Everything you need to know about HPV and more

What is human papillomavirus (HPV)?

- HPV is a group of small DNA viruses that cause warts and certain cancers and precancers of the skin lining the lower genital tract and mouth
- Approximately 100+ types have been fully identified. Another 30 "novel" types have been detected but not fully identified. All differ slightly from each other in their genetic structure.
- This difference in genetic structure determines the location and the type of lesion that each type is likely to cause.
- 23-30 types infect almost exclusively the skin of the lower genital tract. The remaining types infect skin on other areas of the body, including the hands, feet, etc.

What are low- and high-risk HPV types?

- The genital HPV types can be divided into two broad groups (low-risk and high-risk HPVs) depending upon their association (or lack of association) with cancers of the lower genital tract.
- Low-risk HPV types (6, 11, 42, 43, 44, 54, 61, 70, 72, and 81) are virtually never found in cancers. Therefore, they are also called non-carcinogenic HPV.
- High-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) have been identified in cancers of the cervix, vagina, vulva, anus, and penis. Therefore, they are also called carcinogenic HPV.
- The most common types ($\geq$ 90%) detected in genital warts are HPV 6 and HPV 11.
- The most common HPV type detected in both normal women and in women with cervical cancer is HPV 16.
- The majority of cervical cancers (80%) are caused by just 4 HPV types (16, 18, 31, and 45).

How common is HPV?

- Genital HPV is very common. It is the most common viral sexually transmitted infection (STI) and is likely to be the most common STI overall.
- Many estimates have placed the lifetime likelihood of getting genital HPV to be in the range of 75-90%.
- The risk of exposure to HPV is estimated to be approximately 15-25% per partner.
- Most people who get HPV never know they have it, as they do not develop genital warts, an abnormal Pap test, or other manifestations of HPV that they can identify.
- Approximately 1-2% of the population has genital warts and the lifetime risk is estimated to be about 10%.

- Approximately 2-5% of women have a Pap test with cell changes due to HPV at any one screening.

What are the symptoms of HPV?

- HPV rarely causes symptoms.
- External genital warts are most commonly felt as raised bumps, but may be so small that they often go unnoticed.
- Occasionally newly forming warts and vulvar intraepithelial neoplasia will be slightly itchy, but most HPV lesions do not cause soreness, itching, burning or any other symptoms. When those symptoms occur, look for other causes such as yeast or irritation from soaps or spermicides that may cause these symptoms whether or not warts are present.
- Certain symptoms may occur with cervical cancer and should be evaluated. These include bleeding during or after intercourse, irregular vaginal bleeding between periods, and a persistent abnormal discharge without itching or burning. However, these symptoms most often occur for other reasons.

What can genital HPV cause?

Most people who get HPV do not get significant lesions.

- Once an individual is infected with HPV, one or more of the following may occur:
    - Latent HPV infection - most people who get HPV do not have any detectable warts or other HPV-related disease (i.e. histological-detectable cell changes). They probably have HPV in very low numbers (perhaps 1 HPV) per infected cell. Therefore, latent HPV cannot be detected by visual inspection, cytology or even by HPV testing, and individuals with "latent" HPV are not contagious. However, because the virus can move from latency to "expressed" HPV disease such as warts or cervical cell changes, it is not possible to guarantee that the individual will remain non-contagious indefinitely. Consistent condom use has been shown to reduce the risk of transmitting HPV by about 70%.
    - Subclinical HPV infection - this term applies to changes in the skin cells of the lower genital tract that cannot be seen with the "naked" eye. The most common "subclinical change" is intraepithelial neoplasia of the cervix (cervical "precancerous change", dysplasia, CIN 1, 2 or 3) that can be seen after application of vinegar (acetic acid) to the skin, followed by close examination, usually with magnification, of areas that turn white (acetowhite areas).. Subclinical HPV can be found anywhere in the lower genital tract, but "acetowhitening" is very non-specific and often not due to HPV, even in the cervix. Therefore clinicians should be somewhat wary of applying the term "subclinical" HPV unless a biopsy has confirmed the diagnosis.

- Clinical HPV - warts and precancerous changes on the external genitalia (vulvar perianal and penile intraepithelial neoplasia as well as cervical and other lower genital tract cancers usually can be seen with the "naked" eye. The most common clinical manifestations of HPV are:
    - Condyloma acuminata - when a wart is raised and "cauliflower" (papillary) shaped it is called a condyloma acuminata. Most "cauliflower" warts are caused by "low-risk" HPV 6 or 11. Condyloma acuminata are the most common (65%) of the external vulvar and penile HPV lesions. . They can also be found in the vagina and anus. Only 3% of cervical lesions are of this type.
    - Condyloma planum - warts that are flat are called "flat" warts or condyloma planum. Most external warts that are flat are secondary to HPV 16 or to other "high-risk" types. When biopsied, some pathologists will read these as VIN (vulvar intraepithelial neoplasia warty type). They should, however, be treated as genital warts and not as a true pre-cancerous condition.
    - High-grade intraepithelial neoplasia - "precancerous" HPV lesions may occur on the vulva , the perianal and anal canal area, and the penis . Most of these lesions are flat. They can be very white due to thick layers of keratin, or red due to increased blood supply, or various shades of brown to dark gray due to increased pigment.
    - Cancer - HPV is the cause of virtually all cancers of the cervix, as well as about 80% of vaginal cancers, 50% of penile cancers, and 90% of anal cancers. In any of these areas, cancer may appear variously as a nodule, erosion or ulcer, a thickening, etc.
- Immune mediated regression
    - Most HPV lesions eventually resolve due to a host immune response to the virus. This is particularly true for genital warts and CIN 1 because neither are truly precancer. Even approximately 40-50% of CIN2 will resolve spontaneously. CIN3 is considered a true cancer precursor, although some CIN3 may also resolve secondary to an immune mediated regression.
    - Whether an immune mediated regression clears that HPV type from the body completely, or just suppresses it to the point where it is not likely to be contagious nor cause HPV-induced disease in the future is not known for sure. However, the end-result is essentially the same since neither "cleared" nor "permanently suppressed" HPV would be likely to present a future threat.

How is HPV transmitted?

- HPV is primarily transmitted through genital skin-to-genital skin sexual contact.
- Penetrative intercourse is not required.
- The exact risk of developing genital warts after having one episode of sexual intercourse with someone who has genital warts is not known, but several studies would appear to establish a risk in the range of 65% or more.

- Likewise, most studies of women with cervical HPV disease indicate that approximately 64-70% of their partners will have HPV penile lesions if evaluated clinically. Most often, these are so small that neither partner is aware of their presence.
- The most common time interval from exposure to HPV to development of genital warts is 4 weeks to 8 months. However, HPV can remain latent in some people for years or decades before developing warts or cervical disease, so it is usually not possible to determine exactly when, or from whom, an individual contracted the virus.
- When one partner has HPV lesions caused by a particular virus type, it is most likely that the other partner shares the same virus type, although this is often impossible to prove. Several studies indicate that "shared HPV" does not "ping-pong" back and forth. There is evidence that using condoms may decrease the viral exposure and speed the clearance of HPV related disease. The decreased viral load may allow the individual's own immune system a better chance of eliminating the virus.

Can HPV be passed through oral sex?

- Yes.
- Most couples practice oral sex, yet HPV lesions are very uncommon in the mouth. However, recent studies report high-risk HPV in approximately 1/4 of squamous cell carcinomas of the head and neck worldwide, so oral HPV transmission does occur but only very rarely causes serious problems.

Can HPV be passed in any other way?

- There is no evidence that contaminated toilet seats, doorknobs, towels, soaps, swimming pools or hot tubs, can transmit HPV. However, some unexplained cases of HPV lesions do occur and one should never rule out the possibility that an HPV infection may have been transmitted in a non-sexual event.
- HPV types that cause hand and common warts are different from the types that cause warts in the genital area. The exception is the rare occurrence of warts in the genital area in young children that are due to these "non-genital" HPV types. Likewise, genital HPV types are only very rarely found in lesions outside the genital area. For instance, occasional HPV 31 lesions have been described in the conjunctiva and under the finger nails .

Can I infect my baby?

- Transmission to the baby of HPV 6 or 11 is known to be possible during vaginal delivery but is rare. Most clinicians believe that the risk of cesarean section to both mother and baby exceeds the risk of the baby acquiring laryngeal papillomatosis (HPV 6 or 11 induced warts in the larynx or upper airway).

- Once warts are no longer present, especially if a woman has had no detectable HPV lesions for 6 months or more, transmission of HPV to the baby during vaginal delivery becomes increasingly unlikely.

Will I be contagious after I am treated?

- That depends on two things - how successful the treatment is in destroying the HPV lesions (where potentially infectious HPV particles are known to be present), and how successful one's immunity is in suppressing any HPV that might still be present in apparently normal skin.
- Most people treated for external warts do not have complete resolution even after several treatments. That is because most treatments destroy the HPV lesions but cannot eliminate any HPV in surrounding apparently normal skin. Until the individual's immune system responds and suppresses the remaining HPV, new lesions may appear.
- Once no further HPV lesions can be detected by clinical exam, and no new lesions have appeared over several subsequent months, the chance of shedding enough HPV to be contagious dramatically falls. While it is impossible to tell anyone exactly when they have little-to-no chance of passing HPV to a partner, as months go by with no lesions found (especially if none are found by a skilled clinician), the possibility of being contagious becomes increasingly remote.
- The inability to be 100% sure that an individual with a history of an HPV infection is no longer contagious should encourage honesty whenever a new relationship begins. This should be balanced with the fact that most people are exposed to this virus during their life, and that, for most, this virus does not usually cause great harm.

Will I be contagious if I have spontaneous immune regression?

- Probably not. Spontaneous immune regression does not occur without the immune system recognizing the presence of the virus and suppressing or clearing it.

How can I reduce the risk of getting HPV?

The only way to entirely eliminate the possibility of beingexposed to HPV is abstinence from any form of genital-genital or oral-genital contact.

An HPV vaccine (Gardasil®) was introduced in 2006 . The HPV vaccine presently available protects against the exposure to types 16,18, 6,and 11 The vaccine is FDA

approved for girls and women 9-26 years of age and is highly protective, especially when the vaccination occurs before sexual activity. While the vaccine does not prevent infection with all types of HPV, it provides protection against the HPV types associated with 70% of cervical cancers (16,18), and 90% of external genital warts (6,11). The vaccine however does not protect against HPV 16, 18, 6 or 11 if a woman has already been infected with these types, and it offers limited or no protection against other HPV types. The protection afforded by the vaccine is therefore lower in women who have had sex prior to vaccination. Hence, the primary target for HPV vaccination is girls age 11 & 12 but it may be given as early as age 9, particularly in populations with early onset of sexual activity. Catch-up vaccination is also appropriate for girls and women age 13-26. A bivalent vaccine that protects against HPV 16 and 18 (Cervarix ®) is expected to be on the market in the US by 2010, and is already in use in Europe and other areas of the world.

- Latex condoms protect only those areas of skin that they cover. Many infected individuals have HPV in areas of their skin that are not covered by the condom and that come into contact with their partner's skin. Secretions may also be a source of HPV-infected skin cells that could contact a partner's uncovered skin areas. Despite these issues, recent data indicates that consistent condom use appears to reduce the risk of HPV transmission by about 70%.
- If a sexual partner has ever had sex, even once, with someone other than their partner, their partner may be at risk for contracting HPV or other STIs. Hence, it is prudent for couples contemplating starting a new relationship to test for STIs prior to prudent for couples contemplating starting a relationship to be screened for STIs before having sex. However, because HPV is so very common and most often not detectable, clinical exams for HPV as part of a STI screen have not been recommended by the CDC or AMA.
- Condoms do offer some protection against HPV and very good protection against other STIs. Use them.
- Female condoms cover more of the female introital epithelium at risk for HPV and therefore may be a more protective barrier for both partners. However, the female condom may also be more easily dislodged.
- Spermicidal foams, jellies and creams are not proven, nor are they disproved, to be effective against HPV but they have been shown to be effective against some other STIs. Recent studies in Africa have shown an increased rate of acquisition of HIV when spermicides are used with an HIV-infected partner. If used, spermicides are best used along with condoms, not in place of condoms.

Why do most people not have a lesion detected after being infected with HPV, while others get warts or CIN, and a few get cancer?

- Although this question cannot be answered fully, science is steadily improving on our understanding of how HPV causes both warts and cancer.

- HPV infects the skin when cells from a partner's HPV lesions gain access to tiny breaks in the skin that often occur during skin to skin contact or intercourse. HPV does not infect tissue that lies underneath the skin, nor does it infect blood or other body fluids.
- After an average of 1 to 8 months (but up to years or decades) the HPV infected cells may start to grow abnormally as the virus begins to reproduce itself in large numbers. Whether this occurs at all, and if so, how it is manifest clinically, is largely the result of a complex interplay between the virus and individual immunity.
- For most individuals the immune response appears to dominate and lesions never develop, or they develop but are suppressed by an immune response before the person ever realizes the presence of the lesions.
- Escape from immune suppression of a low-risk HPV type (i.e., 6 or 11) most commonly results in epithelial changes as well as exuberant growth of both underlying blood vessels and stroma. The result is raised "cauliflower" shaped warts. In contrast, similar "escape" of high-risk HPV types (i.e., 16 or 18), results mostly in proliferation of the epithelial (skin) cells with only minimal vascular or stromal growth.
- Treating HPV infected cells may help boost immunity by destroying the cells within which the HPV resides, thereby releasing HPV to disease-fighting dendritic cells and macrophages. A cream which is applied to warts (imiquimod or Aldara®) may directly boost immunity by stimulating these disease-fighting cells to produce natural disease fighting chemicals (cytokines, including interferon).
- Even left untreated, most HPV lesions would eventually disappear due to an immune response, although spontaneous clearance may be very slow for some. However, approximately 10-20% of individuals with HPV lesions do not clear easily, even with treatment.
- Long-term persistence of HPV is not very common. When it happens, the complex interplay of HPV, host immunity, various co-factors, and perhaps, spontaneous mutations in the host cell may eventually result in the development of pre-cancers and cancer of the cervix, vagina, vulva, anus, or penis. Because an individual's immune system can usually suppress (and perhaps even clear) HPV most individuals are not at great risk of getting these cancers.
- Once immunity has completely suppressed a particular HPV, the individual is not likely to again get disease from that HPV type, either from a recurrence of the HPV infection one has already had, or from new exposure to the same HPV type. However, immunity to one HPV type does not confer reliable immunity to a different type.
- One study showed post-treatment women fared better with partners wearing condoms.
- How to reduce the risk of CIN? Stop smoking.

Will I always have HPV?

- The answer to this question is not clear.
- Most people (up to 90%) who test positive for HPV with very sensitive tests for HPV (polymerase chain reaction [PCR] and Hybrid Capture 2) will become HPV negative on the same tests within 6 to 24 months from first testing positive. This is due to an effective immune response to HPV.
- What is not known is whether this means that the virus is actually eliminated from the body or just suppressed to such a low number of HPVs (as in latency) that even these sensitive tests cannot detect it.
- Whether it is completely eliminated or just suppressed does not matter because most people who have an effective immune response to HPV do not ever have lesions develop from this HPV infection.
- A minority of people may be at-risk for having return of warts or other HPV lesions later in life, usually if immunity is seriously compromised.

Diagnosis of HPV-induced disease: Genital warts, and vulvar, peri-anal, anal and penile intraepithelial neoplasia (VIN, PAIN and PIN)

The following serve as the foundation of knowledge needed to address most of the questions that your patients may have about vulvar, penile, and perianal external genital HPV lesions known as genital warts, and vulvar, penile and perianal intraepithelial neoplasia.

How are external genital HPV lesions diagnosed?

- HPV infections detected by cervical screening are almost always subclinical (not seen without the aid of magnification and acetic acid). In contrast, most diagnosed external genital lesions are detectable without the aid of magnification or acetic acid, and are therefore, clinically-apparent. These lesions include external genital warts, vulvar, penile and perianal pre-cancers or cancers. Vaginal and anal genital warts may also be seen without magnification but requires either the introduction of a speculum or an anoscope. As with cervical intraepithelial neoplasia (CIN), vaginal and anal intraepithelial neoplasia (VAIN and AIN) cannot usually be seen without the aid of magnification and acetic acid.
- Visual inspection of the external genital skin with application of acetic acid and/or magnification can be used to aid in the detection of external HPV lesions, but it must be recognized that acetowhitening that occurs on external genital skin is very non-specific.

What do external genital HPV lesions look like?

- The most common external genital HPV lesion is the cauliflower-shaped condyloma acuminata, which is almost always caused by HPV 6 or 11. On keratinized external genital skin these are usually white to flesh colored in appearance depending on the degree that keratin is expressed. On modified mucosa, such as in the introitus, they are more commonly flesh colored and transparent exposing the underlying proliferative blood vessels.
- About 10% of external genital lesions are papular (round topped) in shape. These are most commonly caused by HPV 16, although other high risk HPV types are occasionally causative. These can be flesh colored, or red if increased vasculature predominates, or various degrees of brown or black if the virus induces the cells to produce increased melanin.
- Some external genital HPV lesions are flat with evidence of being thicker than the surrounding skin, or with fine spikes called asperities. This type of HPV-induced skin proliferation can be caused by either high- or low risk HPV types.
- Many external genital HPV lesions are so small or are hidden within the introitus, that they are not noticed by either partner.

What is the difference between genital warts and high-grade external genital HPV lesions?

- The term "genital warts" is most commonly applied to the kind of lesion most typically secondary to low risk HPV types, particularly HPV 6 and 11 which causes about 90% of external HPV lesions.
    - Because these are due to low-risk non-carcinogenic HPV, they are rarely associated with cancer. The only exception is the very rare verrucous (Bushke-Lowenstein) carcinoma which is due to HPV 6.
    - Condyloma acuminata may resolve on their own without treatment due to spontaneous immune regression. Reported rates of spontaneous regression are about 17-20% per each 3 months of follow-up. However, some may have persistence for many years.
    - Any "genital wart" that does not respond to treatment should be biopsied to exclude cancer that may look like a genital wart.
- Any genital bump due to HPV is in essence a 'genital wart'. This includes the papular, often pigmented, usually multifocal lesions caused most commonly by HPV 16 even though histology of these lesions will most often be called high-grade and depending on the location, vulvar intraepithelial neoplasia (VIN 2,3), perianal intraepithelial neoplasia (PAIN 2,3), and penile intraepithelial neoplasia (PIN 2,3). The common name applied by dermatologists to singular or multiple HPV-induced papular lesions is Bowenoid papulosis.
    - Despite the high-grade histologic appearance, these lesions may also resolve spontaneously and often resolve with the same treatments commonly used for condyloma acuminata and other HPV lesions caused by low risk HPV types.
    - High-grade precancer at-risk for invasion (VIN 3, PAIN 3, and PIN 3) is most commonly a solitary lesion that is larger than the more "acute" multifocal papules described above, or may cover large areas of the external genitalia with thickened, flat, often multicolored (red, white and pigmented) epithelium. Such lesions require either multiple biopsies to rule out invasion prior to laser ablation, or need to be excised in their entirety.

How are genital warts and other external HPV lesions treated?

Multiple treatment options for genital warts are available for most areas of the lower genital tract. The choice of treatment may be partially determined by the extent of the genital HPV lesions, whether there is any "precancerous" change that appears at-risk for invasion, and by clinician and (hopefully) patient preference. The following options for treatment of vulvar, perianal and penile lesions are available:

- **Topical chemodestructive agents (Clinician applied)**
    - **Tri-(or Bi)chloracetic acid (TCA or BCA)**

        - 50 to 85% effective if used weekly until warts are gone.
        - The most commonly used office treatment.
        - Most effective strength is 80-85% and is well tolerated, although significant burning occurs in the area applied for 2 to 5 minutes.
        - Shallow skin ulcerations may occur that heal quickly.
        - Totally nontoxic; no toxic agents to absorb, so may be used in pregnancy.
        - Usually applied by clinician during weekly (or every other week) office visits.
        - Can be used in pregnancy, children, in the vagina, perianally, inside the anal canal. penis, urethra.
    - **Podophyllin:** Is an extract of the May apple plant. Is the oldest treatment for genital warts. It works by binding to cellular microtubules, thereby stopping cell division.
        - Marked variability in podophyllotoxin in the resin results in variable effectiveness, toxicity, and side effects. For this reason, podophyllin in 25% benzoin is not as commonly used in the US as it was 10 or so years ago.
        - Best used once a week
        - Should be washed off 4 to 6 hours after it is applied.
        - Often results in pain at the site of application in 1 to 3 days.
        - It should not be used in: pregnancy, children, or in the vagina, or on thinned, ulcerated skin, inside the anal canal.
        - Severe side effects have been reported:
            - Neurotoxicity and bone marrow depression may occur if applied over too large an area.
            - Fetal death when applied during pregnancy.
        - RESPONSE RATE: 32 to 79% after 3 to 6 months of regular weekly application. There is a significant problem with variability of strength of podophyllum preparations, which makes response rates very variable and also increases the risk of side effects.
- **CYTODESTRUCTIVE TREATMENT if above fails, or in combination with chemodestructive agents**
    - **Cryotherapy:** A common office treatment for external genital HPV lesions is destroying them by freezing. Several methods are available.
        - Can use cryoprobe attached to a nitrous oxide tank, Cryo-Vac (to spray liquid nitrogen on each wart), or liquid nitrogen soaked cotton tipped applicators.
        - There are few side effects. Each freeze stings during the freeze but generally no pain is felt afterwards. There is little chance for scarring.
        - Can be used in pregnancy, on the cervix, penis, and perianally.
        - RESPONSE RATE: 63-88% usually done once a week until clear.
    - **Electrocautery:**Burning each wart with electrocautery.
        - Was the mainstay of therapy l5 to 25 years ago. Continues to be an effective option.

        - May be used in pregnancy, on the vulva and, if used carefully, on small warts in the vagina, perianally, penis.
        - Generally works faster than topical agents.
        - Requires local anesthetic.
        - SIDE EFFECTS: May cause scarring because there is far less control over damage to surrounding tissues than with other cytodestructive treatments such as cryotherapy or laser.
        - RESPONSE RATE: 70-90%
        - Is still a good form of treatment, especially in those who have failed treatment with other methods.
        - Is difficult to use with extensive warts unless done under anesthesia, or with several separate treatments of smaller sections done under local anesthetic.
    - **Laser:** Laser uses a high intensity light beam to burn warts. It is very effective but the high cost and maintenance of the equipment has greatly reduced its use. It is rarely used at this time except to treat very high-grade precancerous changes throughout the lower genital tract, or massive warts. Laser is no longer the first line of therapy unless the patient has developed resistant, thick keratotic, or extremely extensive lesions not responsive to local therapy.
        - Requires general anesthesia for large areas to be treated, or local anesthetic for small areas.
        - May be used in pregnancy, in the vagina, cervix, penis, urethra, inside the anal canal and the perianal areas.
        - Depending upon the size of the area treated, may be very painful during the healing phase of 1 to 3 weeks.
        - RESPONSE RATE: Approximately 85%
- **SELF-TREATMENTS AVAILABLE FOR HOME USE**
    - **Condylox®:** purified podophyllotoxin (podophilox). This is a purified podophyllin that eliminates many of the problems with podophyllin resin by removing most of the toxins and standardizing the amount of beneficial podophyllin in the medicine.
        - Comes in a solution or gel form.
        - Best used twice a day x 3 days/week up to 4 weeks.
        - Is usually self-applied by patients.
        - Should not be used in: children, pregnancy.
        - SIDE EFFECTS: irritation to skin. Virtually non-toxic.
        - RESPONSE RATE: Although approximately 80% will have better than 50% reduction in wart volume within 2-4 weeks of beginning treatment, reported total clearance is 37% at 4 weeks and 44% at 8 weeks.
        - As with all treatments, remaining latent virus results in a decreased real cure rate.
        - Because there is no variability in this product, and because the toxic components have been eliminated, purified podophyllotoxin is a much better product than podophyllum.

- **Imiquimod (Aldara® 5% cream)** is an immune response modifier. Although the exact mechanism of action of imiquimod is not definitely known, imiquimod induces cytokines locally, including alpha interferon, various interleukins, and tumor necrosis factor. More recently imiquimod has been shown to influence toll receptors. Cytokines are natural disease-fighting chemicals in the body. Studies would appear to demonstrate reduced recurrence of genital warts post-treatment, likely secondary to stimulation of an immune response to HPV.
    - The cream may work better in females than in males with an overall complete clearance rate of 72% reported in the main FDA trial in females compared to 33% in males when applied 3 times a week for up to 16 weeks.
    - Imiquimod is expensive. Many patients, however, will clear much faster and many will use smaller amounts of the medication, thereby decreasing the per monthly cost.
    - Imiquimod is packaged in 12 individual packets with instructions to use a small amount of the cream on each wart and to discard any remaining cream left in each packet. However, the medicine does not lose its effectiveness and does not need to be discarded. Using the remainder of each packet on subsequent treatment days greatly improves the cost-effectiveness of this product.
    - It has not yet been evaluated for treatment of urethral, vaginal, cervical, rectal or intra-anal disease.
    - It is not approved for use in pregnancy.
    - Imiquimod should be applied sparingly to each wart 3 times per week (Monday-Wednesday-Friday, or Tuesday-Thursday-Saturday) for up to 16 weeks. The treatment area should be washed with a mild soap 6 to 10 hours after application.
    - A major advantage of imiquimod over other home treatments is that the cream can be applied in areas (such as the vulvar vestibule) that are hard to see as its application does not have to be limited exactly to the HPV lesion.
    - It is helpful to be evaluated by a clinician approximately once a month to determine the effectiveness of treatment and whether treatment needs to continue. Use of imiquimod does not preclude treatment by the clinician with other modalities such as TCA, cryo, etc. as the combination may result in much quicker clearance than treatment with any one treatment used alone.
    - SIDE EFFECTS: Local skin reactions such as redness, erosions, itching, flaking and swelling are common but usually mild. If such reactions are severely uncomfortable, do not reapply until the reaction has subsided.
- **Kunecatechin 15% cream (green tea cream, Veregen®)**
    - Kunecatechin 15% cream is a botanical drug product extracted from green tea leaves; a mix of catechins and other components

        - Catechins are bioflavonoids, polyphenols and powerful anti-oxidants shown to enhance immune system function and to fight tumors.
        - Specific FDA-approval indication is the topical treatment of external genital warts (EGWs) including perianal warts in immunocompetent patients ≥18 yrs.
        - 0.5 cm strand is applied in a thin layer over all EGWs TID for up to 16 weeks
        - 53.6% complete clearance vs 35.3% placebo with a 16 week median time to complete clearance
        - Side effects: Erythema, pruritis, burning, pain/discomfort, erosion/ulceration, edema, induration and vesicular rash
- **ADJUNCTIVE AGENTS**
    - **5% 5 F-U (Efudex) and 1% 5 F-U (Fluoroplex).** The agents are creams that were used extensively in the 1980s but have fallen out of favor and rarely used today due to extensive side-effects.
        - Mechanism of action: Inhibits production of both RNA and DNA in the cell, an antiproliferative effect. A hypersensitivity reaction that leads to stimulating the immune system.
        - Apply sparingly to each wart 1 to 3x/week.
        - Success of treatment partly depends upon the amount of inflammatory reaction, so do the complications.
        - Side effects: Very irritating to external skin, may cause deep, difficult to heal ulcerations which are very painful. Has resulted in chronic painful intercourse when used in the entrance to the vagina (the vestibule).
        - RESPONSE RATE: Treatment of external warts with 5-FU is not as successful as when it is used for treatment of vaginal warts. 5 FU is rarely used today. If used at all it is probably best used post-treatment with other methods to help prevent recurrence in the treatment margins (as an adjuvant).

What are the options for treatment of Vulvar Intraepithelial Neoplasia (VIN), Penile Intraepithelial Neoplasia (PIN), and Perianal Intraepithelial Neoplasia (PAIN)?

- **Management of VIN, PIN and PAIN** must be individualized depending upon patient age, symptoms, distribution and size of lesions, malignant potential, psychological issues, and recurrence rates. All modalities for treatment of VIN, PIN and PAIN have high recurrence rates. Management options (many are "off-label") for VIN include observation (VIN 1 and, perhaps VIN 2, only), wide local excision, laser vaporization, cryocautery, 5-fluorouracil (5-FU), imiquimod, skinning vulvectomy and simple vulvectomy (removing the skin of the vulva).
- **VIN, PIN and PAIN in young women and men:** Under the age of 40, most women with VIN, men with PIN and both sexes with PAIN have HPV as the

cause. Considering the significant rate of spontaneous regression of VIN, PIN and PAIN 1 and 2 in young individuals, it is reasonable to either treat small lesions by cytodestruction (electrocautery, laser, freezing, tri- or bichloroacetic acid), by immune stimulation with imiquimod, or to not treat and observe closely since progression to invasion has been rare at this age and spontaneous regression to normal is common. Avoiding aggressive treatment is particularly important in pregnancy, since many will spontaneously resolve postpartum.

- Women who smoke should be encouraged to quit, since spontaneous regression is rare in smokers and recurrence rates are very high in smokers who are treated. Spontaneous regression is unlikely when immunity is compromised, including women who are diabetic, are HIV-seropositive, etc. Serial documentation of lesions by photographs may be helpful.
- **Treatment of VIN3, PIN 3 or PAIN 3** :
    - VIN 3, PIN3, and PAIN3 at any age should be treated, and it is essential that the patient be informed of the requirement for long-term follow-up requiring repeated colposcopy and possible biopsy.
    - Treatment options:
        - Wide local excision by a scalpel of single lesions. Recurrence rates as high as 32% are reported.
        - Laser vaporization may be used on either single lesions or widespread disease. It is a good treatment when extensive multifocal disease occurs in young individuals. Depth of destruction must be tailored to the area being lasered, with 2.5 mm depth in hairbearing and perianal areas and lesser depths in areas such as the labia minora, clitoris and penis where the skin thickness is less than 3mm. Deeper ablation may result in scarring, painful intercourse, and decreased lubrication. Large areas of involvement often require multiple biopsies to rule out invasive cancer prior to laser ablation. Recurrence rates of 5 to 40% have been reported.
        - Cryocautery is rarely used to treat high-grade VIN, PIN and PAIN due to the inability to accurately measure the depth of tissue destruction. However, small focal papules (previously termed Bowenoid papulosis) can usually be safely destroyed by this method. Electrocautery of such lesions is likely also acceptable due to the low malignant potential of these lesions.
        - 5-FU has been used to treat VIN but causes severe pain and has recurrence rates as high as 75%. It may be most helpful as an adjunct to laser, applied post-treatment to healing laser margins to reduce the potential for recurrence.
        - The trend has been away from radical treatment of VIN by skinning vulvectomy, or simple vulvectomy, due to the gross disfigurement that often occurs with such surgery. However, when risk of invasion is high, or extensive symptomatic disease cannot be treated by any other manner, then this approach is justified.

How are anal lesions diagnosed?

- The incidence of anal cancer in individuals practicing anal receptive intercourse is now approaching the incidence of cervical cancer in women in the era prior to initiation of cervical screening.
- This statistic AND the recognition that 90% of anal cancers are caused by HPV and have a precancer stage similar to that of cervical neoplasia, both in natural history and in cytological changes, has initiated training in the taking and reading of anal cytology, and the evaluation of abnormal anal cytology results by high resolution anoscopy.
- Although anal screening is still in its infancy, as increasing numbers of clinicians become trained in these techniques, it is expected that anal screening will increasingly assume an important role in preventive health care.
- High-resolution anoscopy is the technique of colposcopic evaluation of the anus following introduction of an anoscope and application of acetic acid.
- The goal as with cervical colposcopy, is the identification of colposcopically-apparent abnormal appearing areas requiring biopsy and histologic confirmation.

How are anal lesions treated?

The location of AIN makes this more difficult to treat than CIN. Treatment options, depending on the degree of histologic abnormality are:

- **TCA:**often not as effective as elsewhere
- **Imiquimod:** can be applied by patient and probably as effective as elsewhere. This is approved only for treatment of external anal warts, but a randomized clinical trial has demonstrated its effectiveness in the treatment of VIN and it is reasonable to expect that it may be effective in the treatment of PIN and AIN.
- **5FU:** has been used in this area with some success but has the same adverse side-effects as in other areas: 3x per week. for 4 weeks. for perianal or anal lesions. Apply with finger into anus.
- **Infrared coagulation or laser:** ideal, especially for those that fail TCA, imiquimod or 5FU.
- **Electrocautery:** can be used carefully on perianal warts but is best not used in the anus due to potential for scarring.
- **Surgery** with removal of affected tissues if the lesions are too large to remove using one or more of the methods above, or there is concern for occult invasion.

How are urethral lesions detected?

- Most urethral HPV-induced warts are within 0.5 to 1 cm of the urethral meatus and can be visualized either with the naked eye or colposcopically by gently spreading the meatus to expose this area.
- Warts in the urethra are often missed. Introduction of a thin endocervical speculum into the meatus can often aid in visualization.

How are urethral lesions treated?

Treatment options include:

- **Laser & electrocautery:** but these may cause narrowing of the urethral opening (strictures).
- **TCA** may be used for warts right at the urethral opening.
- **Imiquimod (Aldara):** The use of Aldara in the urethra has not been studied, however, there is no contraindication to its use here and it appears to be quite effective when used for intra-urethral warts. To be sparingly applied 2 or 3x week for up to 4 weeks. Patient is taught how to apply a very small amount on the end of a cotton-tipped applicator. The applicator is introduced into the urethra no further than 1 cm. Patient self-applies, and voids 3 to 4 hours afterwards to wash out the cream.

How are vaginal HPV lesions diagnosed?

- Most vaginal HPV lesions are either condyloma acuminata, which are usually visible without magnification once a speculum is inserted, or flat vaginal HPV lesions that histologically are either vaginal intraepithelial neoplasia Grade 1 or 2 (VAIN 1 or VAIN 2).
- VAIN 3 is more commonly a single lesion and sometimes an extension of CIN3 to the adjacent vagina or residual post-hysterectomy when CIN3 was present at the time of the hysterectomy.
- Most VAIN is found during the colposcopic evaluation of women with abnormal cervical cytology. Therefore, women with abnormal cervical cytology should also have colposcopic evaluation of the vagina following application of acetic acid and rotation of the speculum to allow visualization of all vaginal walls. Application of Lugol's to the vaginal wall can also help in localization, as HPV-induced lesions are usually sharply marginated non-staining areas. Care needs to be taken to not overdiagnose areas that do not take up Lugol's, as recent tampon use, intercourse, vaginal candidiasis and other non-specific causes of non-staining may mimic vaginal lesions.
- Vaginal lesions that are thick, or have mosaic or punctation, abnormal vessels, or are found in the follow-up of an AGC or HSIL Pap should be biopsied to rule out VAIN 3.

How are vaginal lesions treated?

The natural history of vaginal HPV lesions (including vaginal intraepithelial neoplasia [VAIN]) is not well understood. Most likely, host immunity produces spontaneous resolution of low grade lesions in most cases. Therefore, it is best to not overly aggressively diagnose and treat these lesions. However, until spontaneous or treatment-aided regression occurs, these lesions may serve as a significant viral reservoir and all high-grade VAIN 2,3 should be treated.

- **Treatment of VAIN 1 and vaginal warts**
    - Many will elect to not treat vaginal warts or VAIN1 in expectation that spontaneous resolution will occur for many, and perhaps most.
    - Specific indications for treatment include:
        - Desire to avoid repeated intensive evaluation for abnormal Paps
        - Concern about occult higher-grade disease
        - Cosmetic and/or concerns about sexual transmission of HPV.
    - **Treatment options for low-grade vaginal HPV lesions are limited:**
        - **Cryotherapy** with liquid nitrogen. The use of a cryo-probe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.
        - **Tri- or Bichloroacetic acid (TCA of BCA)**
            - May work well on small individual lesions.
            - Is best applied colposcopically with the wooden end of a cotton tipped applicator
        - **Imiquimod**
            - Imiquimod use in the vagina is "off label" but several reports in the literature show favorable results.
            - The primary problem is lack of a good patient application option and trials where patients have self-applied imiquimod to the vagina have often demonstrated excessive introital pain and irritation.
            - Imiquimod can be clinician applied directly to individual vaginal HPV lesions under colposcopic guidance, as with TCA, but this requires at least a once-a-week application.
- **Treatment of VAIN 2,3**
    - VAIN 2 in a young woman may reasonably be treated similar to VAIN 1
    - VAIN 3 should be treated. Options for treatment of VAIN 2,3 include:
        - Laser, which requires special expertise, particularly when used in the vagina.
        - Local excision, loop excision, and partial vaginectomy are all options depending on extent of the VAIN and concern for invasion. Risks of injury to bladder, rectum, ureters, and blood vessels require special expertise and are therefore best managed by a specialist with expertise in these techniques.
    - If VAIN involves the vaginal cuff post-hysterectomy for CIN, it is best excised to rule out invasive cancer that has been reported to occur post-hysterectomy within the cuff.

How should pregnant patients with external HPV lesions be managed?

- TCA, liquid nitrogen, or electrocautery can be used to treat external genital HPV lesions at any time during pregnancy.
- Imiquimod is not approved for use in pregnancy.
- Kunecatechins (Veregen) is not approved for use in pregnancy.
- Podophyllin and podophilox should not be used in pregnancy.
- 1% and 5% 5-FU should not be used in pregnancy.
- Laser is best reserved for persistent lower genital tract lesions between 30 & 32 weeks.
- Treatment at this time results in the best opportunity for the patient to be clear of lesions at delivery and potentially reducing the risk of laryngeal papillomatosis.
- C-section vs. vaginal delivery?
    - The only known disease to occur secondary to perinatal transmission of HPV is HPV 6 or 11 induced laryngeal papillomatosis. However, the reported rate of this occurrence is 1-4/100,000 births.
    - This low risk, and reports of laryngeal papillomatosis occurring in children born by C-section, as well as the known risks of C-section have promoted the recommendation that the presence of genital warts not be the sole reason for delivery by c-section.
    - Additionally, no controlled studies have suggested that cesarean section prevents this condition.
    - The one clinical indication for c-section that involves HPV is the presence of extensive vaginal and/or introital warts blocking the birth canal.