HPV PATHOGENESIS
HUMAN PAPILLOMAVIRUS (HPV) AND CERVICAL CANCER

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CERVICAL CANCER SCREEN AND TREAT

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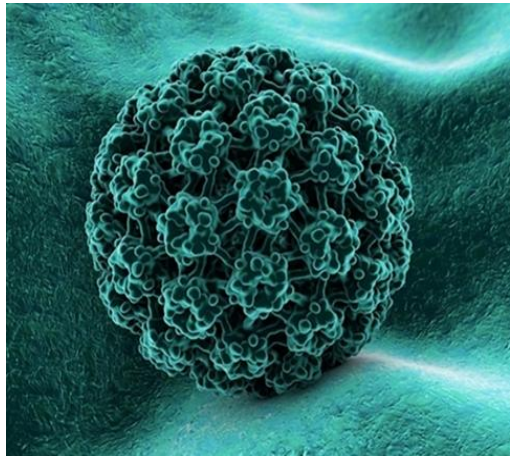
Module objectives

By end of this module, the learner should be able to:

- Discuss the various risk factors for HPV infection & cervical cancer.
- Describe the basic virology of HPV
- Describe the mode of transmission of HPV infection.
- Explain the role of HPV infection in premalignant cervical lesions and cervical cancer.
- Explain the natural progression from HPV infection to cervical cancer.
- Describe the pathogenesis of HPV virus with relation to other risk factors for cervical cancer
- Explain the relationship between HIV and HPV/CIN/ICC
- Outline the prevention of HPV infection

The most important ('necessary') cause for cervical cancer is **persistent infection** with **Human Papillomavirus (HPV)**



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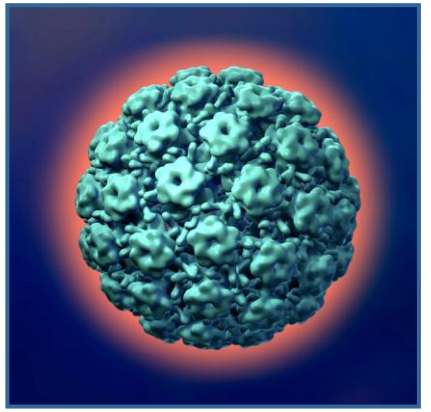
Introduction

- 99.7 % cases of cervical cancer are attributable to the Human papillomavirus (HPV), a sexually transmitted virus.
- Persistent infection with high-risk HPV is a necessary, but not a sufficient cause of cervical cancer.
  - Other risk factors come into play.
- HPV is the most common viral infection of the reproductive tract and the commonest STI in many populations.



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Risk factors for HPV infection and progression to cervical cancer

- Tobacco use
- Early age at sexual debut
- Multiple sex partners or partners having multiple sex partners
- Multi-parity - Having many children
- Lower socio-economic strata
- Not being screened for cervical cancer
- HPV Co-infection with other STIs e.g., Chlamydia, HSV, Gonorrhoea
- Women who are immunocompromised e.g., HIV infected, DM
- Prolonged use of Combined Oral Contraceptives(COCs) for more than 10 years

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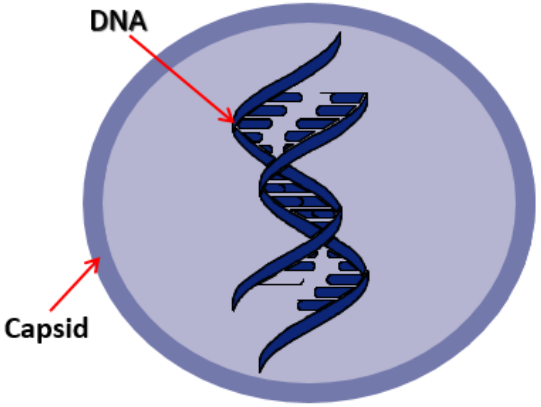
HPV Virology

- HPV is a **non-enveloped double-stranded DNA** virus
- It is the causative organism for cervical cancer
- It is mainly transmitted through **sexual contact** - genitalia to genitalia, skin to skin and skin/mucosa to genitalia;
  - Also spread through non-sexual contact, i.e., vertical transmission. HPV can survive on inanimate objects e.g., hard surfaces for up to 3 hrs. However, transmission through this means has not been proven.



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HPV Virology: HPV Types

There are over 100 subtypes (genotypes) of the HPV virus:

- **High-Risk types:** 16, 18, 31, 33, 35, 45, 52, 53, 59 & others - Cause high-grade intraepithelial lesions and invasive cancer in the reproductive tract (cervix, anus, vagina, penis and vulva) and the oropharynx.
  - Types16 & 18 cause over 70% of precancerous lesions & cervical cancer
- **Low Risk types:** 6 & 11 cause benign lesions i.e., condylomata (>90% of ano-genital warts). External genital warts are very contagious with infectivity >75% and very high recurrence rate following treatment.

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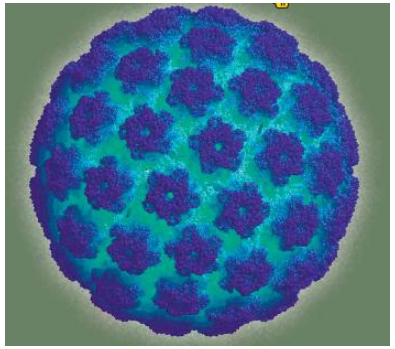
HPV and Cervical Cancer

- There are many types of HPV, and many do not cause problems.
- HPV infections usually clear up without any intervention within a few months after acquisition, and about 90% clear within 2 years.
- A small proportion of infections with certain types of HPV can persist and progress to cervical cancer.



HPV lifecycle & Natural History of Cervical Cancer

Cervical cancer is a rare outcome of HPV infection

- Majority of the infections clear in 1-2 years due to natural body immunity.
- HPV infection is asymptomatic – will only appear when the infection causes invasive cancer or genital warts.
- Only persistent infections have the highest risk of developing cervical cancer.
- Time interval between HPV infection and development of cervical cancer is a minimum of 2 years.

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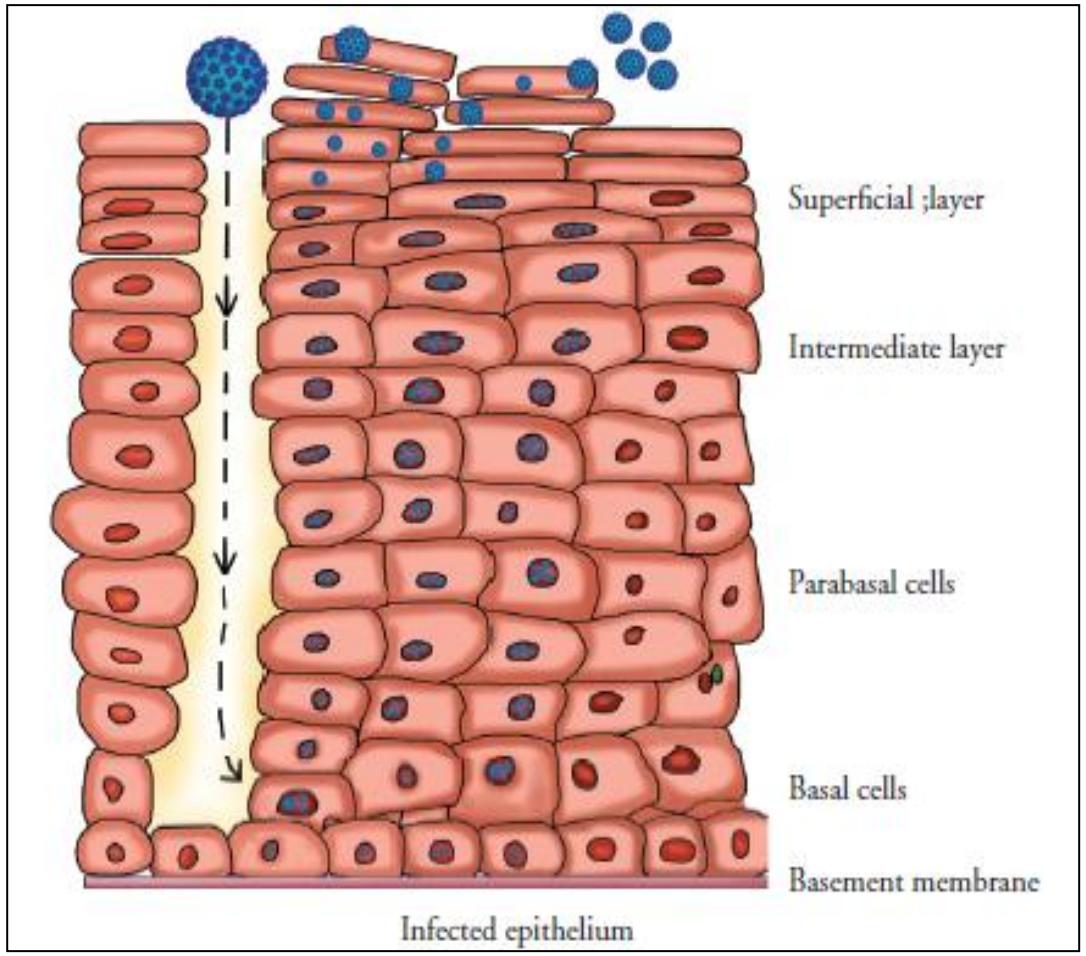
Normal life cycle of HPV infection



1. HPV enters through small breaks in cervical epithelium near SCJ.
2. Infects basal layer of squamous epithelium
3. Divides within cells & is synchronized with epithelial cell division
4. Infected cells move towards surface & is shed off
5. Induces malignant process if infection is persistent.
6. Viral DNA integrates into host DNA & produces harmful onco-proteins *(E6/E7 genes)* and disrupt normal regulatory mechanisms of cell division

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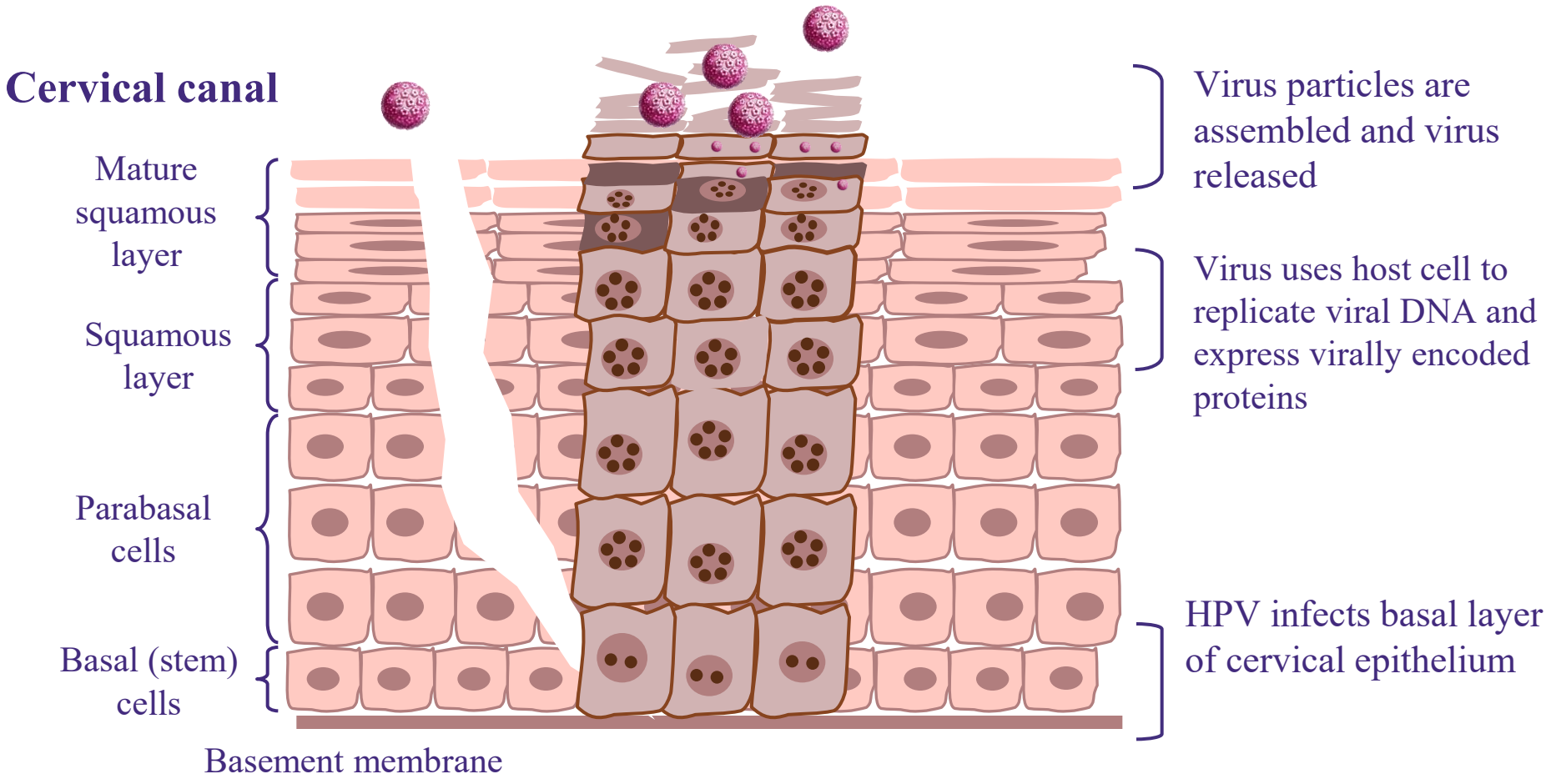
HPV Lifecycle in The Cervix



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Adapted from Frazer IH. *Nat Rev Immunol* 2004; **4:**46–54.

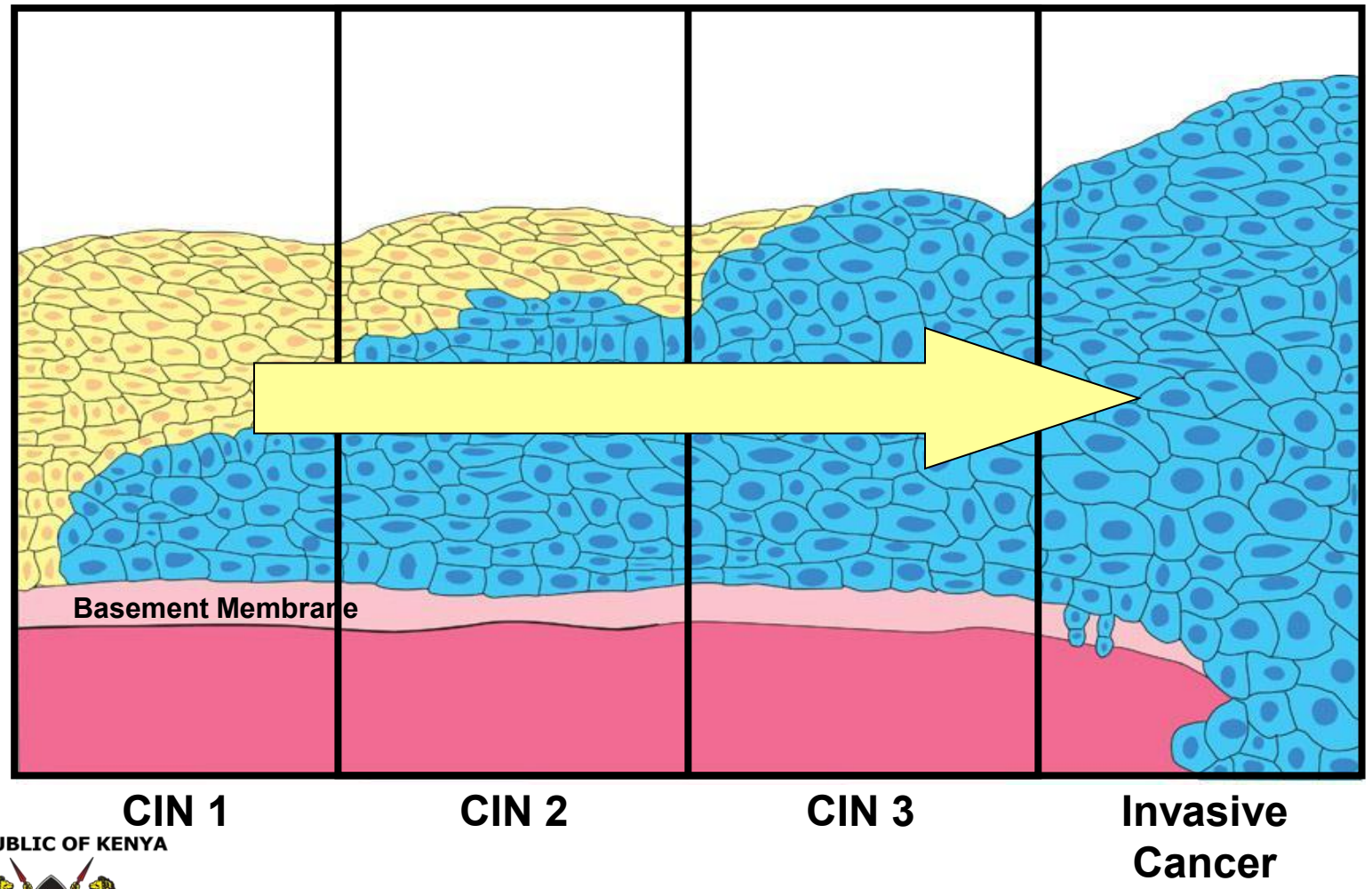
Pre-malignant cervical lesions

- Persistent HPV infection & unregulated cervical epithelial cell division lead to premalignant lesions of the cervix *(also known as pre-cancer/cervical dysplasia)*
- Lesions arising from the squamous epithelium are referred to as **cervical intraepithelial neoplasia (CIN)**,
- Premalignant lesions arising from columnar epithelium are known as **adenocarcinoma in situ (AIS)**

CIN Grading

- CIN lesions are graded according to the degree of dysplais of the cervical squamous epithelium that is made up of dysplastic (abnormal) cells, as:
  1. CIN 1 (Mild dysplasia) – **low grade squamous intraepithelial lesions (LSIL)**
  2. CIN 2 (Moderate dysplasia) – **high grade squamous intraepithelial lesions (HSIL)**
  3. CIN 3 (Severe dysplasia and Carcinoma in situ [CIS]) - **high grade squamous intraepithelial lesions (HSIL)**

Natural History of Cervical Cancer



- Oncogenic HPV types cause a change in the cells of the cervix.
- The nucleus becomes larger, and the healthy cellular material decreases in size.

Prevention of HPV Infection

- **A**bstinence or delayed sexual debut for adolescents (A)
- **B**e Faithful - to one partner for those in relationships (B)
- **C**ondom use - **though it is not 100% effective in preventing HPV*
- **HPV Vaccination** – over 90% efficacy to prevent precancerous lesions in females naïve to vaccine-specific HPV types who are fully vaccinated as per MOH guidelines.
- **Male circumcision**

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HIV and HPV/Cervical premalignancies / Invasive cervical cancer

- HPV and HIV are both are STIs with similar risk factors.
- Due to immunosuppression, HIV-positive women have a higher prevalence and longer persistence of HPV.
- They also have a higher likelihood of having multiple HPV subtypes and greater prevalence of oncogenic subtypes.
- HPV prevalence, persistence and viral load increase with decreasing CD4 count and increasing HIV viral load.
- WLHIV therefore need more frequent screening.

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Points to remember

- Infection with high-risk HPV is a ‘necessary’ cause of cervical cancer.
- HPV is the most common sexually transmitted virus
- Most HPV infections women will be cleared by the body’s immune system.
- Persistent infection with any of the high-risk types of HPV leads to cervical premalignancy (CIN) and invasive cancer.
- Prevention of HPV Infection – ABCs, vaccination, male circumcision
- HIV-positive women have a higher prevalence and longer persistence of HPV because of immunosuppression.

Acetowhite reaction refers to the whitening of an area of the cervical epithelium, when the tissue reacts with 3%–5% acetic acid (normal table vinegar).

This reaction is caused by the coagulation of cellular proteins, which appear opaque.

The opaqueness blocks light from reaching the blood vessels and so appear white when looked at with the naked eye

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Human papillomavirus (HPV)-infected cells are more active and contain more proteins, which causes them to appear more opaque than surrounding normal tissues.

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Thank you

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