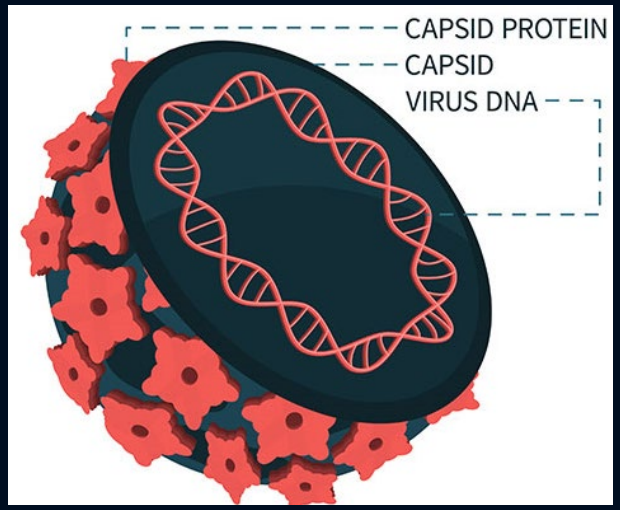
HUMAN PAPILLOMA VIRUS IN UROLOGY

ASSOC. PROF. RĂZVAN BARDAN, FECMS

OVERVIEW

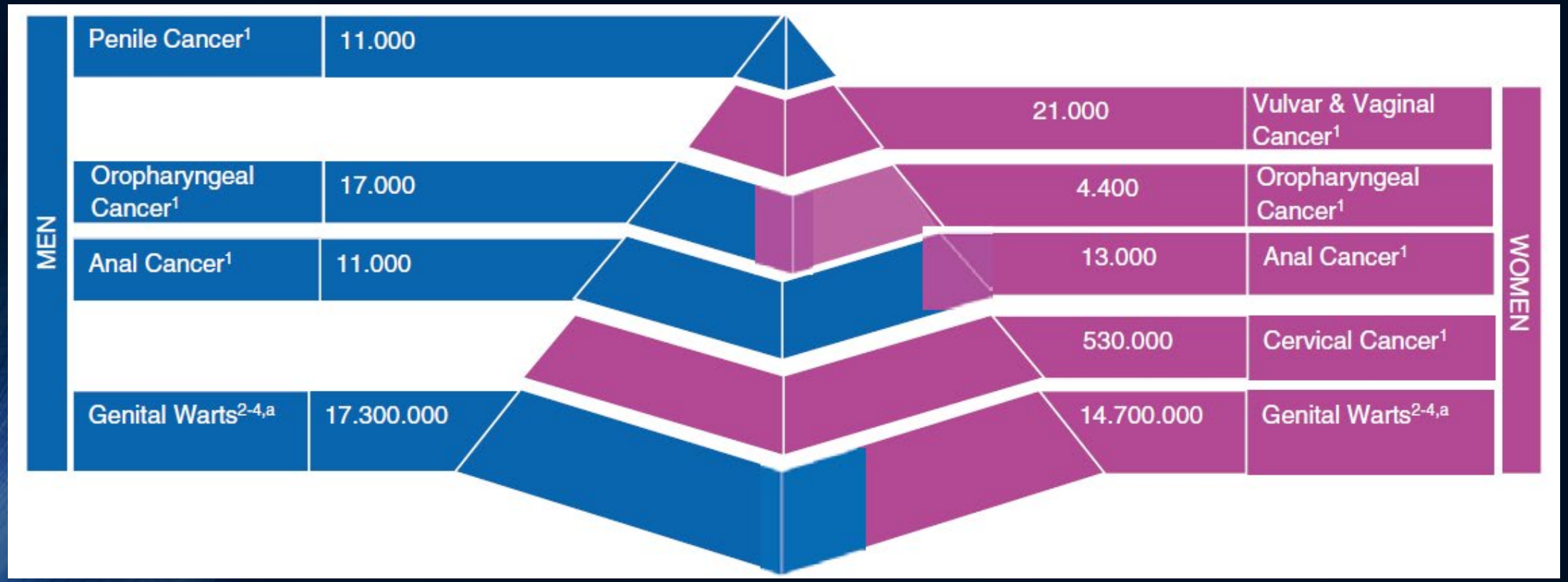
- Human papiloma virus: a double-stranded DNA virus with > 200 Genotypes
- 42 types are genital and sexually transmitted
- **Most common sexually transmitted infection (STI)**:
  - 49% prevalence for any type of HPV and 35% for high-risk HPV in men
  - 50% coinfections (≥ 2 HPV strains)
- 70-80% of sexually active people will come into contact with the virus
- HPV 6 and HPV 11 are considered low oncogenic risk but cause genital warts
- **HPV 16** is the **most common oncogenic variant** (20% of all HPV cases), followed by **HPV 18**
- About **33% penile cancers** and up to **90% anal cancers** are attributed to high-risk HPV infections



EPIDEMIOLOGY

- HPV presence is dependent on study setting
- In men attending urological clinics HPV was detected in 6% of urine samples
- A meta-analysis reported seminal HPV in 4.5-15.2% of patients resulting in seminal HPV being associated with decreased male fertility
- A cross sectional study of 430 men presenting for fertility treatment detected HPV in 14.9% of semen samples
- A systematic review reported a possible association between HPV and altered semen parameters, and in women possible miscarriage or premature rupture of the membrane during pregnancy
- The incidence of non-oncogenic HPV infection has been shown to be higher in men than women

IMPACT OF HPV INFECTION IN WOMEN AND MEN



TRANSMISSION

- HPV typically spreads by sustained direct skin-to-skin or mucosal contact, with vaginal, oral and anal sex being the most common transmission route
- In addition, HPV has been found on surfaces in medical settings and public environments raising the possibility of object-to-skin/mucosa transmission
- HPV-DNA positivity has been reported in transvaginal ultrasound probes and colposcopes after routine disinfection
- HPV prevalence in fingertip samples of female university students: 14.3%
- Further studies on non-sexual and non-penetrative sexual transmission are needed to understand the complexity of HPV transmission
- HPV transmission may also be influenced by genotype, with a higher incidence of HPV 51 and HPV 52 and a high prevalence of HPV 16 and HPV 18 in the general and high-risk male population

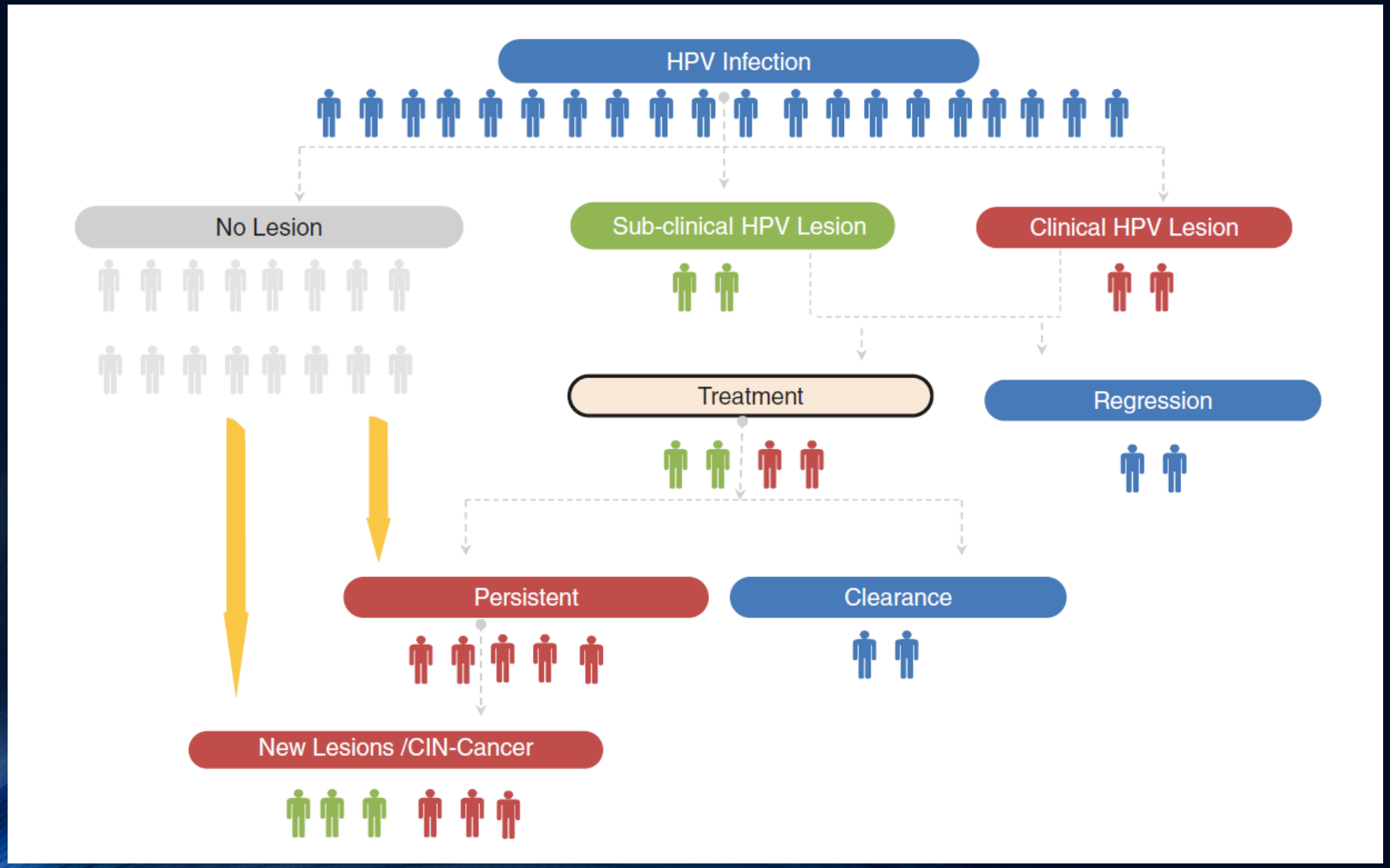
RISK FACTORS

- Risk factors for HPV infection: **early age of first sexual intercourse**, **sexual promiscuity**, **higher frequency of sexual intercourse**, **smoking, poor immune function**, HIV infection
- Incidence and prevalence of overall HPV was considerably higher in men who have sex with men (MSM) compared to heterosexuals
- Overall, the prevalence of HPV in different sites seems to be higher in young, sexual-active adults compared to other population groups
- Stable sexual habits, circumcision and condom use: protective factors against HPV
- Added risk factors for oral HPV infection: alcohol consumption, poor oral hygiene
- Positive HIV status, phimosis, and HPV status of the partner: associated with anogenital HPV status and decreased clearance

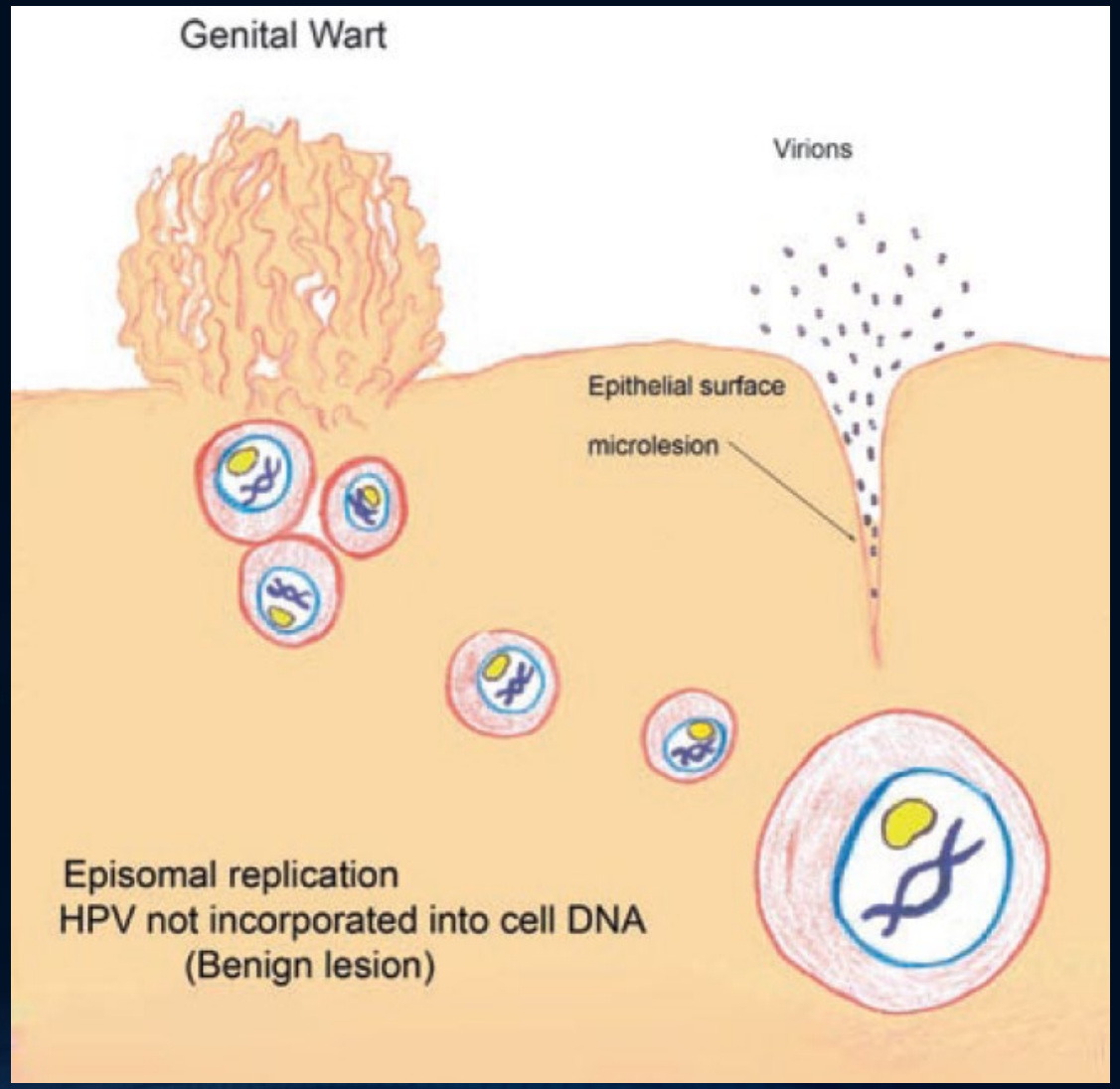
INFECTION CLEARANCE

- HPV time-to-clearance ranges from 1.3 to 42.1 months
- Clearance may be influenced by HPV genotype, patients' characteristics and affected body site
- HPV16 has the highest incidence of high-risk HPV variants and has the lowest clearance across sites
- Approximately 90% of HPV infections do not cause any problems and are cleared by the body within 2 years
- However, treatment is required when HPV infection has cutaneous manifestations, to reduce the transmission risk and to minimise the discomfort caused to patients

THE BIOLOGY OF HPV INFECTION



HPV-RELATED BENIGN LESION FORMATION



DETECTION METHODS

	Test	Analytical	Clinical	Comments
		Sensitivity/ specificity	Sensitivity/specificity for CIN3/cervical cancer	
Based on cell morphology	Pap smear/tissues	Not applicable	Low/high	Limited because of their low-sensitivities Highly dependent on sampling and tissue preservation Cannot type HPV
	Colposcopy	Not applicable	Moderate/low	
	Visual inspection	Not applicable	Low/low	
Detection of HPV proteins	Immunocito/ histochemistry[a]	Low/high	Low/low	
	Electron microscopy[a]	Low/high	Low/low	
	Western blots[a]	Low/high	Low/moderate	
Detection of HPV genomes				
Direct methods	Southern blot[a,b]	Moderate/high	Moderate/high	
	ISH[a,b]	Moderate/moderate	Moderate/moderate	
	Dot blot	Low/high	Low/high	
Signal amplification	HC[c,d,e]	High/high	High/high	
Target amplification	PCR[c,d,e]	High/high	Very high-high/ high-moderate	
	Real-time PCR[d,e]	Very high/high	Very high[f]	
Detection of anti-HPV antibodies				
	ELISA peptides	Low/low	Low/low	
	VLP	Moderate/high	Low/low	
	Fused E6/E7	High/moderate	Low-moderate/high	

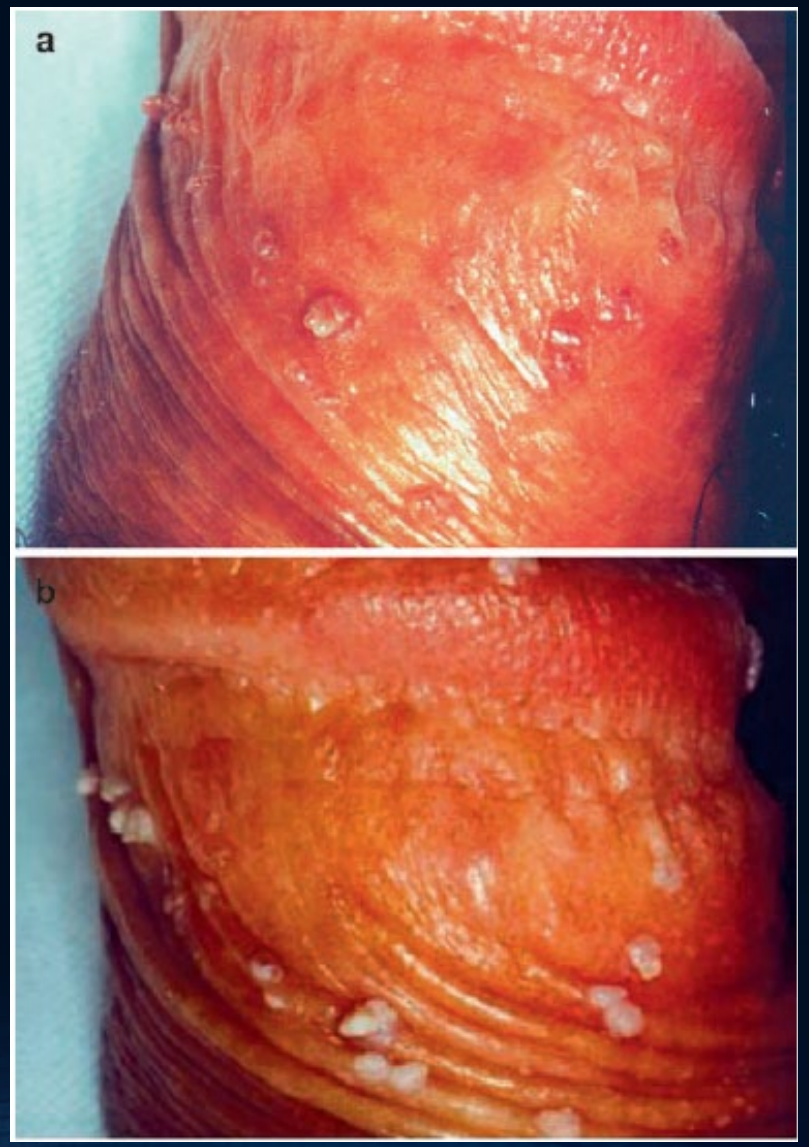
DIAGNOSIS

- There is currently no approved test for HPV in men
- Routine testing to check for HPV or HPV-related disease in men is not recommended
- A physical examination to identify HPV lesions should be carried out
- An acetic acid test to diagnose sub-clinical HPV lesions may be performed
- If the diagnosis is uncertain or there is a suspicion of cancer a biopsy should be carried out

COMMON PENILE CONDYLOMA PRESENTATION

FLORID PENILE LESIONS

THE ACETIC ACID TEST

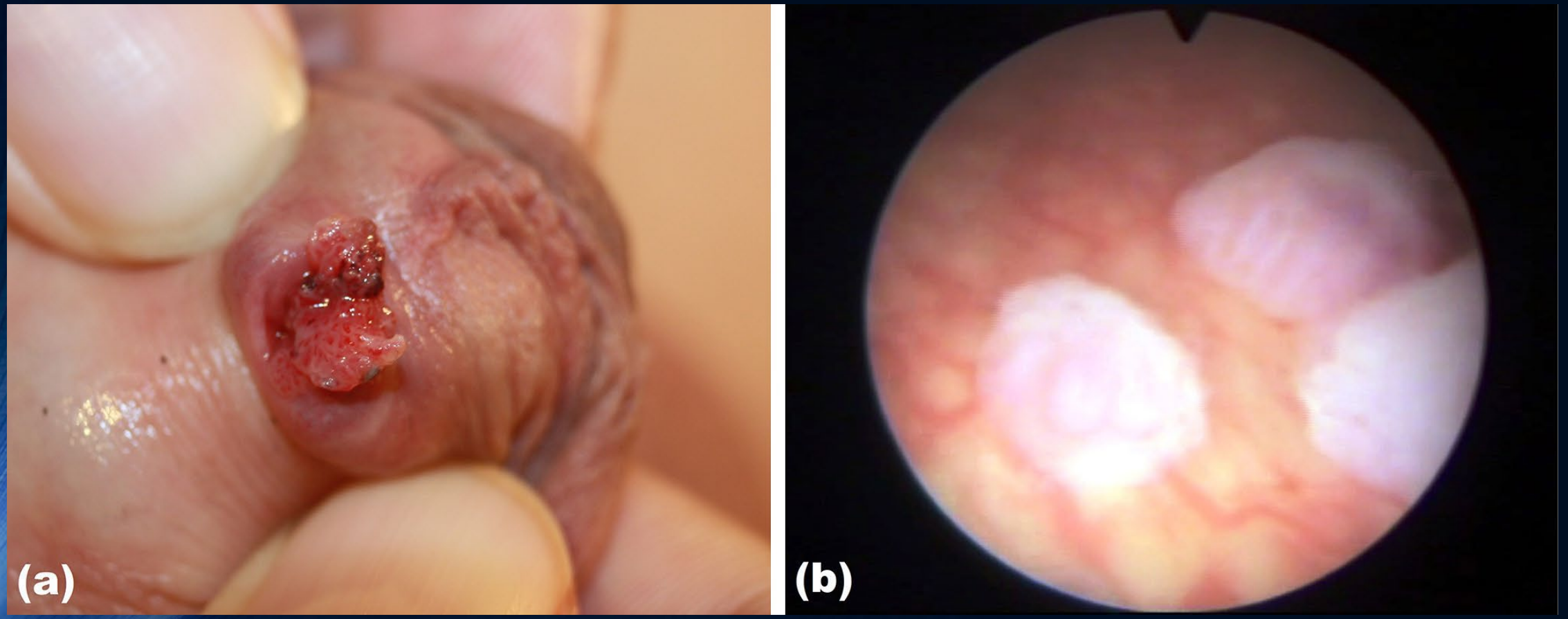


PUBIC CONDYLOMATOSIS

DIAGNOSIS

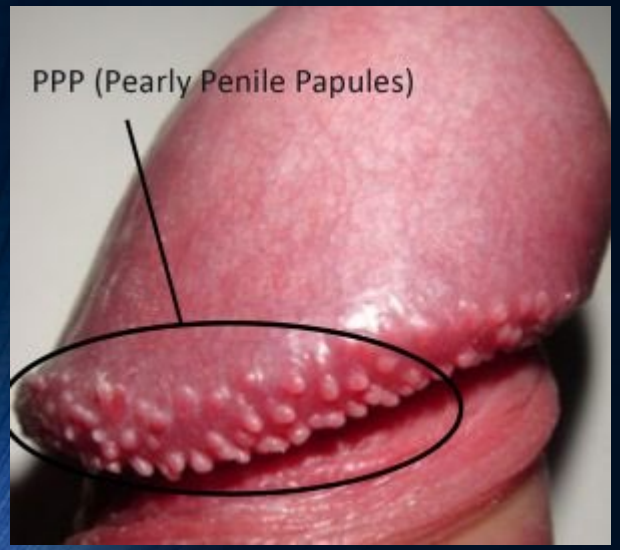
- Intra-urethral condylomas are relatively uncommon and are usually limited to the distal urethral meatus
- Urethrocystoscopy may be used to diagnose the presence of intra-urethral or bladder warts
- Anal warts are also very common, especially in patients engaging in anal sex

URETHRAL AND BLADDER LESIONS



ANAL WARTS

DIFFERENTAL DIAGNOSIS



SELF-APPLICATION THERAPY

- Imiquimod 5% cream showed a total clearance of external genital or perianal warts in 50% of immunocompetent patients as well as in HIV positive patients successfully treated with highly active antiretroviral therapy
  - A Cochrane review of published RCTs found imiquimod to be superior to placebo in achieving complete clearance of warts (RR: 4.03, 95% CI: 2.03–7.99)
  - The recommended treatment schedule is imiquimod 5% cream applied to all external warts overnight three times each week for sixteen weeks
- **In an RCT involving 502 patients with genital and/or perianal warts sinecatechins 15% and 10% showed a complete clearance of all baseline and newly occurring warts in 57.2% and 56.3% of patients, respectively vs. 33.7% for placebo**
  - In addition, sinecatechins 10% has been shown to be associated with lower short-term recurrence rates when used as sequential therapy after laser CO2 ablative therapy
  - Sinecatechins is applied three times daily until complete clearance, or for up to sixteen weeks.
- **Clearance rates of 36–83% for podophyllotoxin solution and 43–70% for podophyllotoxin cream have been reported**
  - A systematic review and meta-analysis confirmed the effectiveness of podophyllotoxin 0.5% solution relative to placebo (RR: 19.86, 95% CI: 3.88–101.65)
  - Podophyllotoxin is self-applied to lesions twice daily for three days, followed by four rest days, for up to four or five weeks

SELF-APPLICATION THERAPY

THERAPY ADMINISTERED BY THE PHYSICIAN

- Physician-administered treatments included cryotherapy (79-88% clearance rate; 25-39% recurrence rate), surgical treatment (61-94% clearance rate), including excision, electrosurgery, electrocautery and laser therapy (75% clearance rate)
- Physician-administered therapies are associated with close to 100% clearance rates, but they are also associated with high rates of recurrence as they often fail to eliminate invisible HPV infected lesions
- However, among all interventions evaluated in a recent systematic review and network meta-analysis, surgical excision appeared to be the most effective treatment at minimising risk of recurrence

ELECTROCAUTERISATION / SURGICAL EXCISION

- This is one of the most effective treatment methods for genital warts and is used successfully in the treatment of both mucosal and cutaneous CA
- The main objective in cauterization is to plan the treatment to avoid causing dermal damage and deep burn
- Otherwise, the risk of scarring is high
- Surgical excision is especially preferable for solitary and giant genital verrucous lesions, as it enables both treatment
- and diagnostic pathological evaluation for precancerous changes
- In urology practice, surgical excision can be performed successfully in cases of anterior urethral CA in particular
- In addition, transurethral resection should be kept in mind as a reliable and effective method in the treatment of rare cases of bladder CA

LASER THERAPY

- This method uses focused infrared energy to vaporize tissue affected by warts
- Of the various lasers available, carbon dioxide laser is used most frequently, especially for intraurethral and common extragenital verrucas

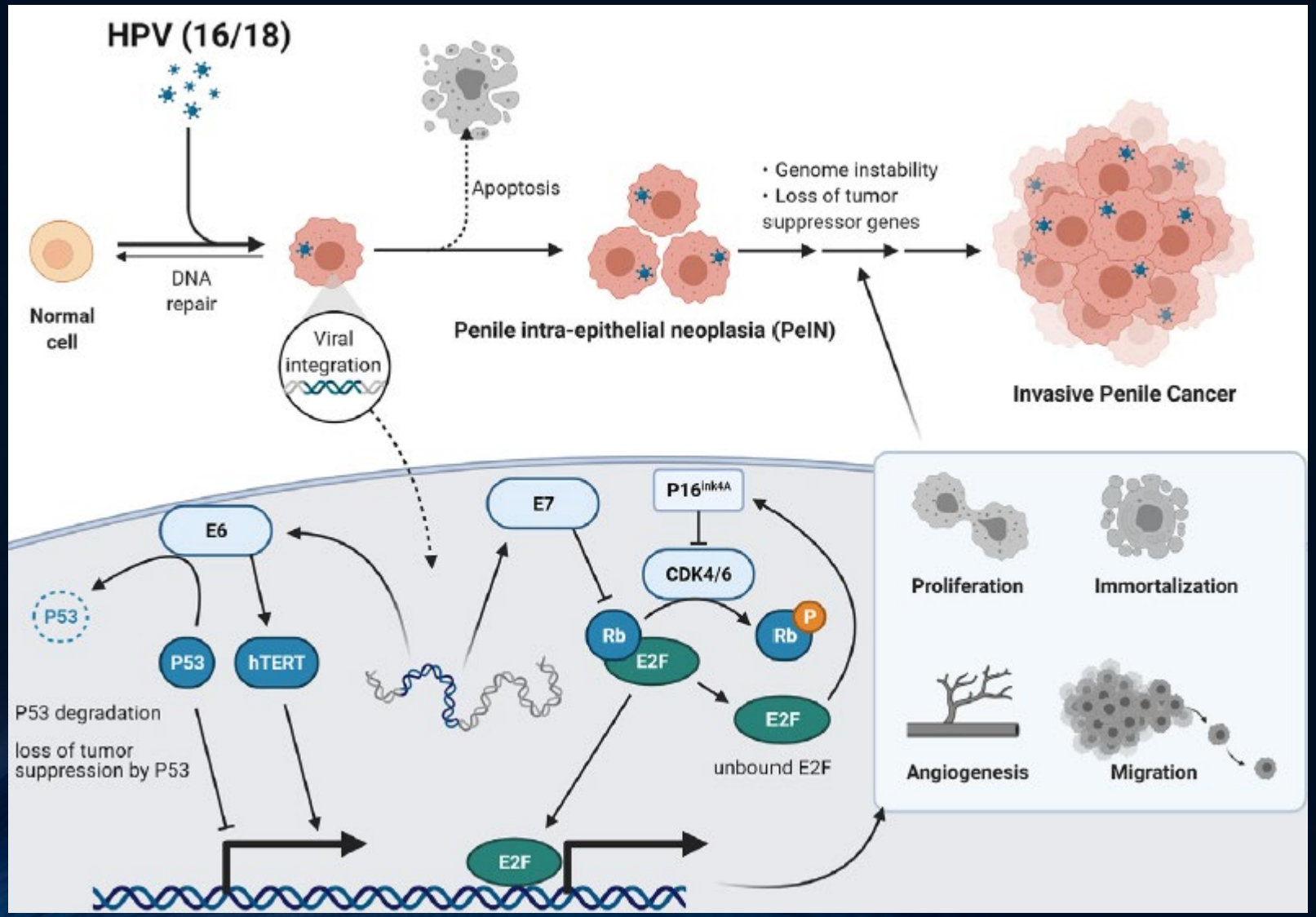
CRYOTHERAPY

- Cryotherapy is widely used in the treatment of genital warts because it is easy to implement, does not require anesthesia, is inexpensive, and has a lower risk of scarring compared to cauterization
- Liquid nitrogen at a temperature of − 196 °C causes necrotic destruction and local inflammation that triggers cellular immune response in HPV-infected keratinocytes

EUROPEAN ASSOCIATION OF UROLOGY GUIDELINES 2023

Recommendations	Strength rating
Use self-administered imiquimod 5% cream applied to all external warts overnight three times each week for sixteen weeks for the treatment of anogenital warts.	Strong
Use self-administered sinecatechins 15% or 10% applied to all external warts three times daily until complete clearance, or for up to sixteen weeks for the treatment of anogenital warts.	Strong
Use self-administered podophyllotoxin 0.5% self-applied to lesions twice daily for three days, followed by four rest days, for up to four or five weeks for the treatment of anogenital warts.	Strong
Use cryotherapy or surgical treatment (excision, electrosurgery, electrocautery and laser therapy) to treat anogenital warts based on an informed discussion with the patient.	Strong

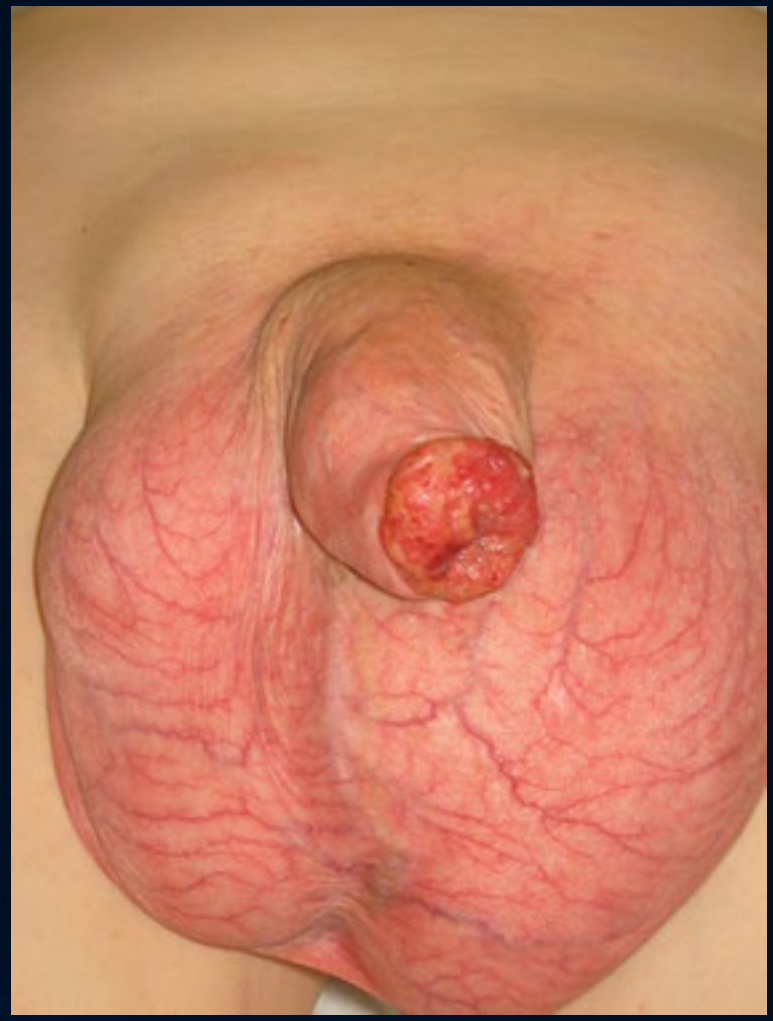
PATHOGENESIS OF PENILE CANCER



PENILE CANCER

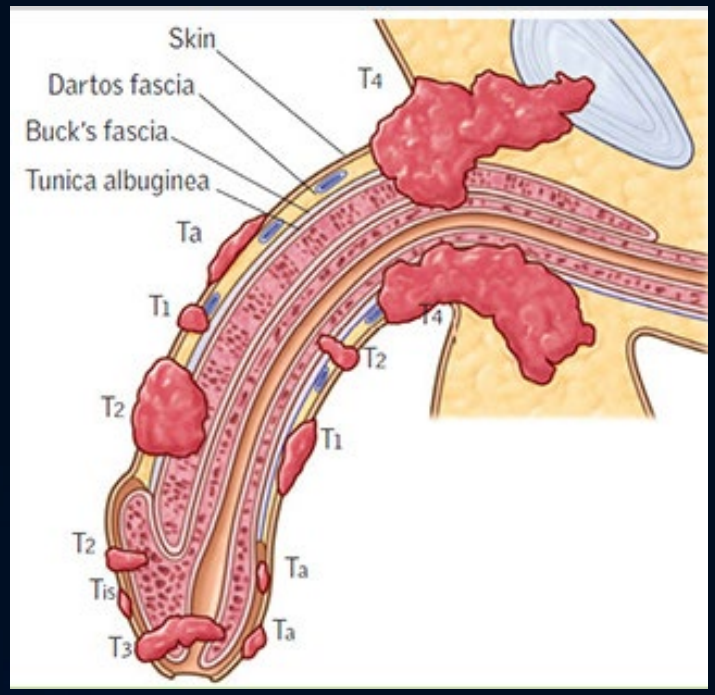
- Maximum incidence: between 60 and 80 years
- HPV-16 was most commonly found in tumor-modified cells
- At onset: small, superficial, papillary / exophytic lesion, possibly ulcerated, at the level of the glans and / or foreskin
- Histopathological form: squamous cell carcinoma
- Diagnosis: biopsy from the lesion

PENILE CANCER



PENILE CANCER

- Natural evolution: invasion of cavernous bodies ➔ metastasis in the inguinal lymph nodes, but also to distance
- Time interval from the appearance of the first symptoms to the first physician presentation: > 6 months
  - Enough for the tumor to become invasive
- Untreated patients die after approx. 2 years of tumor evolution



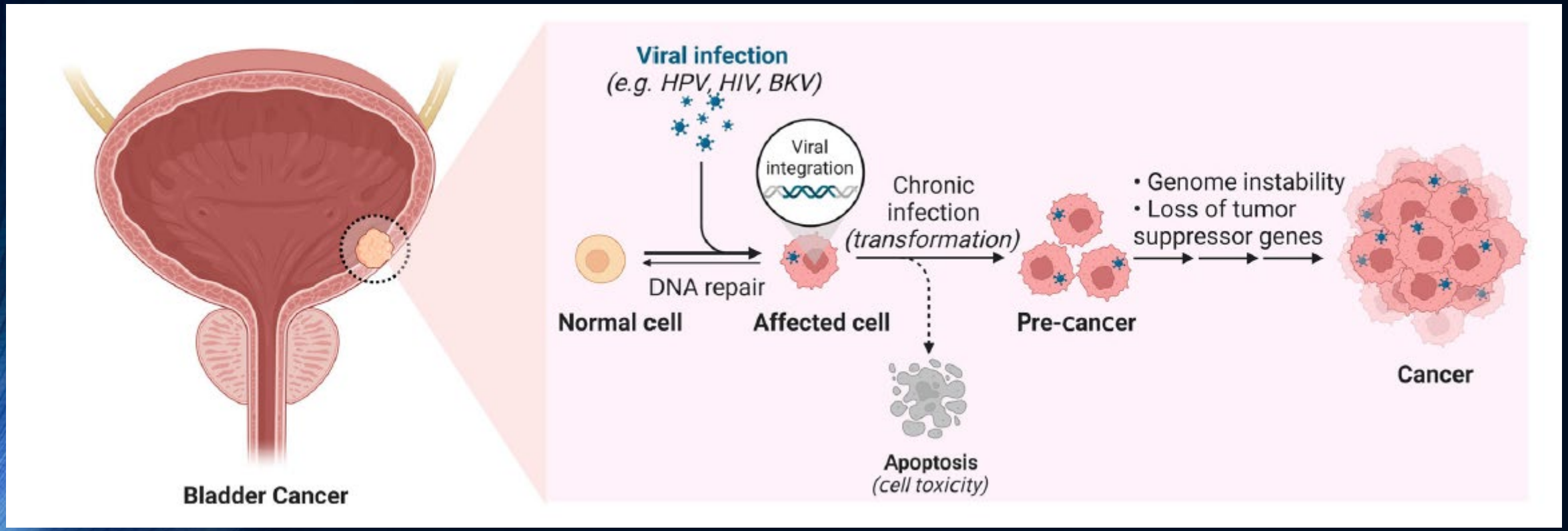
PENILE CANCER

- **Treatment:**
  - Initially: excision of the tumor + circumcision (resection of the glans)
  - If we have positive margins: amputation of the penis
  - In locally advanced cases: emasculation + dissection of the inguinal lymph nodes
  - Combination therapy: external radiotherapy + chemotherapy (Vincristine/Cisplatin, Bleomycin, Methotrexate), before or after surgery

PENILE CANCER

- **Evolution:**
  - Early forms: cure in 68% of cases (without relapses)
  - Invasive forms: tumor recurrence in 46% of cases (after treatment)
    - 5-year survival > 40%
  - Metastatic forms: 5-year survival < 18%

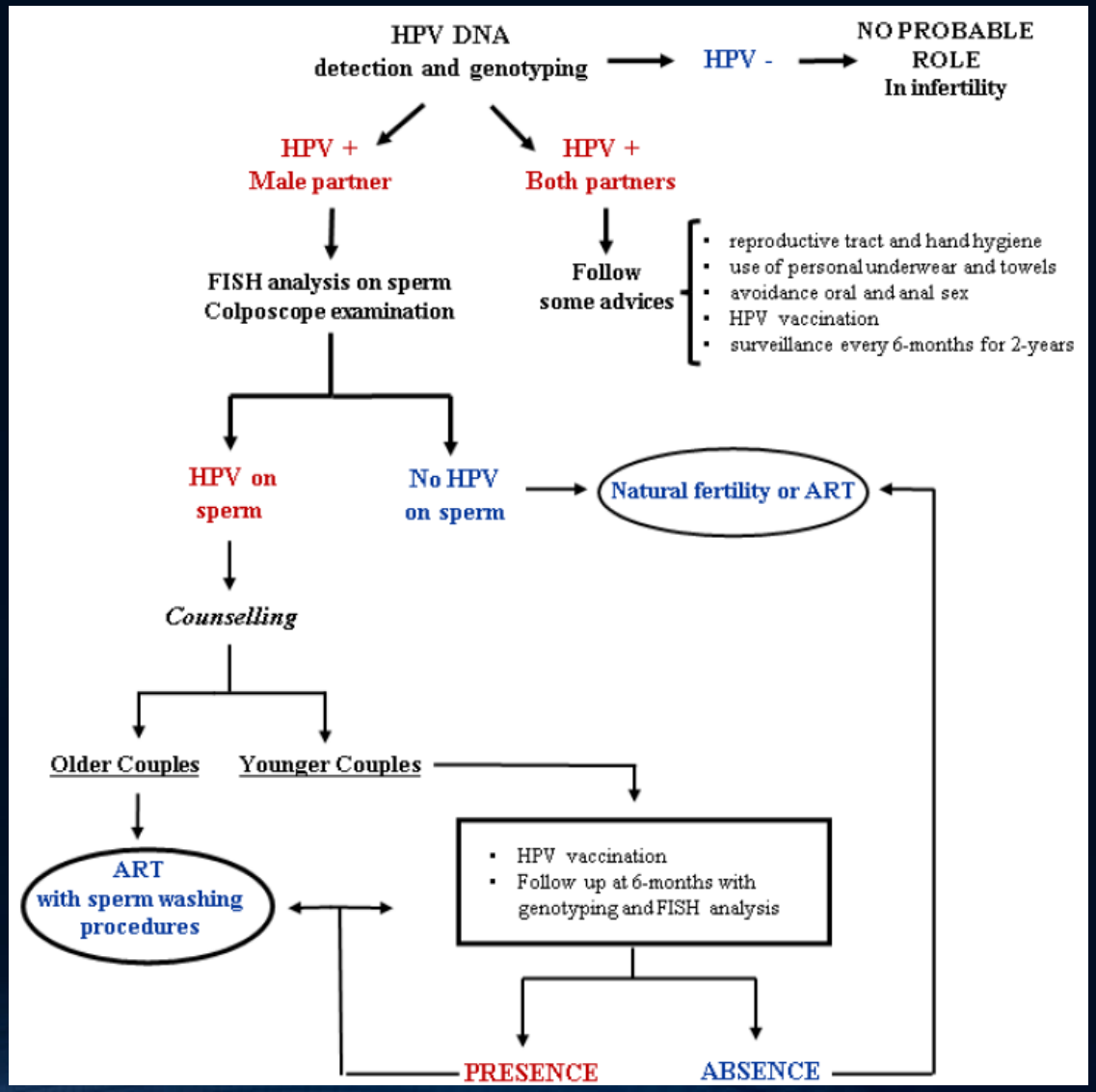
HPV AS RISK FACTOR FOR BLADDER CANCER



IMPACT OF HPV INFECTION ON MALE FERTILITY

Type of Infection	Effect	Reference
HPV positivity	Increased risk of DFI > 30%, asthenozoospermia, ASAs production, and negative ART outcome (alteration in fertilization, implantation, and development of the embryo).	[28–30]
hrHPV genotype	Reduced sperm count and motility alterations.	[27,31]
Multiple HPV infections	Hypospermia, abnormal viscosity, and increased seminal pH.	[24]
HPV16 or HPV31	Sperm genomic DNA breaks and increased apoptotic events.	[32]
HPV16 and HPV18	Exonic modification of p53 gene.	[33]

MANAGEMENT OF HPV-POSITIVE MALES



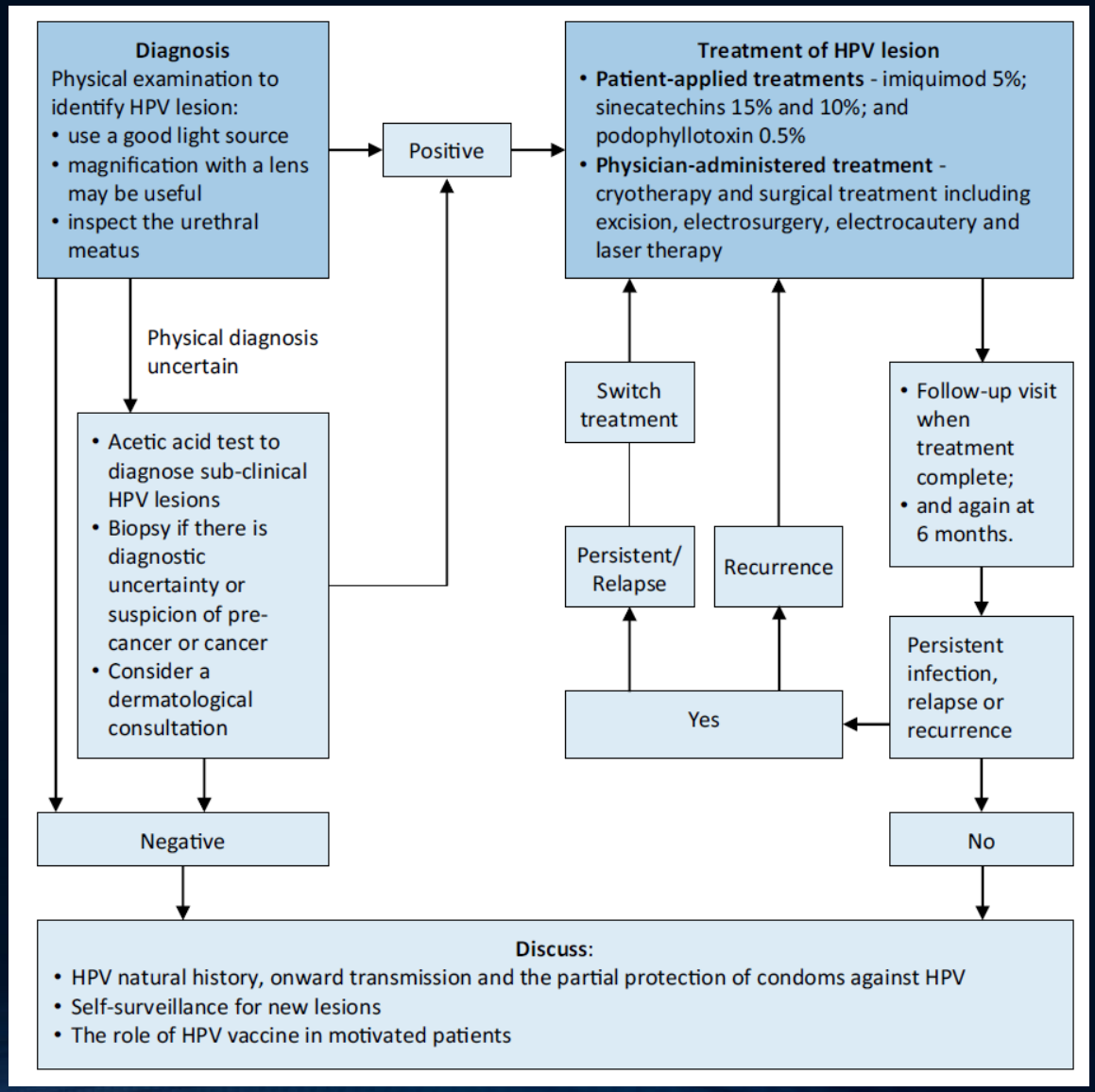
HOW CAN WE REDUCE THE EXPOSURE TO HPV?

- Limiting the number of sexual partners
- The role of barriers, condoms
- Circumcision
- Vaccination

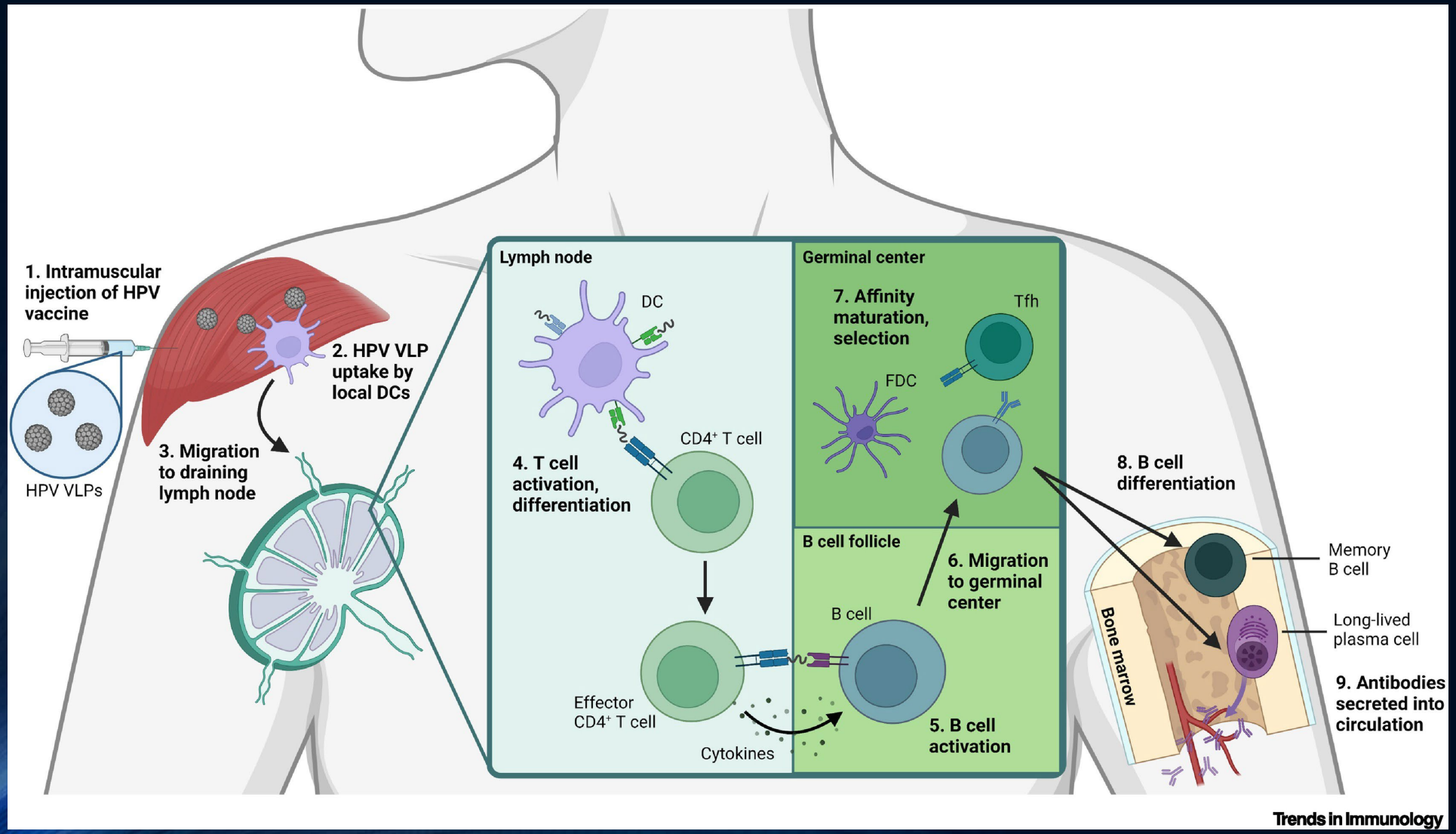
IS CIRCUMCISION INDICATED FOR THE REDUCTION OF HPV PREVALENCE?

- Male circumcision is a simple surgical procedure which has been shown to reduce the incidence of sexually transmitted infections including HIV, syphilis and HSV-2
- Two systematic reviews and meta-analyses, showed an inverse association between male circumcision and genital HPV prevalence in men
- It has been suggested that male circumcision could be considered as an additional one-time preventative intervention likely to reduce the burden of HPV-related diseases in both men and women, particularly among those countries in which HPV vaccination programs and cervical screening are not available

DIAGNOSIS AND THERAPY ALGORITHM



HPV VACCINES – MECHANISMS OF ACTION



THERAPEUTIC VACCINATION

- A systematic review including a total of 5,294 patients reported vaccine efficacy against persisting (at least six months) anogenital HPV16 infections of 46.9% (28.6-60.8%) and against persisting oral infections of 88% (2–98%)
- A vaccine efficacy of 61.9% (21.4–82.8%) and 46.8% (20-77.9%) was observed against anal intraepithelial neoplasia grade 2 and 3 lesions, respectively
- The systematic review reported no meaningful estimates on vaccine efficacy against penile intraepithelial neoplasia grade 2 or 3, and no data were identified for anal, penile or head and neck squamous cell cancers

PROPHYLACTIC VACCINATION

- Men play an important role in transmitting the virus to women
- Male immunization helps to prevent HPV transmission, thereby reducing the HPV load and incidence of HPV associated disease in women
- National vaccine programs have been implemented in a total of 87 countries, with female-only vaccination in 68 countries and both male and female vaccination in 19 countries
- The Centers for Disease Control and Prevention (CDC) recommended vaccination between the ages of 9 and 26 years for both males and females, with routine vaccination at age 11–12
- The recommended vaccination schedule is two doses given 6–12 months apart for individuals aged 9–14 years and three doses at 0, 1–2, and 6 months for those aged 15 and older
- The rationale for starting vaccination at an early age is to provide protection before first sexual contact, thereby gaining maximum benefit from the prophylactic effect of the vaccine

PROPHYLACTIC VACCINATION

- The aim of male vaccination is to reduce the rate of anal and penile cancers as well as head and neck cancers
- A systematic review and meta-analysis reported that vaccination is highly effective against genital HPV related diseases in HPV-naive males, supporting the early vaccination of boys with the goal of establishing optimal vaccine induced protection before the onset of sexual activity
- An RCT including 1,124 subjects demonstrated high efficacy of the quadrivalent HPV vaccine vs. placebo against HPV6/11/16/18-related persistent infections
- Furthermore, the vaccine elicited a robust immune response and was well tolerated with mild vaccination-related adverse events e.g. injection-site pain and swelling

CONCLUSIONS

- HPV can induce condylomatosis in men, but also penile or anal cancer
- The most exposed group: MSM
- There is currently no accepted method of testing/screening for men
- Male sexual partners of women who test positive for HPV do not need to be tested for HPV
  - In most of the cases the partner has no role in the persistence of the virus
  - Testing for HPV can give inconsistent results
- Vaccination of boys should be considered