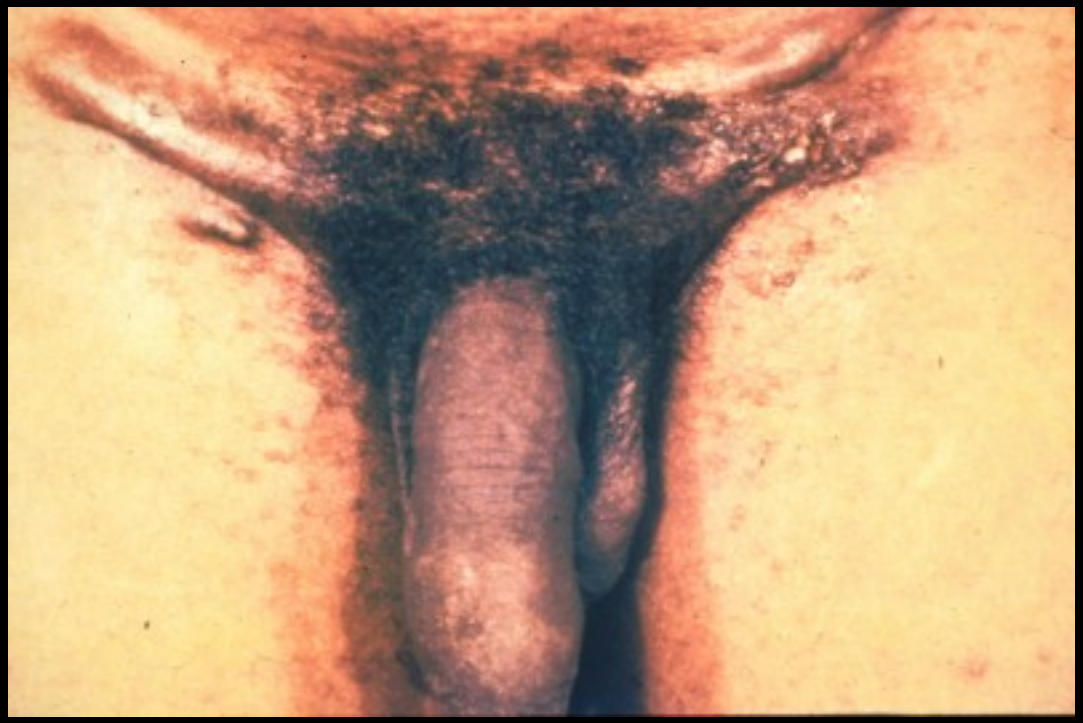
Granuloma inguinale, male



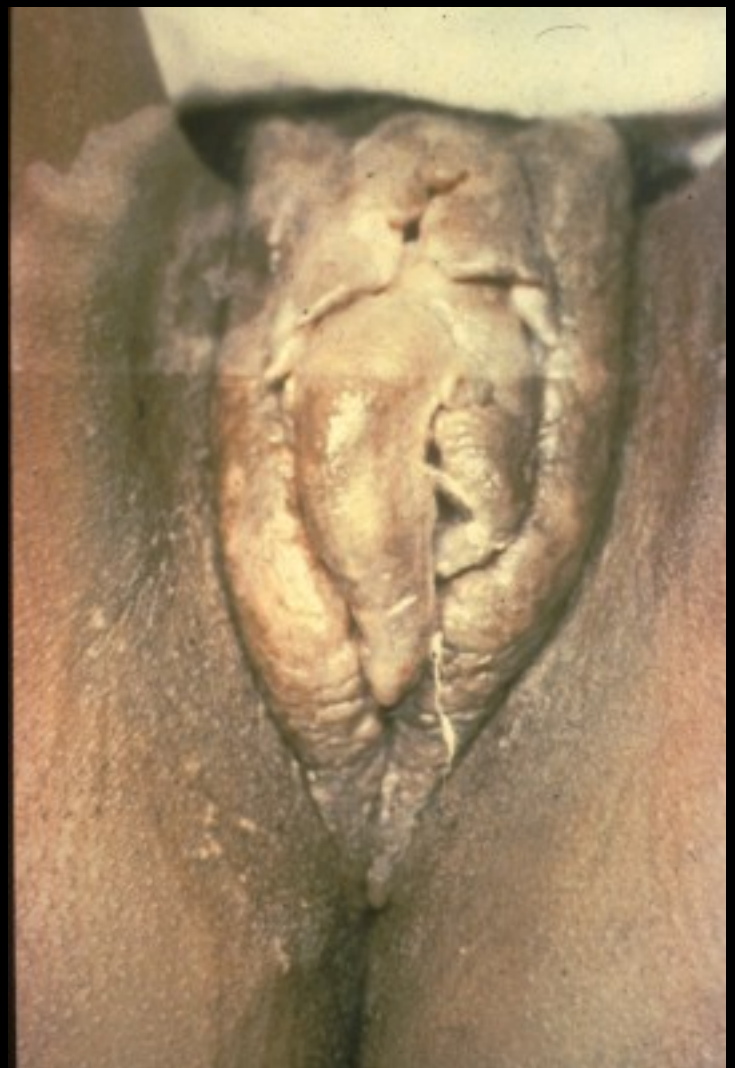
Granuloma inguinale, female



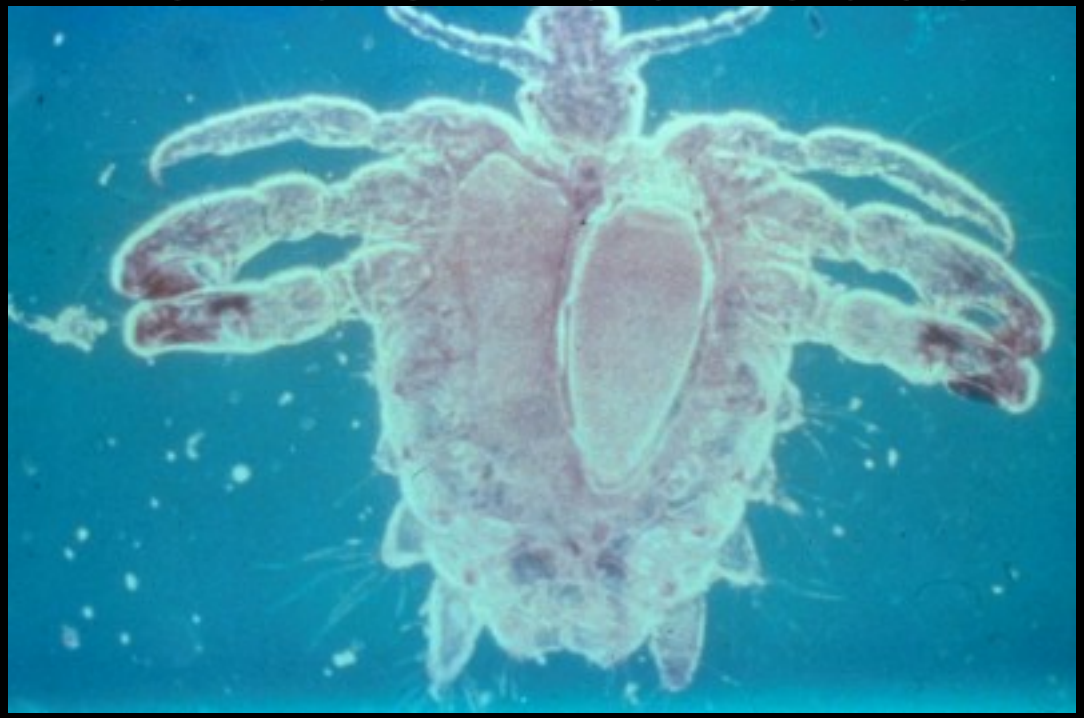
LGV lymphadenopathy



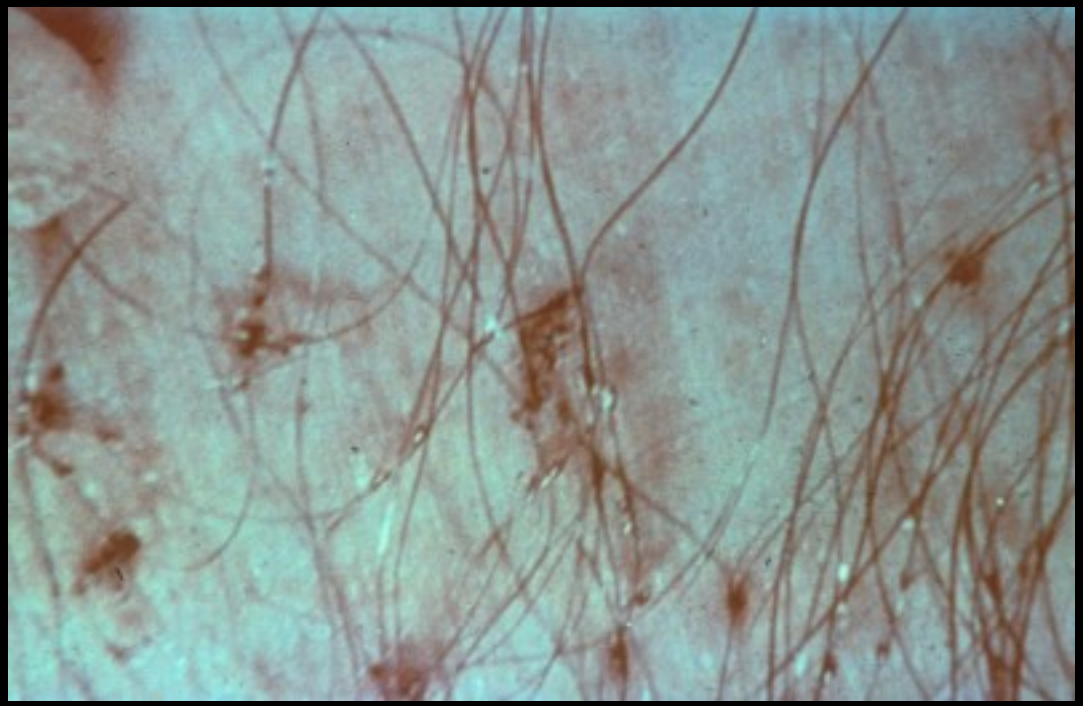
Chronic lymphogranuloma venereum in female. Genital elephantiasis

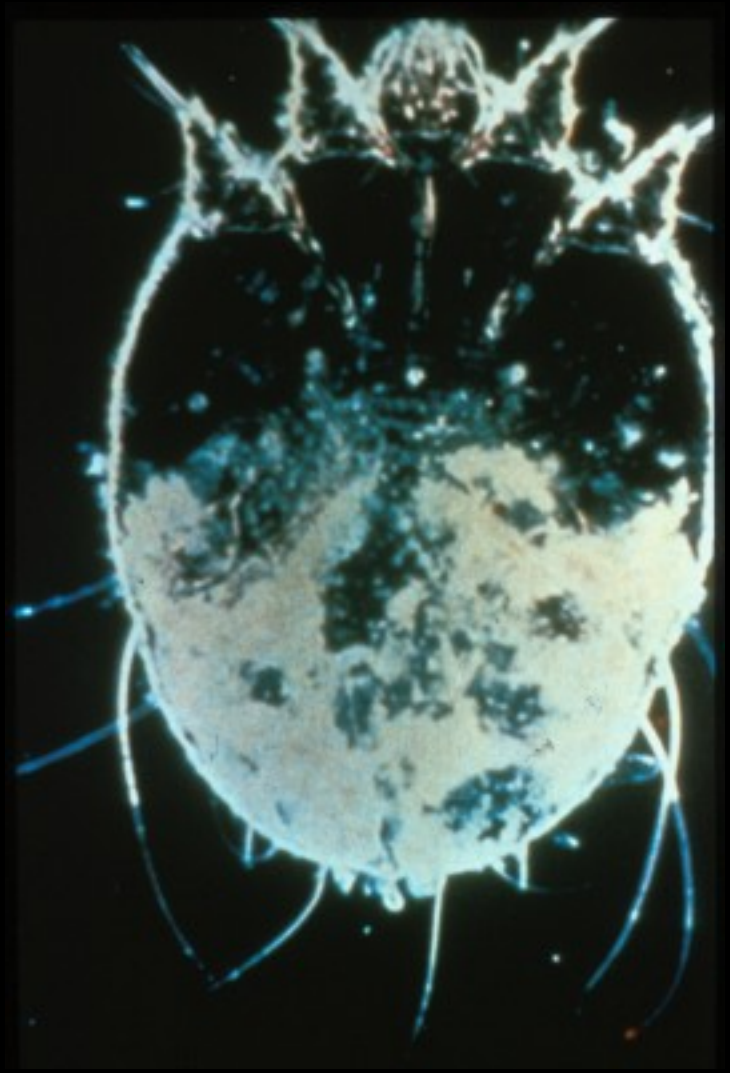


Female Crab Louse

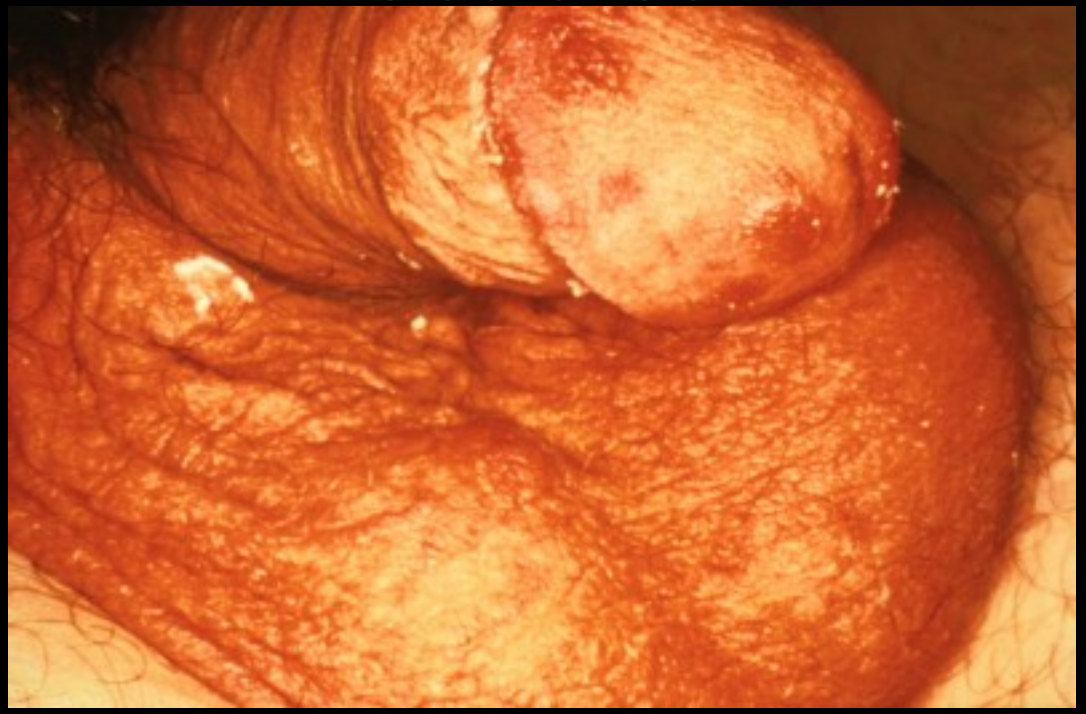


Lice in pubic area





Scabies



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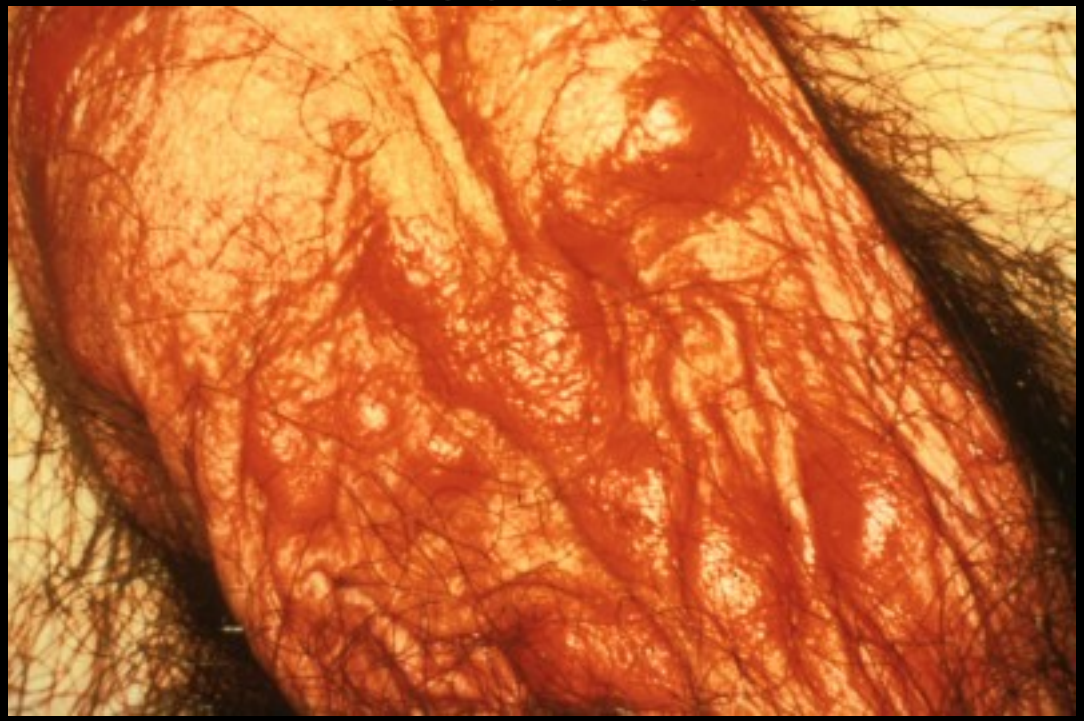

Lichen Sclerosus

- Chronic skin disorder-most often affects genital/perianal areas
  - Most often seen in women >50 yrs
  - Cause not fully understood
- Presentation: white crinkly or thickened skin-primarily on non-hair bearing areas of vulva-localized or extensive; itchy and/or sore, can cause adhesions/scarring/fissures