HPV: OVERVIEW, EPIDEMIOLOGY AND TRANSMISSION

Overview

- Human papillomaviruses (HPV) are extremely common DNA viruses that only infect humans. HPV infects epithelial cells.
- There are more than 100 types of HPV, which can be subdivided into either cutaneous or mucosal categories depending on their tissue preference. There are more than 40 types of HPV that infect the anogenital and oropharyngeal mucosa. These can be broadly split into "high-risk" (hrHPV) and "low-risk" (lrHPV) types based on their association with the development of malignancy.
- Immunisation against HPV infection is available in the form of the nine-valent vaccine (HPV9).
- Most HPV infection is transient (i.e. becomes undetectable by DNA testing after 6–12 months). The majority of HPV infections do not progress. Virus that remains persistent is the key to pathogenesis.
- Individuals should be reassured that a diagnosis of HPV infection does not mean that they will get cancer.
- Low-risk HPV:
    - Infection with lrHPV types causes warty lesions in the anogenital and oral areas.
    - HPV 6 and HPV 11 cause approximately 90% of genital warts and are only rarely associated with precancer or cancer of the lower genital tract.
- High-risk HPV:
    - Persistent infection with hrHPV types causes virtually all cancers of the cervix and a significant proportion of cancers of the anus, oropharynx, vagina, vulva and penis. hrHPV infections are usually subclinical.
    - The 14 most oncogenic HPV types include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Types 16 and 18 are most commonly

associated with development of cancer, together accounting for about 70% of invasive cervical cancers. However, not all infections with HPV 16 or 18 progress to cancer. In addition, HPV 16 is strongly associated with anal, oropharyngeal and HPV-associated vulvar cancer.[1,2]

Clinical presentations

- Genital warts (condyloma acuminata): HPV infects the penis, scrotum, perineum, anal canal, perianal skin, vaginal introitus, vulva, and cervix.
- Squamous intraepithelial lesions (SILs) of the vagina, cervix, anus, penis: HPV infection has been clearly linked to nearly all SILs and cancers of the cervix and anus. HPV is also linked to a subset of penile, vulval and vaginal cancer.
- Oropharyngeal cancer.
- Infection of the respiratory mucosa: this can occur, especially (but not exclusively) in children.

Subclinical HPV infection

- Subclinical infection with HPV cannot be detected by visual inspection, and can be hrHPV and/or lrHPV.
- Subclinical HPV infection is most commonly detected by cervical cytology or biopsy specimens.
- Most anogenital HPV infections are subclinical.
- HPV DNA testing is currently available only as an adjunct to cervical cytology. HPV DNA testing has no clinical utility in sexually transmitted infection (STI) screening. hrHPV testing has been shown to be effective as a primary screening test to reduce cervical cancer rates for both unvaccinated and vaccinated people with a cervix.[3] Vaccination is the first line of prevention and regular screening with hrHPV testing is the second line of prevention. There are no routine screening tests clinically available for HPV detection from oropharyngeal, anal, or male genital specimens. Neither are there any approved serologic or blood tests.

Epidemiology of Anogenital HPV infection

- HPV is very common, perhaps universal, amongst sexually active populations. It can be regarded as an inevitable consequence of being a normal sexually active adult.
- On average, 80% of sexually active adults will have some form of HPV infection during their lives.
- The incidence of HPV infection increases in proportion to the number of sexual partners.
- For most people, infection with each HPV type is transient and becomes undetectable by HPV DNA testing within the first 12 months. HPV infection may become latent (undetectable) and reactivate years later, or infection may persist (remains detectable).
- The latency period of anogenital HPV infection is highly variable but is usually 3–6 months. Warts will often appear 3–6 months after HPV infection, but latency periods of many months or even decades have been reported.[4-6] Evidence for extended latency periods is seen in immunocompromised and normal individuals who, despite having been sexually inactive for many years, can suddenly develop warts or cervical abnormalities. It is important to emphasise that developing genital warts during a long-term relationship does not necessarily imply the presence of other sexual contacts.

In females

Generally speaking, the same HPV genotypes cause cervical cancer everywhere in the world with very little variation from region to region.[7] There is no evidence of a significant population-based or genetic predisposition for cervical cancer. This means that risk is directly related to the amount and timing of exposure to HPV infection, the likelihood of persistence, and access to preventative healthcare. Worldwide, 10.5% of women are positive for HPV DNA in the cervix.[8] Smoking is an independent risk cofactor that may increase the risk of the development or progression of lesions once HPV infection has occurred.[9] In an international meta-analysis, the highest prevalence of HPV is seen in young women (rate of 20–25% in those aged 20 years) falling to a prevalence rate of 10% at age 30 years, and reducing gradually thereafter.[10] Most HPV infection in women occurs after initiation of sexual activity and is transient, although in some cases HPV infection remains latent and may reactivate years later.[11] There is a rapid loss of detectable HPV in the first 6–12 months after infection, with HPV becoming undetectable

in 80–90% of individuals by 2 years.[12] Rates of HPV infection in young women are 28% after 1 year with one sexual partner, increasing to 49% after 36 months, and remaining high with the acquisition of each new partner.[13,14]

The key step in cervical carcinogenesis is overt measurable hrHPV persistence, which strongly increases the risk of the development of high grade CIN or AIS at a year or two after infection.[15,16] Some infections may become quiescent (latent) or undetectable,[17] but the proportion of HPV infections that become latent is unknown. In older women, detection of new HPV infection is likely to represent reactivation of infection rather than acquisition of a new, recent infection.[18,19] Reactivation is also thought to be the main source of newly detected HPV infection in HIV-positive and immunocompromised women who report no new sexual partners.[20]

Studies of anal HPV infection in women suggest that it is far more common than originally thought.[21-23] Women with a history of vulval or cervical high-grade SIL or cancer are also at increased risk of anal HPV infection and HPV-related disease. In these studies anal intercourse was not a consistent risk factor for either anal HPV infection or anal SIL.[24]

In males

The reported genital prevalence of specific HPV types and their clearance in males vary widely and males have a lower seroconversion rate than females of the same age, potentially meaning that they have a higher risk of reinfection throughout life.[25]

Heterosexual men

HPV infection is common among heterosexual men. At any one time, the prevalence of anogenital HPV of any type was 53%, and the overall median time to undetectable HPV was 7.5–12 months.[26,27] Few studies have evaluated the frequency of anal HPV in heterosexual men, but anal HPV was detected in 157/1305 heterosexual men (12%) in one study.[28]

Men who have sex with men (MSM)

The burden of anogenital HPV infection is highest in MSM, especially HIV-positive MSM.[29] An American study on urban HIV-negative MSM showed an overall prevalence of anal HPV infection of 57%, with the most common virus being hrHPV-16.[30] The prevalence rate did not vary across age groups, and anal HPV was independently associated with a history of receptive anal intercourse (odds ratio 2.0) and having >5 sex partners in the preceding 6 months (odds ratio 1.5).[30] The most common site of HPV infection in

HIV-negative MSM is the anal canal.[31] Anal HPV has been associated with an increased risk of HIV acquisition in MSM.[32]

Transmission of anogenital HPV infection

- HPV is spread from close skin-to-skin contact.
- Condoms provide some, but not complete, protection against HPV infection, but their use is recommended to prevent other sexually transmitted infections.
- Transmission in the genital region does not necessarily require penetrative intercourse.
- If one member of a stable partnership has anogenital HPV infection, the other is likely to be either infected or immune to that infection.
- Because of variable latency, HPV infection may develop during a long-term relationship and does not necessarily imply other sexual contacts.

Sexual transmission

HPV infection results from skin-to-skin contact and can be transmitted by both penetrative and non-penetrative sexual contact (genital-genital, oral-genital, anal-genital, oral-anal).[13] Other types of contact may also play a role, such as spread through fingers or sex toys from genital areas infected with HPV.[33] Anogenital HPV infection can be transmitted to the mouth through oral sex.[34] However, the mouth appears to be a less hospitable environment for genital strains of HPV than the genital area.[35-38] Anal intercourse is not required for spread to the anal canal. The prevalence of HPV infection is much lower in virgins (4% vs 22% in sexually active women in a report from Sweden).[39] The virus is not transmitted via blood or body fluid, e.g. semen.

Although not proven, it is generally believed that clinically visible warts offer the greatest possibility for transmission, and that treating warts decreases that possibility. Transmission often occurs because subclinical infections are common and asymptomatic, and warty lesions frequently go unnoticed, especially in areas that are not easily inspected for the presence of warts. Type-specific concordance (both partners infected with the same HPV type) is common in heterosexual couples (almost 25%).[40]

Condom use

Consistent use of condoms has been shown to reduce the risk of HPV infection acquisition and genital warts (by about 30–60%).[41-43] Condom use may reduce the risk

of HPV infection recurrence when both partners are infected,[44-46] although the extent to which recurrence is due to re-infection is not known.

Non-sexual transmission

Vertical transmission in utero is very rare[47] (see Pregnancy and Breastfeeding document; the document on management of HPV infection in children may also be of interest). Autoinoculation may occur rarely.[48] While HPV DNA has been found on fomites (inanimate objects), there is no evidence to suggest that this is a method of transmission.[49,50]

Immunity and vaccination

Immunity from natural infection is generally poor. Naturally produced antibodies provide partial protection, although many people do not seroconvert.[51,52] Previous infection does not necessarily create long-term immune memory so does not prevent future re-infection with the same HPV type.

Vaccination with the HPV vaccine is a very effective method of preventing HPV acquisition (see HPV Vaccines document).

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