STD TREATMENT GUIDELINES TABLES: HPV VACCINE

ACIP HPV Vaccine Recommendations

Author/Citation	*Population*	*Summary Points*
CDC (Markowitz LE, Dunne EF, Sariaya M, Lawson HW, Chesson H, Unger ER). Quadrivalent Human Papillomavirus Vaccine, Recommendations of the Advisory Committee for Immunization Practices (ACIP) MMWR 2007;56(RR02):1-24.	Females	➢ Routine administration of quadrivalent vaccine at 11-12 years, vaccination through age 26 years.
CDC.FDA Licensure of Bivalent Human Papillomavirus Vaccine (HPV2, Cervarix) for Use in Females and Updated HPV Vaccination Recommendations from the Advisory Committee on Immunization Practices (ACIP) MMWR, May 28, 2010; 59(20):626-629	Females	➢ Routine administration of either quadrivalent of bivalent vaccine at 11-12 years, vaccination through age 26 years.
CDC. Recommendations on the Use of Quadrivalent Human Papillomavirus Vaccine in Males-Advisory Committee on Immunization Practices (ACIP), 2011. MMWR 2011;60(50):1705-1708.	Males	➢ Routine administration of quadrivalent vaccine at 11-12 years, vaccination through age 26 years. ➢ MSM should be vaccinated through age 26 years. ➢ HIV-infected should be vaccinated through age 26 years.

Vaccine Efficacy Evaluations

Author/Citation	*Study Design, vaccine*	*Population, Sample Size*	*Outcome*
1.Paavonen J, et al. 2009	RCT, bivalent	Women, 15-25 years, ATP vaccine n=8093, control, n=8069	VE in females for cervical precancers, mean f/u time was 34.9 months after third dose.
2.Kjaer SK, et al. 2009	RCT, quadrivalent	Women, 16-26 years,per protocol vaccine n=7864, control, n=7865	VE in women for cervical precancers and anogenital warts, mean f/u time 42 months post dose 1 (elected to use Future I/II publication in 2010 for cervical precancer as more recent and a combined analysis—difference in VE for cervical precancer)
3.Joura EA, et al. 2007	RCT, quadrivalent	Combined analysis of 3 RCTs Women, 16-26 years, Per protocol vaccine, n=7811, placebo n=7785	VE in females for vulval and vaginal precancers, mean f/u time was 3 years.
4.Palefsky JM, et al. 2011	RCT, quadrivalent	Men who have sex withmen, 16-26 years, per protocol vaccine, n=194, control n =208	VE in males for anal precancers
5.FUTURE I/II Study Group. 2010	RCT, quadrivalent	Combined analysis of 4 RCT Women, 16-26 years, ATP vaccine, n=9087, control, n=10,292 (HPV16 only 1204)	VE in females for cervical precancer, mean f/u time 3 years after first dose. (Most recent and comprehensive analysis of cervical precancer)

Vaccine Efficacy Summary Tables

Table 1. Vaccine Efficacy for Prevention of Cervical, Vulvar, Vaginal, Anal Intraepithelial Neoplasia 2+, Clinical trials using an according to protocol or per protocol assessment

Reference	Outcome	Vaccine	Number	% Efficacy	(CI)
1†	CIN2+	Bivalent	14,656	92.9	96.1% CI (79.9-
2*	CIN2+	Quadrivalent	15,729	98.2	98.3)
					95% CI (93.3-99.8)
3*	VIN2+	Quadrivalent	15,596	100	95% CI (42.0-100)
3*	VaIN2+	Quadrivalent	15,596	100	95% CI (31.0-100)
4	AIN2+	Quadrivalent	402	74.9	95% CI (8.8- 95.4)

CIN=cervical intraepithelial neoplasia, VIN=vulvar intraepithelial neoplasia, VaIN=vaginal intraepithelial neoplasia, AIN=anal intraepithelial neoplasia

†mean follow-up was 34.9 months post dose 3

*Pooled analysis Protocols 007, 013, 015. Mean follow-up time 42 months post dose 1 (true for 2, check on 3)

Table 2. Vaccine Efficacy for Prevention of Cervical, Vulvar, Vaginal, Anal Intraepithelial Neoplasia 1 Clinical trials using an according to protocol or per protocol assessment

Reference	Outcome	Vaccine	Number	% Efficacy	(CI)
1	CIN1	Bivalent	NA	NA	NA
5	CIN1*	Quadrivalent	15,261	95.9	96.1% CI (91.3-98.4)
5	VIN1*	Quadrivalent	15,334	100	95% CI (74.1-100)
5	VaIN1*	Quadrivalent	15,334	100	95% CI (4.0-100)
4	AIN1	Quadrivalent	222	73.0	95% CI (16.3-93.4)

CIN=cervical intraepithelial neoplasia, VIN=vulvar intraepithelial neoplasia, VaIN=vaginal intraepithelial neoplasia, AIN=anal intraepithelial neoplasia

*Undjusted vaccine efficacy for HPV 6, 11, 16, 18 associated lesions

Table 3. Vaccine Efficacy for Prevention of Cervical, Vulvar, Vaginal, Anal Intraepithelial Neoplasia 2+, Clinical trials using an intention to treat assessment

Reference	Outcome	Vaccine	Number	% Efficacy	(CI)
1	CIN2+	Bivalent	17,349	52.8	96.1% CI (37.5-64.7)
2*	CIN2+	Quadrivalent	17,683	51.5	95% CI (40.6-60.6)
3*	VIN2+	Quadrivalent	18,174	62	95% CI (10-85)
3*	VaIN2+	Quadrivalent	18,174	82	95% CI (17-98)
4	AIN2+	Quadrivalent	551	54.2	95% CI (18.0-75.3)

CIN=cervical intraepithelial neoplasia, VIN=vulvar intraepithelial neoplasia, VaIN=vaginal intraepithelial neoplasia, AIN=anal intraepithelial neoplasia

*Pooled analysis Protocols 007, 013, 015. Mean follow-up time 42 months post dose 1

Table 4. Vaccine Efficacy for Prevention of Genital Warts, Clinical trials of Quadrivalent HPV Vaccine using an according to protocol or per protocol assessment

Reference	Sex	Number	% Efficacy	(95% CI)
4†	M	402	100	(8.2-100)
5*	F	15,334	99.0	(96.2-99.9)

*Unadjusted vaccine efficacy for HPV 6, 11, 16, 18 associated lesions

†Data presented as anal condyloma. Overall condyloma from package insert efficacy 89.3% (95% CI 65.3%-97.9%) [6].

Special Populations (HIV)

Author/Citation	*Study Design*	*Population, Sample Size*	*Outcome*	*Summary Points*
Wilkin T, et al. 2010	AID Malignancy Consortium Protocol 052, single-arm, open-label, multicenter clinical trial (pilot study) of safety and immunogenicity of HPV4 in HIV-1 infected men	112 participants, 109 HIV-infected men received at least 1 vaccine dose, 123 participants excluded (primarily due to HGAIN or HSILS)	Week 28 seroconversion, baseline predictors of antibody concentrations, geometric mean concentration and 95% CI, immunogenicity, and adverse events	➢ Seroconversion noted for all 4 types (>94%) ➢ For all types, higher baseline concentrations were associated higher concentrations at week 28. ➢ No grade 3, 4, 5 events related to vaccination ➢ 1 death due to hepatocellular carcinoma, unrelated to vaccination ➢ Grade 2 injection site reactions observed in 9 (8%).
Levin MJ, et al. 2010	Stratified into 3 groups based on CD4% nadir and CD4%, randomly assigned to HPV4 or placebo 3:1 (90 subjects HPV4, 30 placebo)	120 HIV-infected children ages 7-12 years, baselind CD4% was >=15, at least 3 months HAART for subjects with CD4%<25	Adverse events, seroconversion, geometric mean titers	➢ AE similar between arms, and similar to that reported for HIV-uninfected children ages 9-15 years. ➢ No alteration of CD4 or HIV viral load during trial ➢ Seroconversion high and consistent with that reported in HIV-uninfected children—although HPV 6, 18 levels were 30-50% lower than that achieved by historical controls-noted is the antibody levels equivalent to that achieved in young adults in vaccine trials ➢
Kahn J, et al. 2012	Baseline evaluation for a clinical trial of HPV vaccine in HIV-infected women	99 16-23 year old HIV-infected women from 14 sites, mean age 21.4	Vaccine type HPV seropositivity and DNA positivity	➢ 23.2% DNA and seronegative to all 4 types ➢ 45.5% DNA negative and seronegative to HPV 16/18, 9.1% seropositive and DNA positive for HPV-16
Kahn J, et al. (2012)	Phase II, open-label, multicenter trial of HPV4 in standard dosing	99 16-23 year old HIV-infeced women from 14 sites	4 weeks post dose 3 immunogenicity (comparison to historic HIV-uninfected 16-23 controls from clinical trial,	➢ Seroconversion to all vaccine types >92% group A and 100% Group B ➢ Pain in 26.3% and induration in 2%, systemic reactions –highest grade was headache in

		Exclusion: recent anogenital warts, CIN2/3, active OI or bacterial infection, IGG, blood/plasma products, steroids, analysis of women DNA and seronegative	Villa et al),safety, Grade 1-4 AE, 2 groups ART naïve or no HAART for at least 6 months, Group B receiving HAART for at least 6 months with HIV RNA x 2 <400 copies/mL	15.2%
Weinberg A, et al. 2012	RCT of immediate vs delayed HPV4 (96 weeks delay)	Aged 7-12 year old HIV-infected boys and girls (all but 2 on HAART)	Type specific antibodies to HPV 6, 11, 16, 18 at 4 and 72 weeks,	➢ Type-specific antibodies to HPV6, 11, and 16 were detected in 100% and ≥94% of children at 4 and 72 weeks, respectively, after the third QHPV dose. ➢ Corresponding numbers for HPV18 were 97% and 76%, respectively. ➢ 69 and 39% developed mucosal IgG to HPV 16, 18, and 60 and 52% developed specific CTLs ➢ A fourth dose of QHPV administered to Rx-Immediate participants increased cLIA titers against all vaccine-contained genotypes to 100% seropositivity for HPV6, 11, and 16 and to 96% for HPV18. ➢ Higher HPV antibody concentrations at week 28 were the strongest predictors of higher antibody concentrations at week 96 for all HPV genotypes (P < .0001). HPV 18 abs lower at 72 weeks (immunocompetent >90% HPV 18, this study showed 76% positive), 4th dose increased titers
Money, et al. abstract 2013	Longitudinal study of seroresponse to HPV4 in HIV infected women.	193 HIV-infected women (mean age 36)	Seroconversion at month 7,12	➢ Seroconversion for HPV types 6, 11, 16, and 18 was 88.5%, 99.0%, 99.5%, and 94.8% respectively. ➢ GMTs fell at 12 months substantially across all

				HPV types.
Firnhaber CS, et al. abstract	Cross-sectional evaluation of seroprevalence to HPV 6, 11, 16, 18	487 women from SA, Botswana and Brazil (Median age was 27 years in Botswana, 36 in SA, and 34 in Brazil)	HPV serology to 6, 11, 16, 18	➢ 65% of the women had sero titers to any of the 4 HPV types, 30% had titers to HPV 16. ➢ <3% had all 4 HPV types

STD Clinics

Author/Citation	***Study Design***	***Population, Sample Size***	***Outcome***	***Summary Points***
Gaffga NH, et al. 2012	Cross-sectional	HPV sentinel surveillance, women attending different clinics and receiving routine pap smears in 5 US cities from 2003-2005	HPV type prevalence, by clinic, age group and city	➢ Between 15.2%-17.1% of women aged 18-29 years with any vaccine-preventable HPV type and attending an STD clinic venue ➢ This study assess the sample size needed to measure vaccine type impact—smallest for HPV16 and in youngest population
Meites E, et al. 2012	Survey to STD Surveillance Network	42 STD clinics in SSuN	Survey responses on HPV vaccine implementation	➢ 7 clinics were offering HPV vaccine—all offered quadrivalent HPV vaccine ➢ Clinics not offering vaccine, 63% regularly referred elsewhere for vaccination. ➢ Funding for clinics offering vaccine included VFC, 317, or other. 1 clinic had a vaccine manufacturer donation. All clinics offering vaccine offered at no cost. ➢ Most common barriers were was cost, staff time, f/u of issues/coordination, ensuring completion. Less common identified barriers were vaccine supply and consent. None reported lack of interest.
Dempsey AF, et al. 2007	Cross-sectional analysis of medical records	STD clinics, 66,537 visits	Evaluation of STD clinic visit due to HPV	➢ Of the 66,537 visits included in the study, 10.3% were HPV-related. Of the 3085 HPV-related "new problem" visits, only 281 non-HPV diagnoses were made, with

	(1994–2004) from a single STD clinic.			nonspecific urethritis and CT being the most common diagnosis for males and females, respectively. ➢ Nearly 25% of the 14,574 follow-up visits were for HPV. ➢ Concluded that HPV vaccine could impact this workload
Dunne EF, et al. Unpublished	Cross-sectional	Females attending STD clinics in 5 locations in the US, and receiving cervical cancer screening HPV Sentinel Surveillance	Evaluation of vaccine type exposure in women attending STD clinic venues	➢ Most all women were naïve to at least one vaccine type infection, the majority were naïve to HPV 16/18 ➢ 46.6% would have the full benefit of vaccination ➢ All women through age 26 years should be vaccinated, and STD clinic venues should consider vaccination ➢ There are barriers that need to be addressed with regard to vaccination in STD clinic venues including cost of vaccine, consent for minors, and administration/program needs ➢ Limitations of assessment include small sample size, limited generalizability

Table 2 (Dunne et al): Prevalence of HPV 6, 11, 16, 18 DNA and seropositivity in females aged 14-26 years attending STD clinics, HPV Sentinel Surveillance, 2003-2005

	HPV16 (%)	HPV 18 (%)	HPV 16/18* (%)	HPV 6 (%)	HPV 11 (%)	HPV 6/11* (%)	Any 4 Types (%)	All 4 Types (%)
DNA positive	105 (11.9)	33 (3.8)	8 (0.9)	40 (4.6)	13 (1.5)	0	170 (19.3)	0 (0%)
Seropositive	207 (23.5)	67 (7.6)	33 (3.8)	289 (32.8)	78 (8.9)	52 (5.9)	418 (47.5)	6 (0.7%)

DNA positive *and* seropositive	50 (5.7)	4 (0.5)	1 (0.1)	24 (2.7)	7 (0.8)	0	78 (8.9)	0 (0%)
DNA positive *and/or* seropositive	262 (29.8)	96 (10.9)	48 (5.5)	305 (34.7)	84 (9.5)	54 (6.1)	470 (53.4)	6 (0.7%)
Naïve	**618 (70.2)**	**784 (89.1)**	**570 (64.8)**	**575 (65.3)**	**796 (90.5)**	**545 (61.9)**	**874 (99.3)**	**410 (46.6)**

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