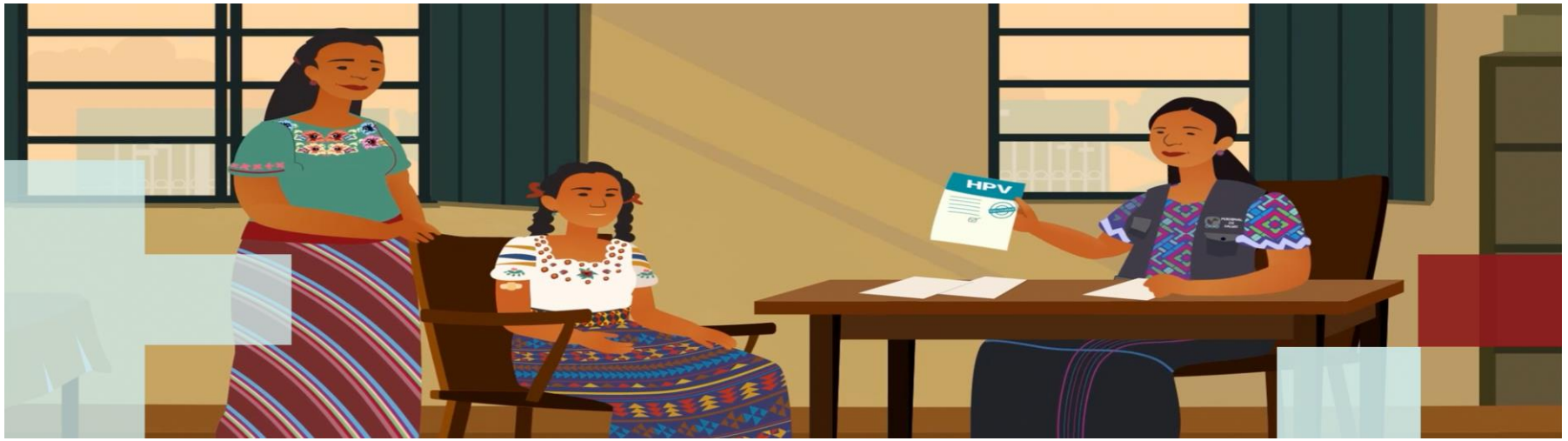
Human Papillomavirus (HPV)



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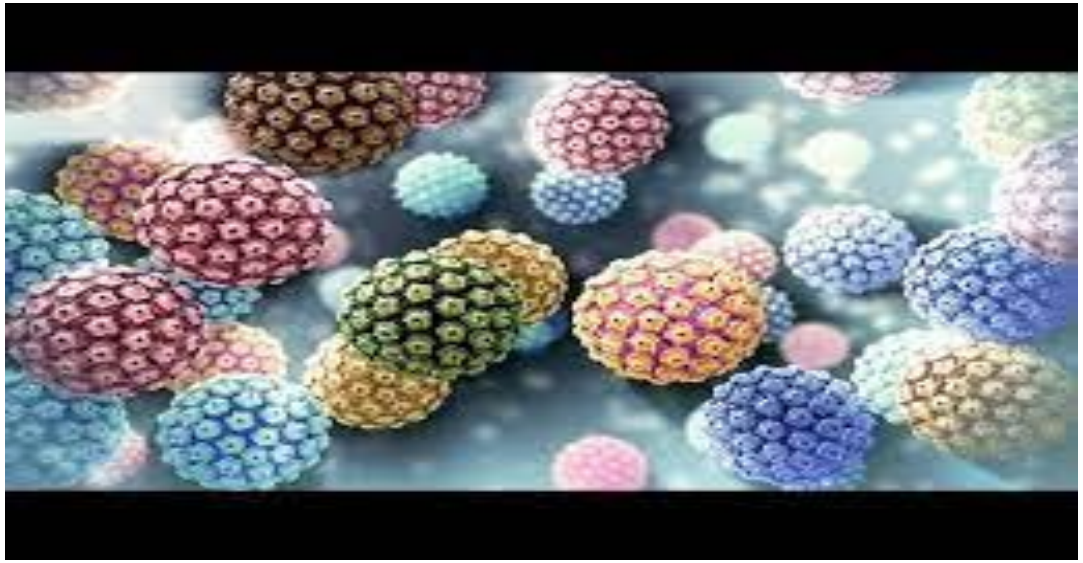
Papillomaviruses constitute the genus of the Papillomaviridae family.

nonenveloped, 8000 base-pair, **double-stranded DNA virus** with a diameter of 55 nm.

At least **210** HPV types have now been characterized, and many others have been recognized.



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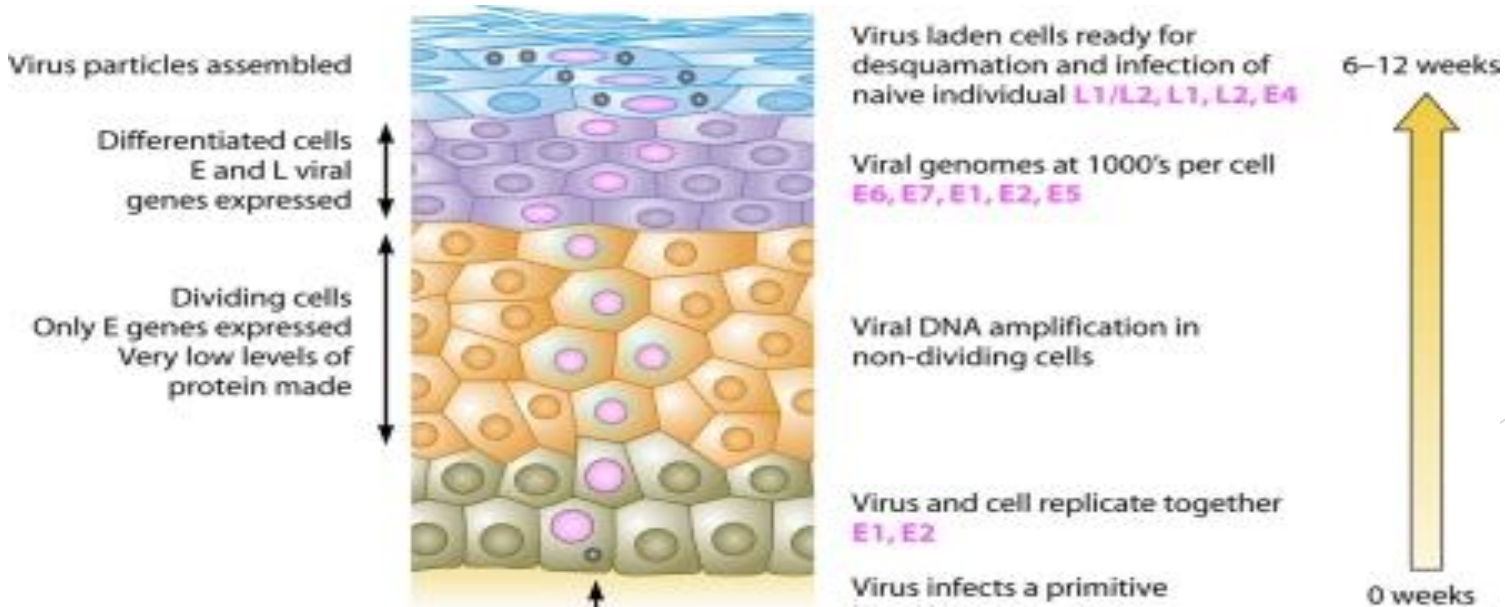
HPV **targets** basal keratinocytes after microtrauma allows exposure of these cells to the virus.

The HPV replication cycle is completed as keratinocytes undergo differentiation.

Infection is transmitted by contact with virus contained in these desquamated keratinocytes (or with free virus) from an infected individual.



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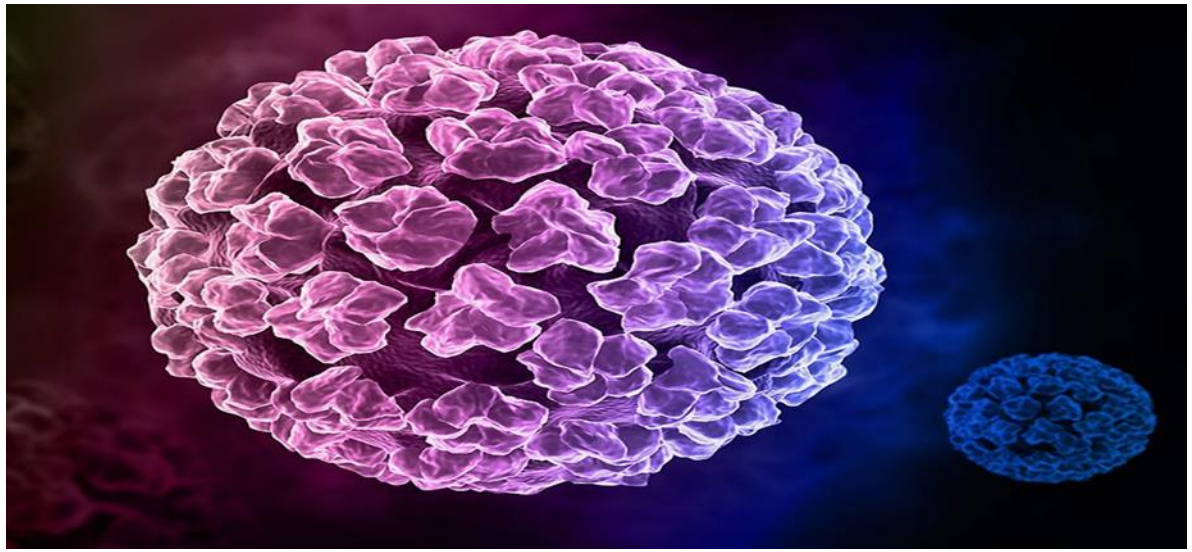
Unlike many viral infections, HPV infection has no viremic phase.

This lack of viremia may account for the incomplete antibody response to HPV infection.

Natural HPV infection of the genital tract gives serum antibody response in 60–70% of individuals.

Significant protection, although incomplete, against type-specific reinfection is associated with the presence of antibody.



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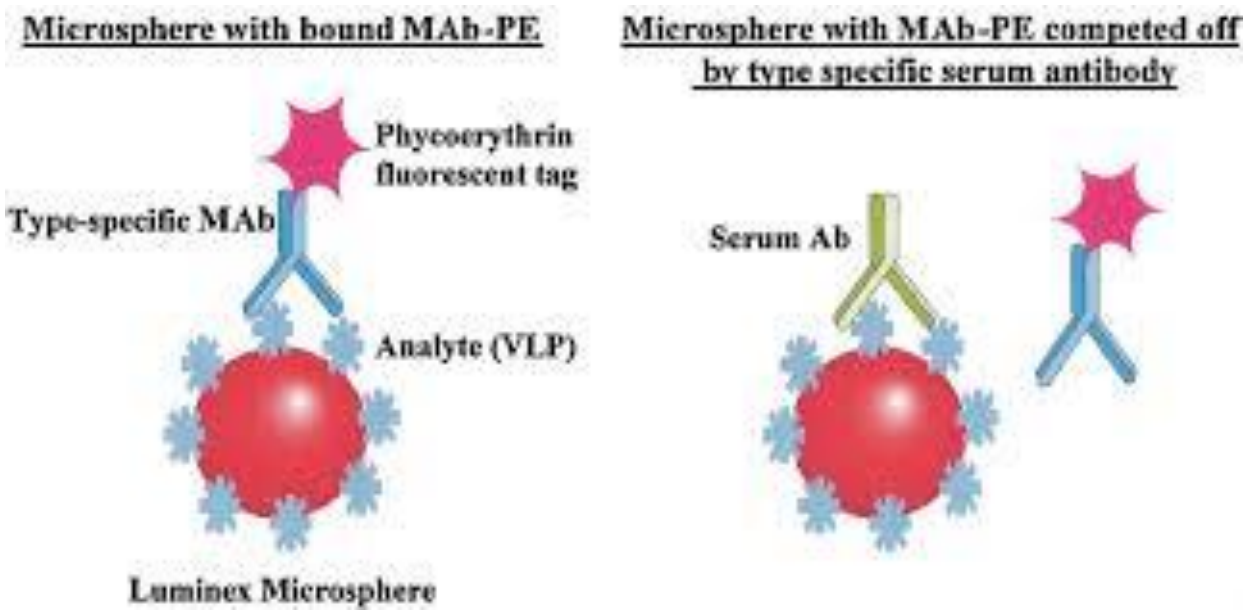
Serum antibodies likely reach the cervical epithelium and secretions by transudation and exudation.

Therefore, protection against infection relates to the amount of neutralizing antibody at the site of infection and lasts as long as sufficient levels of neutralizing antibodies are present.



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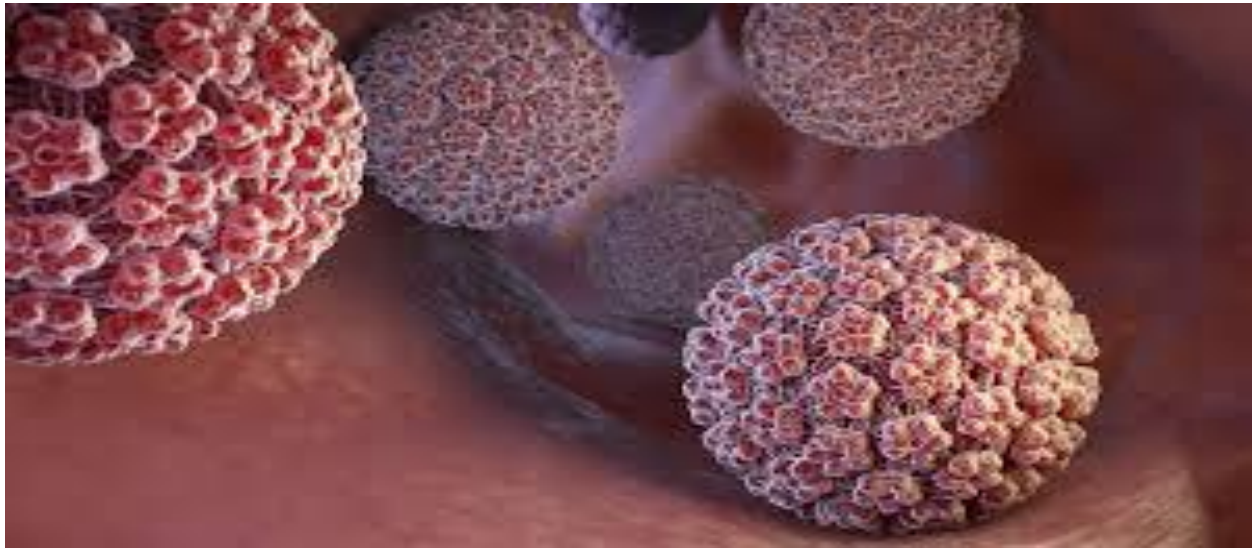
A cell-mediated immune response plays an important role in controlling progression of HPV infection.

Histologic examination of lesions in individuals who experience regression of genital warts demonstrates infiltration by T cells and macrophages.

CD4+ T-cell regulation is particularly important in controlling HPV infections, as evidenced by the higher rates of infection and disease in immunosuppressed individuals, particularly those who are infected with HIV.



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At least 12 human papillomavirus (HPV) types are considered oncogenic, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.

HPV16 alone accounts for approximately 53% to 73% of cervical cancers in the general population and HPV18 for another 12% to 21%. The other oncogenic HPV types each account for under 5% of cervical cancers.

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1. HPV is a common STI.

2. cervical cancer the fourth most common cancer in women worldwide.

3. Nearly all cervical cancers contain oncogenic HPV DNA sequences.

4. Rates of cervical cancer in women with HIV were elevated significantly compared with the general population—3 to 4 times overall.

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Most of these relative risks increase with:

decreasing CD4 T lymphocyte (CD4) cell counts, and cervical cancer is itself associated with advanced HIV.

The percentage with adenocarcinoma histology compared with squamous cell carcinoma is lower in women with HIV than in the general population.

Several studies found decreased incident detection, persistence, and progression of HPV and CIN with effective antiretroviral) therapy (ART).

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People with HIV have an increased incidence of anogenital tumors (vulva, vagina, penis) and OPC relative to the general population.

Low CD4 counts in people with HIV have been associated with increased risk of anal cancer.

Before HPV vaccinationhe incidence of anogenital warts was 60.2 per 10,000 women (aged 20–24 years) and 53.8 per 10,000 men (aged 20–24 years), but with several-fold greater rates in people with HIV.
Low-grade vulvar lesions and genital warts were both found to decrease with ART.

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Clinical Manifestations:

Most warts are asymptomatic.

warts can be associated with itching or discomfort.

Oral and genital (condyloma acuminata), and anal warts are usually:
flat, papular, or pedunculated growths on the mucosa or epithelium.

The lesions may measure a few millimeters to 1 to 2 centimeters in diameter.

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In severe immunosuppression cases :

- marked enlargement
- dyspareunia
- dyschezia
- cosmetic concerns

Low-grade squamous intraepithelial lesions (LSIL) and HSIL in the cervix, vagina, vulva, and anal canal:

often asymptomatic

bleeding

itching

pain

Odor

visible/palpable mass

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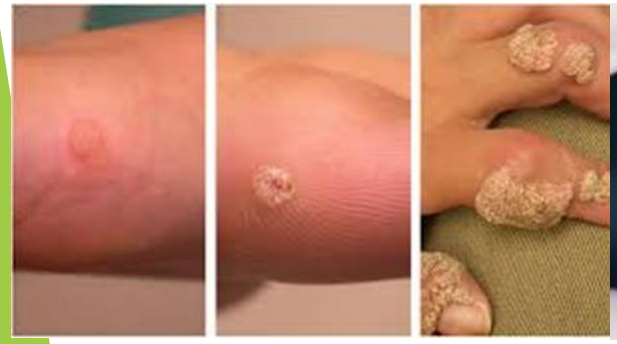
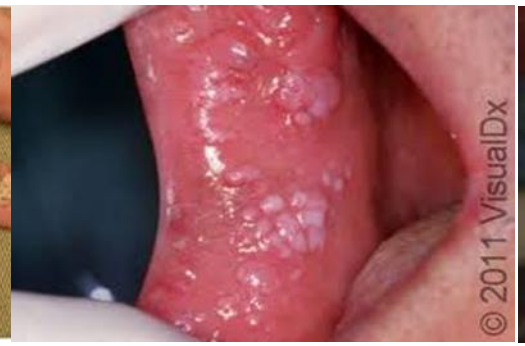
CLINICAL MANIFESTATIONS:

- Cutaneous Warts(1,2,4,27)
- Deep plantar warts(1,2,27)
- Common warts
- Plane warts(3,10)
- Epidermodysplasia Verruciformis(5,8,9,12,14,15,17)
- Anogenital Warts
- Recurrent Respiratory Papillomatosis(6,11)
- Oral squamous cell papillomas(HPV-6, 11,16)
- Oral verrucae vulgaris are (HPV-2,4,57)
- Focal epithelial hyperplasia of the oral cavity (Heck disease) HPV-3,13 and tends to regress spontaneously.





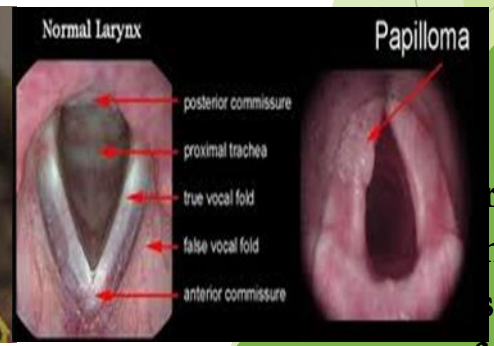


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TABLE 1. Human Papillomavirus (HPV)-Induced Lesions and Associated HPV Types

Lesion	Low-Risk HPV Types	High-Risk HPV Types
Squamous Papilloma	6, 11	
Verruca Vulgaris	2, 4	
Condyloma Acuminatum	6, 11	16, 18
Heck Disease	13, 32	
Fungiform Papilloma	6, 11	
Inverted Papilloma	6, 11	16, 18
Cylindrical Papilloma	6, 11	
Oropharyngeal Carcinoma		16, 18

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Risk factors for cancer progression include :

- ✓ the grade of oncogenicity of the HPV type
- ✓ immune status
- ✓ the presence of other sexually transmitted infections
- ✓ number of births
- ✓ young age at first pregnancy
- ✓ hormonal contraceptive use
- ✓ smoking

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Screening cervical cancer:

is an important part of routine health care for people who have a cervix. This includes women and transgender men who still have a cervix.

Screening tests are used to check for disease when there are no symptoms. Typically, it takes 15-20 years for abnormal cells to become cancer, but in women with weakened immune systems, such as untreated HIV, this process can be faster and take 5-10 years.

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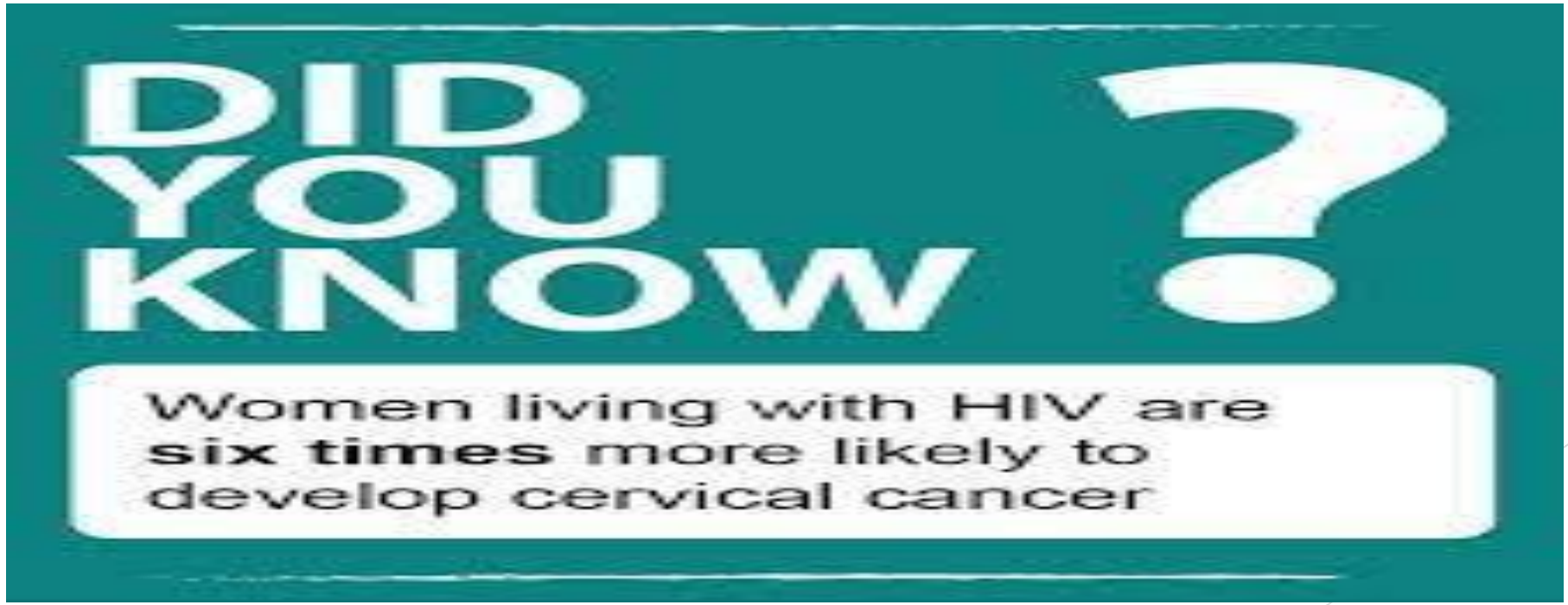
Screening cervical cancer

Previously Cervical cancer is the only type of cancer caused by HPV with a **recommended screening test** for detection at an early stage.

The other cancers may not be detected until they cause health problems.

The goal of **screening for cervical cancer is to find precancerous cell changes** before they become cancer and when tretment can prevent cancer from developing.



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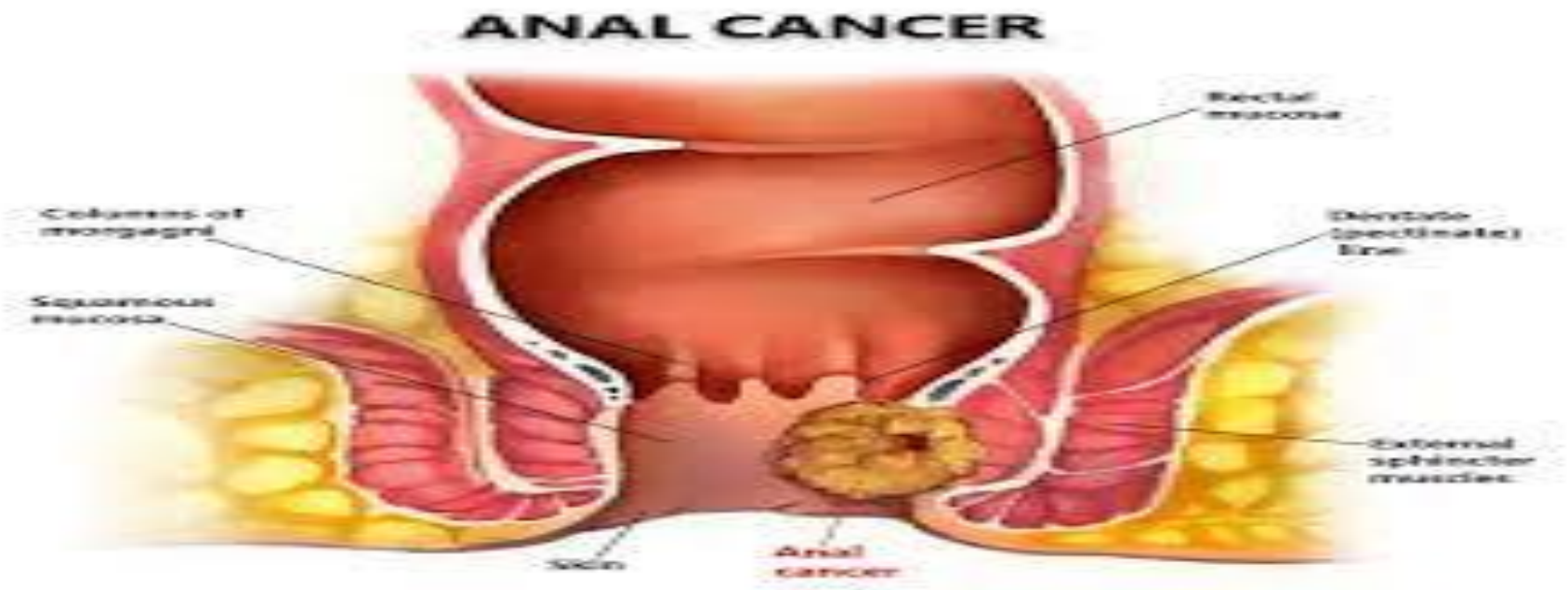
Screening anal cancer(July 9, 2024)

high incidence of anal cancer in people with HIV
the high progression rate of anal HSIL to anal cancer in the absence of treatment.



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risk of anal cancer:

1. Older age
2. longer known duration of immune suppression and HIV infection
3. history of AIDS
4. Smoking
5. positive HPV16 or 18 status
6. higher grade of cytologic abnormality

People with HIV who meet any of these criteria should be screened and referred **for HRA as soon as feasible**.

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Screening anal cancer(July 9, 2024)

People with HIV, regardless of history of anal intercourse:
1.anal symptoms:

unexplained itching
anal bleeding
pain
presence of perianal lesions

2. MSM and transgender women aged 35 years and older
other people with HIV aged 45 years and older, should be assessed annually .

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- A new study has been published in The Lancet Global Health showing that almost 1 in 3 men over the age of 15 are infected with at least one genital human papillomavirus (HPV) type, and 1 in 5 are infected with one or more of what are known as high risk, or oncogenic, HPV types.

These estimates show that men frequently harbour genital HPV infections and emphasize the **importance of incorporating men in efforts to control HPV infection** and reduce the incidence of HPV related disease in both men and women.

Some countries have also chosen to vaccinate boys to further reduce the prevalence of HPV in the community and to prevent cancers in men caused by HPV.

- Global and regional estimates of genital human papillomavirus prevalence among men: a systematic review and meta-analysis
  Available online 15 August 2023, Version of Record 15 August 2023

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key to prevention and control across the life course:

- Boosting public awareness
- access to information
- Services
- Reduction of number of sex partner(monogamouse relationship)

Preventing Disease

Cervical Cancer Screening

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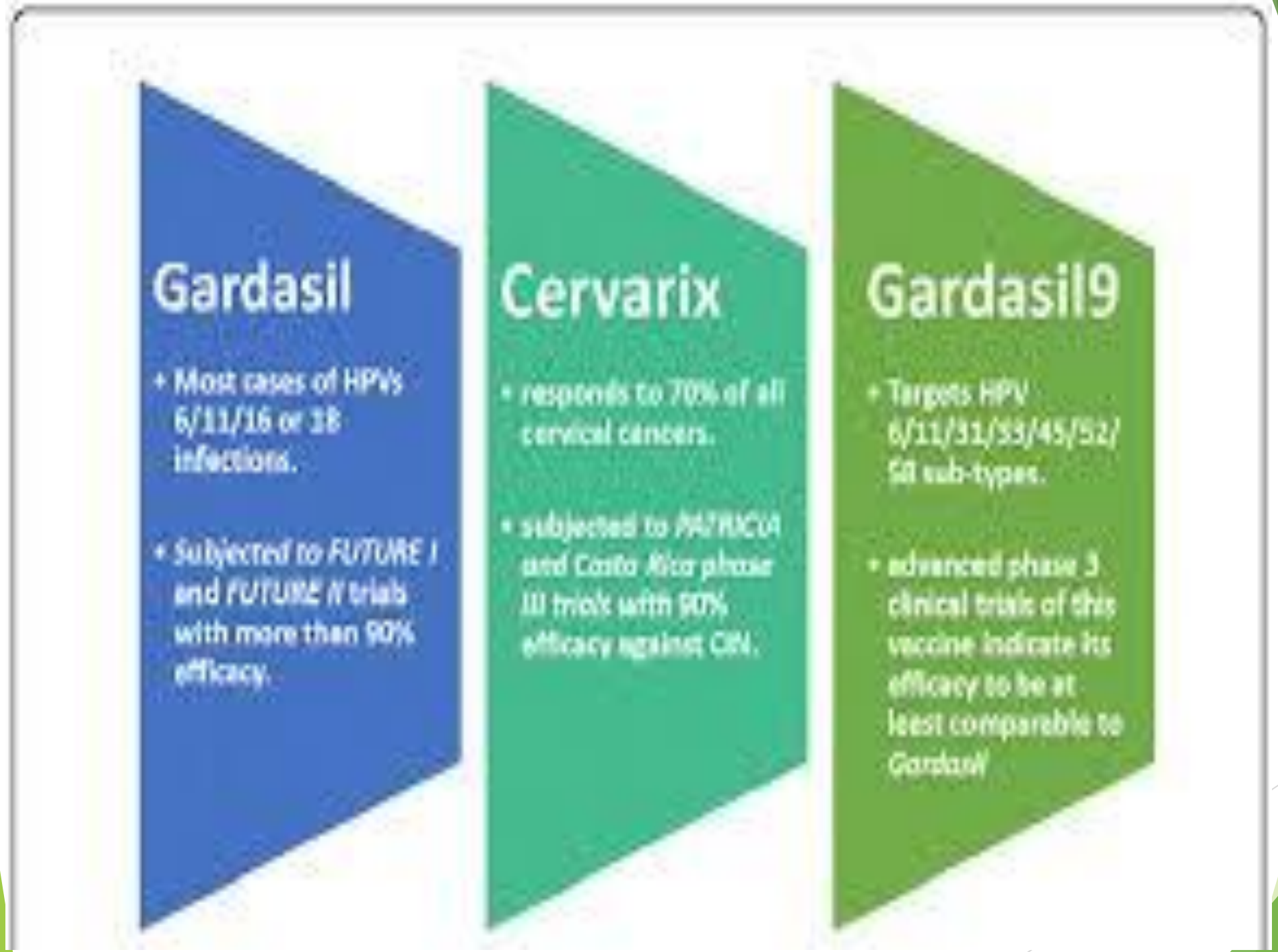

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HPV vaccine is recommended for routine vaccination at age 11 or 12 years.

Administer three doses of 9-valent HPV vaccine (Gardasil 9) at 0, 1 to 2, and 6 months .
Ideally, the series should have been initiated at age 11 or 12 years but may be started as early as age 9 years. The two-dose series is not recommended in people with HIV.

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For people with HIV aged 27 to 45 years who were not adequately vaccinated previously:

HPV vaccine is not routinely recommended; instead, shared clinical decision-making regarding HPV vaccination is recommended for people who may be at risk for a new HPV infection.

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For people who were adequately vaccinated with **bivalent or quadrivalent** HPV vaccine:

Some experts would **consider additional vaccination with 9-valent** HPV vaccine, but data are lacking to define the efficacy and cost-effectiveness of this approach.

HPV vaccination is not recommended during pregnancy .

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Other important ways to prevent HPV infection include:

- being a non-smoker or stopping smoking
- using condoms
- voluntary male circumcision

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The use of male latex condoms is strongly recommended for preventing transmission or acquisition of HPV infection, as well as for preventing HIV and other sexually transmitted infections (STIs) .

use of latex male condoms has been associated with 70% lower incidence of oncogenic HPV infection among women.

In circumstances when a male condom cannot be used properly, a female condom should be considered for heterosexual vaginal intercourse and for heterosexual or male same-sex anal intercourse.

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Male Circumcision

Male circumcision is associated with :

lower risk of penile cancer and of cervical cancer in sexual partners
Relevant data in men with HIV, however, are limited.

findings to date suggest that the effects of circumcision against HPV infection (while protective) may be less in people with HIV than in those without.

Male Circumcision

no clinical trials have assessed whether circumcision of men who have HIV reduces the risk of genital or anal HPV-related cancer or precancer (such as AIN) or oncogenic HPV infection of the anal or oral mucosa for them or their sexual partners.

Evidence is insufficient to recommend adult male circumcision solely to reduce the risk of oncogenic HPV infection in men with HIV or their sex partners.

Preventing Oropharyngeal Cancer:

no adequate methods currently exist to determine the site of HPV-associated oropharyngeal precancer or cancer to target biopsy or treatment.

It also should be noted that rates of non-HPV-associated oral cancer also are increased in people with HIV,and potentially malignant oral disorders can be diagnosed and followed by biopsy in some cases.

Diagnosis of genital and oral warts is made by :

visual inspection and can be confirmed by biopsy.

biopsy is needed only if:

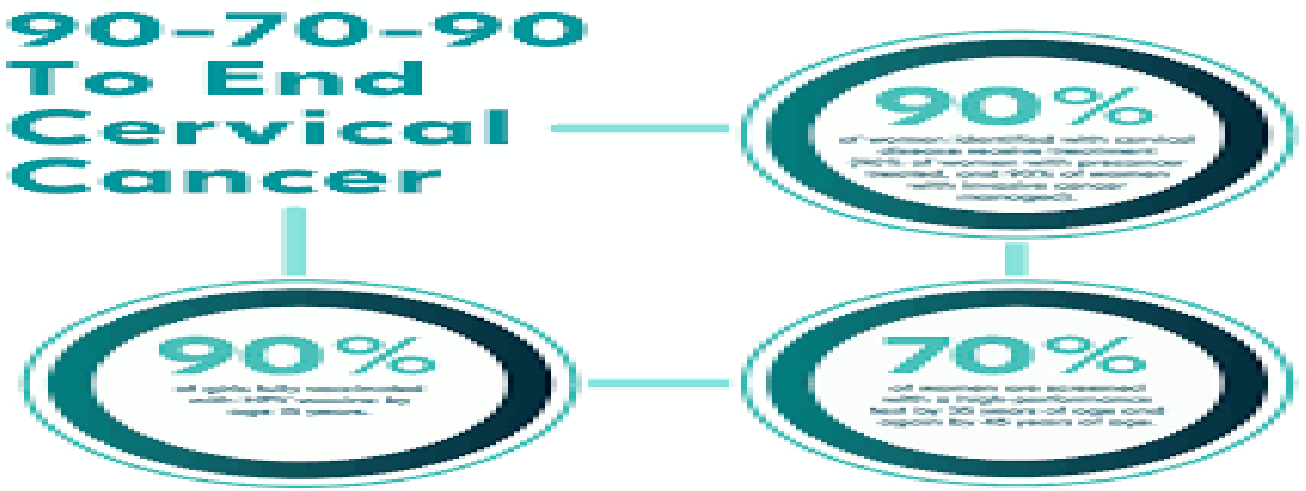
- the diagnosis is uncertain
- the lesions do not respond to standard therapy
- warts are pigmented, indurated, fixed, bleeding, or ulcerated

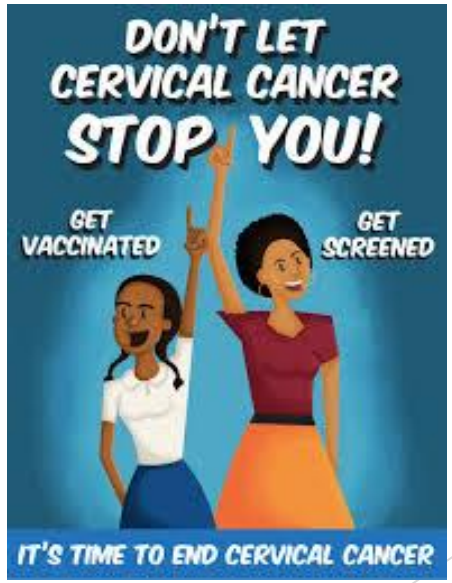
No data support the use of HPV testing for screening, diagnosis, or management of visible genital/oral warts or oral HPV disease in people with HIV.

All countries have made a commitment to eliminate cervical cancer as a public health problem.

The WHO Global strategy defines elimination as reducing the number of new cases annually to 4 or fewer per 100 000 women and sets three targets to be achieved by the year **2030** to put all countries on the pathway to elimination in the coming decades:

90% of girls vaccinated with the HPV vaccine by age 15
70% of women screened with a high-quality test by ages 35 and 45
90% of women with cervical disease receiving treatment.





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PREVENT CERVICAL CANCER IN THREE SIMPLE STEPS

VACCINATE

PAP SMEAR

HPV TEST

Why screening starts at age 21?

absolute incidence of ICC is exceedingly low among women with HIV under 25 years

provide a 3- to 5-year window prior to age 25, when the risk of ICC in women with HIV exceeds that of the general population.

People aged 21 to 29 years with HIV should have cervical cytology at the time of initial diagnosis with HIV .

Why is cytology only used to screen for cervical cancer in women under the age of 30?

there is a relatively high prevalence of transient HPV before age 30 years, which may lead to unnecessary colposcopy. If cytology reveals ASC-US and reflex hr-HPV testing is performed, repeat cytology should be evaluated in 6 to 12 months .

If repeat cytology shows ASC-US and reflex hr-HPV is positive, individuals should be referred for colposcopy

There are ongoing studies to evaluate the use self-testing for HPV screening in people with HIV

Overview of Cervical Cancer Screening Guidelines

	<21 Years	21–24 Years	25–29 Years	≥30 Years	Comments
NIH OAR Adult and Adolescent OI Guidelines (specific to people with HIV)	No screening recommended	**Cytology Only** •Cytology yearly • If normal cytology on 3 consecutive annual tests, adjust to every 3 years	**Cytology Only** •Cytology yearly If normal cytology on 3 consecutive annual tests, adjust to every 3 years	**Co-testing**[a] •Co-testing yearly • If normal cytology and hr-HPV negative on 3 consecutive years, adjust to every 3 years. **Cytology Only** •Cytology yearly •If normal cytology on 3 consecutive years, adjust to every 3 years	

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WHO (HIV-specific guidance) Updated July 2021	<21 Years No screening recommended	21–24 Years No screening recommended	**25–29 Years** **Preferred** •Primary HPV test[b] (provider-obtained or self-collection every 3–5 years)	**≥30 Years** **Preferred** •Primary HPV test[b] (provider-obtained or self-collection every 3–5 years)

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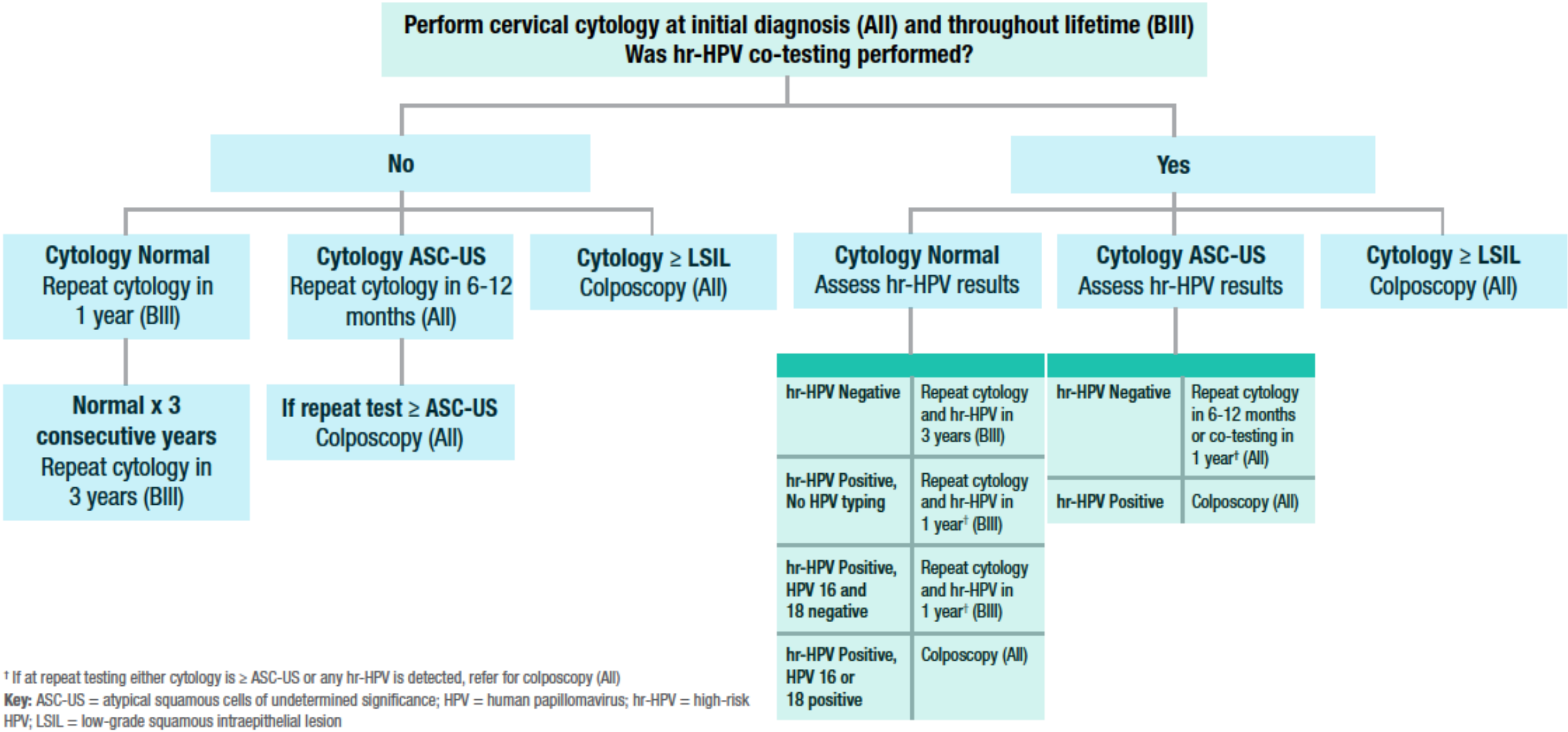
SCREENING ALGORITHM FOR CERVICAL CANCER IN PEOPLE WITH HIV AGED 30 YEARS AND OLDER



† If at repeat testing either cytology is ≥ ASC-US or any hr-HPV is detected, refer for colposcopy (AII)

Key: ASC-US = atypical squamous cells of undetermined significance; HPV = human papillomavirus; hr-HPV = high-risk HPV; LSIL = low-grade squamous intraepithelial lesion

Cervical cancer screening in people with HIV should continue throughout their lifetime (and not, as in the general population, end at 65 years of age)

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Following hysterectomy:

- for benign disease, routine screening for vaginal cancer is not recommended for people with HIV.

- people with a history of high-grade CIN, adenocarcinoma *in situ*, or ICC are at increased risk and should be followed with annual vaginal cuff cervical cytology.

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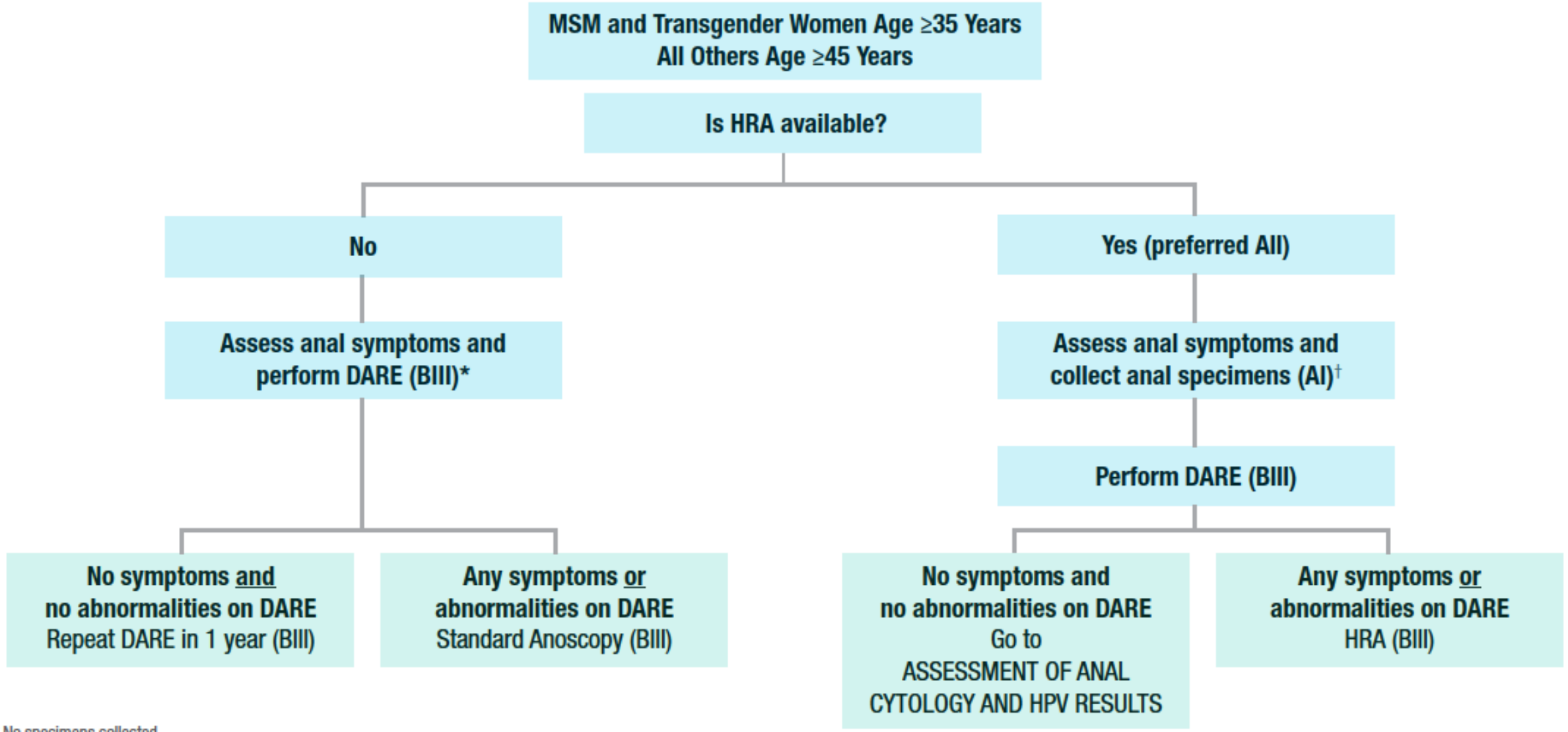
SCREENING ALGORITHM FOR ANAL CANCER IN ASYMPTOMATIC PEOPLE WITH HIV

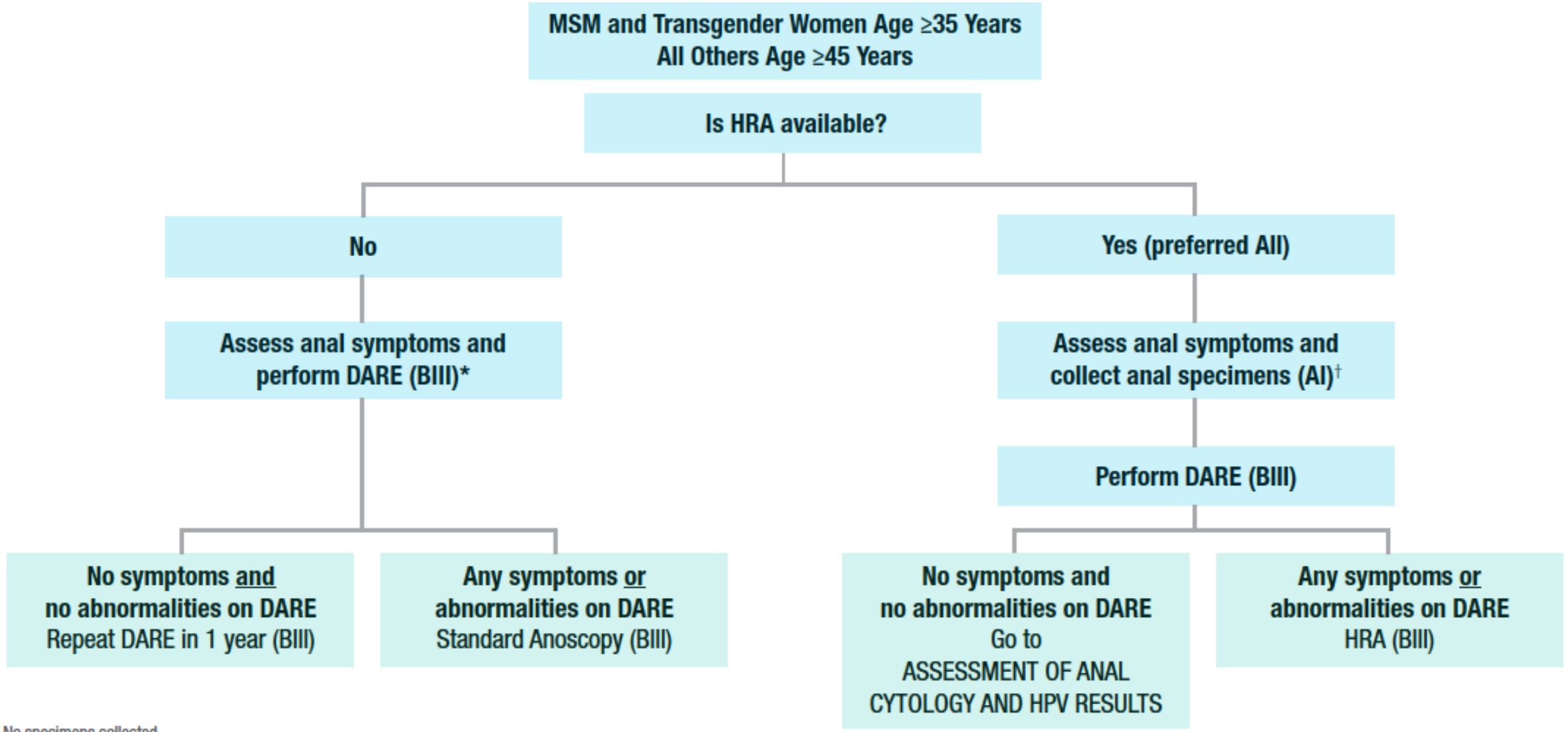


* No specimens collected

† Collect any specimens either for cytology or for cytology with HPV co-testing prior to DARE. HPV testing without cytology is not recommended (BIII)

Key: DARE = digital anorectal exam; HPV = human papillomavirus; hr-HPV = high-risk HPV; HRA = high-resolution anoscopy; MSM = men who have sex with men

SCREENING ALGORITHM FOR ANAL CANCER IN ASYMPTOMATIC PEOPLE WITH HIV



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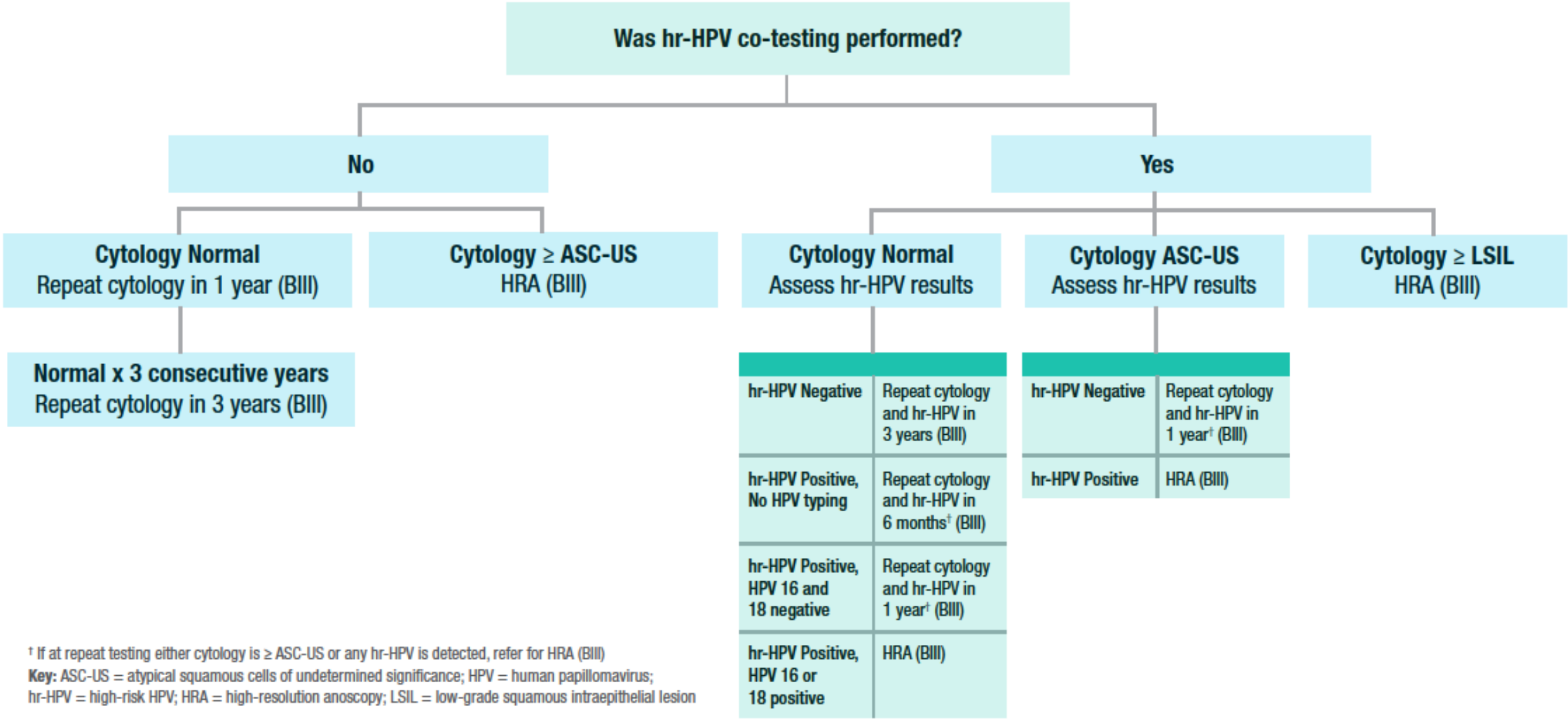
ASSESSMENT OF ANAL CYTOLOGY AND HPV RESULTS IN PEOPLE WITH HIV



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