Human Papillomavirus (HPV) and Trichomonas: Common, Concerning, and Challenging Sexually Transmitted Infections

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Human papillomavirus (HPV) and Trichomonas are two of the most common **sexually transmitted infections (STIs)** in the Unites States and worldwide, with prevalences exceeding those of *Chlamydia* and *N. gonorrhea* infections. Both infections have epidemiologic associations and can have serious health consequences.

Human Papillomavirus (HPV) Infection

HPV is the major cause of cervical and anal cancers, as well as oral and anogenital condylomas. HPV is a DNA virus of which over 90 types have been identified. Approximately 30 types are sexually transmitted and infect the anogenital area of both men and women. Data from the National Health and Nutrition Examination Survey[1] have provided the first national estimate of the prevalence of HPV infection among women in the United States aged 14 to 59. Overall, 26.8 percent of women tested positive for one or more strains of HPV. Prevalence of HPV was highest in women ages 20-24. Among all participating women, the prevalence of high-risk types of HPV was 15.2 percent. The prevalence of HPV types 6, 11, 16, and 18—the types targeted by Quadrivalent HPV vaccine was 3.4 percent overall.

Persistence of high-risk types of HPV (16, 18, 31, 33, 35, 45) causes cervical dysplasia and cancer. Worldwide, types 16 and 18 account for the majority of cervical cancers, and one or more of these types can be found in 90% of high grade intraepithelial precursor lesions.[2] Non-oncogenic types 6 and 11 are the etiologic agents for the majority of genital warts. Currently, cytology is used to screen for HPV related diseases. However, cytology as a cervical cancer screening method has a number of limitations, including the sensitivity to detect histologically significant disease. The sensitivity and specificity of cervical cytology ranges from 57% to 90% and from 65% to 97%, respectively.[3] These limitations have led to a considerable interest in using a combination of high-risk HPV type testing and cytology for screening. The combined approach increases the sensitivity substantially compared with either test alone, and has a negative predictive value of 99% to 100%.[4]

Studies with the HPV vaccine have demonstrated safety with relatively few adverse events reported.

Most women clear newly acquired HPV infection spontaneously, and the prevalence of HPV DNA positivity drops with age from a peak in adolescence and the early 20s.[5] Current guidelines have therefore incorporated testing for high-risk HPV only for women 30 years of age and older, and triaging cervical cytology management based on HPV test results. In the absence of cervical lesions, treatment is not recommended for subclinical genital HPV infection or low grade lesions such as **cervical intraepithelial neoplasia 1 (CIN1)**.[6] In clinical care, no anti HPV treatment is available, only treatment of lesions caused by HPV infection. Preventing HPV infection is therefore important.

Currently, there are two prophylactic vaccines approved by the **US Food and Drug Administration (FDA)** for preventing HPV infection. These vaccines are a quadrivalent HPV vaccine (made by Merck and Co, and approved in June 2006) and a bivalent HPV vaccine (made by Glaxo-SmithKline, and approved in October 2009). The quadrivalent vaccine is directed against HPV types 6, 11, 16, and 18 and is FDA-approved for preventing cervical cancer, genital warts, and precancerous or dysplastic genital lesions caused by HPV types 6, 11, 16, or 18. The bivalent vaccine is directed against HPV types 16 and 18 to prevent cervical cancer and precancerous lesions. Recommendations from the ACIP and the ACS are shown in Table 1.

Studies with the HPV vaccine have demonstrated safety with relatively few adverse events reported. The protective element of the vaccine is the high concentration of HPV type-specific neutralizing antibody. In the **Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE I/II)** study, almost all women who received the quadrivalent HPV vaccine became anti-HPV 6, 11, 16, and 18 seropositive one month after the third vaccine dose (99.8%, 99.8%, 99.8%, and 99.5% seropositive, respectively).[7] The study also showed that the vaccine prevented 98-100% of CIN grades 1 to 3 or adenocarcinoma in situ, and vaginal, vulvar, perineal, and perianal intraepithelial lesions associated with vaccine-type HPV when administered to subjects who had not been previously exposed to HPV. The vaccine also reduced the rate of vulvar, vaginal, and perianal lesions by 34% and cervical lesions by 20% regardless of the type of HPV infection. The FUTURE II study showed that the efficacy of the vaccine in preventing HPV-16 and -18-related CIN 2 and 3 and adenocarcinoma in situ was lower (44%) for those women with previous exposure to the vaccine types.[7]

In Rhode Island, state-supplied vaccine is available for routine vaccination at 11-12 years of age and catch-up vaccination for females 13-18 years of age. As of July 2010, the state also began supplying the vaccine for permissive use in males nine through 18 years of through the universal state-supplied vaccine program. Vaccine recommendations from both the ACIP and the American Cancer Society are shown in Table 1.

HPV and HIV co-infection

Highly active antiretroviral regimens have revolutionized the treatment of

Table 1. Comparison of Advisory Committee on Immunization Practices and American Cancer Society Recommendations for Human Papilloma Virus (HPV) Vaccination

Advisory Committee on Immunization Practices	American Cancer Society
Quadrivalent HPV vaccine: Routine HPV vaccination with 3 doses of vaccine is recommended for girls AND boys 11 and 12 years of age with catch-up for females and males aged 13 to 26 years if not vaccinated previously or have not completed the series. Bivalent HPV vaccine: Routine HPV vaccination with 3 doses of vaccine is recommended for girls 11 and 12 years of age with catch-up for girls and women aged 13 to 26 years if not vaccinated previously.	Quadrivalent or bivalent HPV vaccine: Routine HPV vaccination with 3 doses of vaccine is recommended for girls 11 and 12 years of age with catch-up for girls aged 13 to 18 years if not vaccinated previously or have not completed the series.
Quadrivalent or bivalent HPV vaccine: Girls as young as 9 years of age can be vaccinated.	Quadrivalent or bivalent HPV vaccine: Girls as young as 9 years of age can be vaccinated.
Quadrivalent HPV vaccination is recommended for all female and male individuals.13 through 26 years of age. Bivalent HPV vaccine is recommended for all girls and women 13 through 26 years of age.	Quadrivalent or bivalent HPV vaccine: HPV vaccination is recommended for all females 13 through 18 years of age. The American Cancer Society has no recommendation regarding the use of either HPV vaccine in men and boys.
Quadrivalent or bivalent HPV vaccine: The vaccine is not licensed for use in girls younger than 9 years of age or women older than 26 years of age. Quadrivalent HPV vaccine is contraindicated for persons with a history of immediate hypersensitivity to yeast. Bivalent HPV vaccine in prefilled syringes is contraindicated for persons with anaphylactic latex allergy.	Data are insufficient to recommend for or against universal vaccination of women 19 to 26 years of age. HPV vaccination is not recommended for women older than 26 years of age.

individuals infected with HIV and have resulted in dramatic reductions in morbidity and mortality.[8] While mortality due to HIV infection or AIDS declined, mortality due to malignancies has increased and now represents an increasing proportion of overall deaths among persons with HIV infection.[9] HPV infections are more prevalent and persistent in HIV-infected women, with a prevalence of 64% compared to 28% in HIV-uninfected women.[10] HIV-infected women have been reported to have a higher prevalence and persistence of HPV infection and to have an increased risk for abnormal **Papanicolaou (Pap)** smears as well as cervical cancer.[11] Therefore, the burden of HPV infection is greater among HIV-infected rather than HIV-uninfected women.

A concern in HIV-infected women is that the high prevalence of previous exposure to HPV 6, 11, 16 and 18 would decrease the vaccine's efficacy. One study, evaluating 767 HIV-infected and 390 uninfected women, the DNA prevalence of one or more of HPV types 6, 11, 16, and 18 was 15.9%; specifically, type 6 was 3.1%, 11 was 0.9%, 16 was 5.7%, and 18 was 6.1% (6.7% in HIV- uninfected women).[10] Thus, although HIV-infected women have a much higher prevalence of these four types than HIV- uninfected women, the majority of them (84-89%) did not have the types contained in the vaccine. Preventing infection of the four vaccine HPV types could decrease the impact of HPV infection among HIV-infected individuals. The immunogenicity and safety of an HPV vaccine in HIV-infected women is being evaluated.

In terms of managing HPV related diseases in HIV infected women, the **American Society for Colposcopy and Cervical Pathology (ASCCP)** guidelines recommend that HIV-infected women be managed in the same manner as women in the general population.[6] At present, insufficient data are available to support the use of HPV testing for triage of HIV-seropositive women aged 30 years and older. Based on the lack of sufficient data, the DHHS guidelines recommend a referral for colposcopy for any cervical cytologic abnormality found in HIV-seropositive women, regardless of the presence or absence of high-risk HPV types.

Trichomonas vaginalis Infection

Trichomonas vaginalis (*T. vaginalis*) is a sexually transmitted protozoan parasite. In the United States, an estimated 3.7 million people have the infection, but only a third develops any symptoms of trichomoniasis. In a nationally representative sample, the prevalence of trichomoniasis among 14–49-year-old women in the United States was 3.1%, corresponding to 2.3 million women with trichomoniasis compared with a prevalence of 0.33% and 2.5% for *Neisseria gonorrhea* and *Chlamydia trachomatis* infections respectively (NHANES).[12] Infection is more common in women than in men, especially non-Hispanic black women, and older women are more likely than younger women to have been infected.[12] The prevalence is likely to be underestimated as the infection is not reportable like many other STIs, available

diagnostic methods are often insensitive, and the clinical awareness of the infection is often limited to women and not their male partners. The symptoms of *T. vaginalis* infection are less pronounced in men, and the detection of infection is more complicated. Studies of male STD clinic patient populations have reported prevalences between 11 and 17%. The prevalence of *T. vaginalis* among male sexual partners of infected women is over 73%.[13] Males with *T. vaginalis* infections are often untreated, both because of lack of symptoms and due to lack of treatment as male partners of women with known *T. vaginalis*. *T. vaginalis* re-infection among women is therefore common.

T. vaginalis causes vaginitis, pelvic inflammatory disease, and several adverse obstetric sequelae (e.g. premature rupture of membranes, low birth weight, preterm labor). Recent advances in TV diagnostics have led to an improved understanding of the epidemiology of this pathogen. *T. vaginalis* is also associated with prolonged HPV carriage and increased risk of acquiring HIV infection. Studies have suggested that *T. vaginalis* may increase the rate of HIV transmission by approximately twofold.[14] This fact can translate into a significant problem in light of the high *T. vaginalis* prevalence globally.

Until recently, lack of sufficiently sensitive and specific diagnostic tests has limited the accurate diagnosis and recognition of this infection. Diagnosis of vaginal trichomoniasis can be done by microscopy of vaginal secterions (wet mount), culture, rapid antigen detection, and **nucleic amplification tests (NAAT)**. Microscopy detection is highly insensitive in detecting T vaginalis and culture is time consuming. There are several nucleic acid tests available although only one, the Affirm VP III hybridization assay, has been FDA approved.[15] Other commercially available tests like the Gen-Probe Aptima T vaginalis **transcription-mediated amplification (TMA)** tests are being evaluated and may be even more sensitive in detecting *T. vaginalis.*[16]

With increasing evidence of complications associated with trichomonas infections, screening for *T. vaginalis* should be encouraged, especially as treatment with metronidazole 2 gm or tinidazole 2 gm in single doses is easy and highly effective.

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