



Q/ Does qHPV vaccine prevent anal intraepithelial neoplasia and condylomata in men?

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EVIDENCE-BASED ANSWER

A/ YES. Quadrivalent human papillomavirus (qHPV) vaccine reduces rates of anal intraepithelial neoplasia (AIN) by 50% to 54%, and persistent anal infection by 59%, associated with the 4 types of HPV in the vaccine (6, 11, 16, and 18) in young men who have sex with men (MSM); it also reduces external genital lesions by 66%, and persistent HPV infection associ-

ated with the same 4 HPV types by 48 to 59% in all young men, heterosexual men, and MSM (strength of recommendation [SOR]: **B**, randomized, placebo-controlled trials [RCTs]).

In addition, the vaccine is associated with a 50% to 55% decrease in recurrent high-grade AIN and anogenital condylomata in older MSM (SOR: **B**, cohort studies).

Evidence summary

Two RCTs that evaluated qHPV in young men for preventing outcomes associated with the 4 HPV subtypes in the vaccine (6, 11, 16, and 18) found that it reduced them by 50% to 66% using an intention-to-treat protocol (TABLE¹⁻⁴).

Vaccination reduces AIN and persistent infection in MSM

The first RCT evaluated a subset of 602 MSM from the second, larger RCT for preventing AIN and persistent HPV infection.¹ The intention-to-treat population included men with 5 or fewer lifetime sexual partners who had engaged in insertive or receptive anal intercourse or oral sex within the last year, were not necessarily HPV-negative at enrollment, and received at least one dose of vaccine (or placebo).

The vaccine reduced AIN associated with the 4 HPV types (6.3 vs 12.6 events per 100 person-years; relative risk reduction [RRR]=50.3%; 95% confidence interval [CI], 25.7-67.2; number needed to treat [NNT]=16 to prevent one AIN case per year) and with HPV of any type (13 vs 17.5 events per

100 person-years; RRR=25.7%; 95% CI, -1.1 to 45.6). It also reduced the rate of persistent HPV infection with the 4 HPV vaccine subtypes (8.8 vs 21.6 events per 100 person-years; RRR=59.4%; 95% CI, 43%-71%; NNT=8 to prevent one persistent HPV infection per year).

Investigators in the study also evaluated vaccine efficacy in a smaller subset (194 men) using per-protocol analysis and found higher prevention rates (78% for AIN due to HPV types 6, 11, 16, and 18). Investigators followed these subjects every 6 months for 36 months with polymerase chain reaction testing for HPV DNA, high-resolution anoscopy with anal cytology, and anal biopsy and histology if there were atypia.

The vaccine decreases persistent HPV infection and external genital lesions

The second RCT, including both MSM and heterosexual men, found that qHPV vaccine reduced rates of persistent HPV infection by 48%, and external genital lesions (condylomata or intraepithelial neoplasia involving the penis, perineum, or perianal area) by 66% associated with HPV types 6, 11, 16, and 18 using the intention-to-treat protocol.²

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TABLE

HPV vaccine in men: What the studies show

Outcomes evaluated	Type of study	Population	Outcomes	Data analysis, by protocol type	Results (reduction compared to placebo)	Comments
AIN and persistent HPV infection associated with HPV types 6, 11, 16, and 18	Placebo-controlled double-blind RCT ¹	602 MSM, ages 16-25 yr	AIN grades 1, 2, and 3	ITT	50.3% (95% CI, 25.7%-67.2%)	PP group (n=194) included only men who tested negative for HPV before vaccination (serum, anal cytology, anal biopsies), who were proven to have received all vaccine doses, and who had 5 or fewer lifetime sexual partners
				PP	77.5% (95% CI, 39.6%-93.3%)	
			AIN grades 2 and 3	ITT	54.2% (95% CI, 18%-75.3%)	
				PP	74.9% (95% CI, 8.8%-95.4%)	
Persistent anal HPV infection	ITT	59.4% (95% CI, 43%-71.4%)				
	PP	94.9% (95% CI, 80.4%-99.4%)				
External genital lesions (condylomata and intraepithelial neoplasia in genital area) and persistent HPV infection associated with HPV types 6, 11, 16, and 18	Placebo-controlled double-blind RCT ²	4065 males, ages 16-26 yr	External genital lesions	ITT	65.5% (95% CI, 45.8%-78.6%)	PP group (n=2805) met same criteria as in previous trial ¹
				PP	90.4% (95% CI, 69.2%-98.1%)	
			Persistent anal HPV infection with types 6, 11, 16, and 18	ITT	47.8% (95% CI, 36%-57.6%)	
				PP	85.6% (95% CI, 73.4%-92.9%)	
Recurrence of high-grade AIN (unspecified HPV type) after qHPV vaccination vs no vaccination	Nonconcurrent cohort ³	202 MSM, ages 20-79 yr (mean 40 yr), with previously treated high-grade AIN	12/88 (13.6%) high-grade AIN recurrence, vaccinated men	Not applicable	qHPV associated with decreased recurrence risk of high-grade AIN; HR=0.50 (95% CI, 0.26-0.98; P=.04)	Subset with high-grade AIN recurrence HPV types 6, 11, 16, and 18: qHPV associated with decreased recurrence risk HR=0.47 (95% CI, 0.22-1.04; P=.05)
			35/114 (30.7%) high-grade AIN recurrence, unvaccinated men			
External genital lesions (anal condylomata), unspecified HPV type	Cohort, vaccinated and unvaccinated with qHPV ⁴	313 MSM, mean age 42 yr, followed for 981 days	Development of anal condylomata, either new or recurrent	ITT	Vaccinated 8.6% (3.7 per 100 person-years)	HR=0.45 (95% CI, 0.22-0.92)
					Unvaccinated 18.8% (7.3 per 100 person-years)	

AIN, anal intraepithelial neoplasia; CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; ITT, intention to treat analysis; MSM, men who have sex with men; PP, per protocol analysis; qHPV, quadrivalent human papillomavirus vaccine; RCT, randomized controlled trial.

Investigators used the same protocols used in the first RCT, and the per-protocol population again had higher prevention rates (84% for any HPV type, 90% against the 4 vaccine types). The only adverse effect of the vaccine was injection site pain (57% vs 51% with placebo; $P < .001$).

The vaccine also helps older MSM

A nonconcurrent cohort study that evaluated qHPV vaccination among older MSM with previously treated high-grade AIN found a 50% decrease in recurrence rates in the 2 years after vaccination.³ Investigators recruited HIV-negative men, some of whom chose vaccination (not randomized), and followed them for 2 years. Study limitations included using medical records for data col-

lection and the predominance of white, non-smoking men with private insurance.

A post-hoc analysis of older men without previous anal condylomata (210 men) or with treated condylomata and no recurrence in the year before vaccination (103 men) found that qHPV vaccination was associated with 55% lower rates of anal condylomata.⁴

Recommendations

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends routine use of qHPV vaccine in males ages 11 through 21 years, and optional use in unvaccinated men as old as 26 years.⁵

JFP

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