HPV Vaccination in HIV-Positive Men and Women
Challenges and Opportunities

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Disclosures

- Merck and Co - Research grant support, advisory boards

Outline

- Rationale for vaccinating HIV-positive men and women
- Recent data from vaccine studies of HIV-negative men and women
- Vaccination issues specific to HIV-positive individuals
- Recent data from vaccine studies of HIV-positive men and women

Rationale for vaccinating HIV-positive men and women

HIV+ men and women are at higher risk of anogenital HPV infection and cancer than the general population

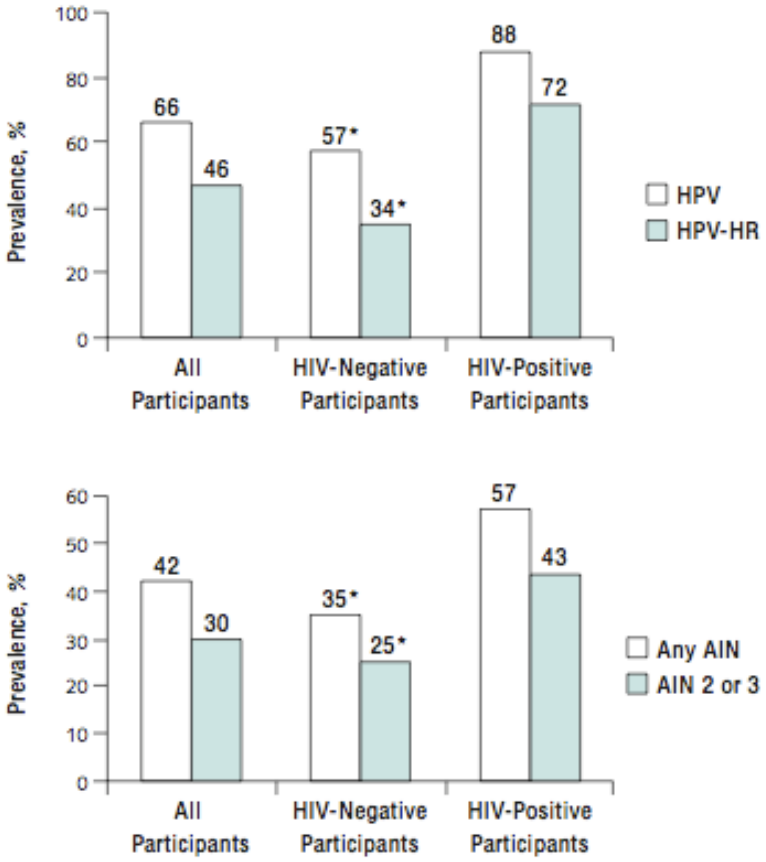
Table 6. Relative risks* (by human immunodeficiency virus [HIV] exposure group) of human papillomavirus-associated anogenital cancers among 309 365 patients with acquired immunodeficiency syndrome (AIDS) (AIDS–Cancer Match Registry, United States, 1978–1996)

HIV exposure category	Relative risk (95% confidence interval) [No. of observed cancers]									
	Cervix		Vulva/vagina		Anus (women)		Anus (men)		Penis	
					Invasive cancers					
Homosexual contact†	NA‡		NA‡		NA‡		59.5 (51.5–68.4)	[197]	2.8 (1.0–6.1)	[6]
Heterosexual contact	4.9 (2.7–8.2)	[14]	7.1 (2.3–16.4)	[5]	8.0 (1.7–23.4)	[3]	—	[0]	—	[0]
Intravenous drug use§	7.0 (4.7–10.0)	[29]	5.5 (1.8–12.8)	[5]	7.3 (1.5–21.4)	[3]	5.9 (2.7–11.2)	[9]	7.1 (2.8–14.6)	[7]
Hemophilia/transfusion‖	—	[0]	—	[0]	—	[0]	—	[0]	—	[0]
Other/unknown¶	1.1 (0.0–6.2)	[1]	7.0 (0.9–25.3)	[2]	6.4 (0.2–35.9)	[1]	17.1 (7.4–33.7)	[8]	2.7 (0.1–15.1)	[1]
All	5.4 (3.9–7.2)	[44]	5.8 (3.0–10.2)	[12]	6.8 (2.7–14.0)	[7]	37.9 (33.0–43.4)	[214]	3.7 (2.0–6.2)	[14]
					In situ *cancers*					
Homosexual contact†	NA‡		NA‡		NA‡		99.8 (81.4–121.2)	[102]	6.1 (3.0–10.9)	[11]
Heterosexual contact	4.5 (4.0–5.1)	[251]	5.1 (1.7–12.0)	[5]	—	[0]	—	[0]	9.5 (0.2–52.8)	[1]
Intravenous drug use§	4.6 (4.2–5.1)	[371]	2.2 (0.5–6.3)	[3]	17.2 (0.4–96.0)	[1]	5.6 (1.2–16.5)	[3]	7.2 (2.3–16.8)	[5]
Hemophilia/transfusion‖	3.9 (2.1–6.5)	[14]	—	[0]	—	[0]	—	[0]	15.8 (0.4–87.9)	[1]
Other/unknown¶	5.0 (4.0–6.2)	[86]	9.0 (1.9–26.3)	[3]	—	[0]	7.9 (0.2–43.7)	[1]	9.0 (1.1–32.4)	[2]
All	4.6 (4.3–5.0)	[722]	3.9 (2.0–7.0)	[11]	7.8 (0.2–43.6)	[1]	60.1 (49.2–72.7)	[106]	6.9 (4.2–10.6)	[20]

Frisch et al; JNCI 2000; 92: 1500-10

Population-based data

Figure. Prevalence of anal human papillomavirus (*HPV*) and anal intraepithelial neoplasia (*AIN*).



Chin-Hong et al Ann Int Med 2008; 149; 300-6

Recent reports of incidence in anal cancer since introduction of ART

Piketty C, Selinger-Leneman H, Grabaret S, et al. AIDS. 2008;22:1203-1211

75/100,000 person-years among HIV+ MSM since 1999

D'Souza G, Wiley D, Li X, et al. J Acquir Immune Defic Syndr. 2008;48(4):491-499.

137/100,000 person-years among HIV+ MSM since 1996

Patel P, Hanson H, Sullivan S, et al. Ann Intern Med. 2008; 10(148):728-736

78/100,000 person-years among HIV+ MSM since 2000

Engels EA, Biggar, RJ et al. Int J Cancer 2008; 123:187-94

11/100,000 person-years among HIV+ men and women since 1996

Prophylactic Efficacy of GARDASIL®
CIN & AIS

Per-Protocol Population (Protocols 007, 013, and 015)
Mean Follow-Up - 44 months

Endpoint**	GARDASIL® Cases (N = 9075)	Placebo Cases (N = 9075)	% Efficacy	95% CI
HPV 6/11/16/18-related CIN or AIS	9	225	96	(92, 98)
By Type				
HPV 6-related	0	47	100	(92, 100)
HPV 11-related	0	12	100	(65, 100)
HPV 16-related	8	137	94	(89, 98)
HPV 18-related	1	61	98	(91, 100)
By Disease				
CIN 1	7	170	96	(91, 98)
CIN 2/3	2*	110	98	(93, 100)
AIS	0	7	100	(31, 100)

** Subjects are counted only once per row, but may be in more than one row
* One case was a co-infection with HPV 52, the other was a co-infection with HPV 51 & 56

Vaccination of HIV-positive populations

Questions:

1) Is HPV vaccination safe and effective in boys and men?

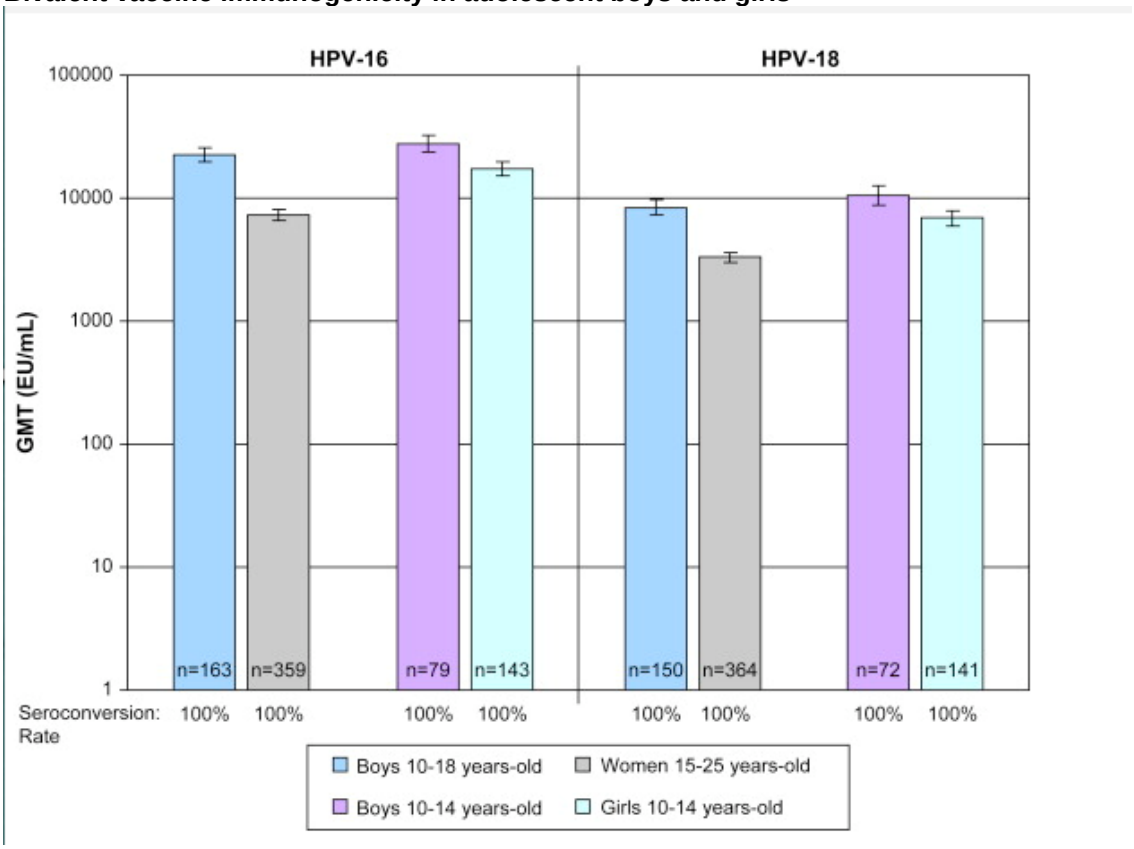
Immunogenicity bridging studies

Table 5
Immunogenicity bridging studies

Study	Vaccine	Study Groups: Age years (N)	Serologic Assay	% Sero-conversion[a]	Major Conclusions*
Reisinger KS et al. 2007 [12]	Gardasil®	Boys: 9–16 (567)	cLIA	≥99.5 for all types	GMTs for boys non-inferior to those in girls
		Girls: 9–15 (617)		≥99.6 for all types	Boys GMT 1.1–1.5 fold higher than girls
Block SL et al. 2006 [26]	Gardasil®	Boys: 10–15 (510)	cLIA	≥99.7 for all types	GMTs for boys and girls non-inferior to those in women
		Girls: 10–15 (506)		100 for all types	Boys GMT 1.8–2.7 fold higher than women's
		Women: 16–23 (513)		≥99.1 for all types	Girls GMT 1.7–2.0 fold higher than women's
Pedersen C et al. 2007 [27]	Cervarix™	Girls: 10–14 (158)	ELISA	100 for both types	GMTs for girls non-inferior to those in women
		Women: 15–25 (458)		100 for both types	Girl's GMT 2.1–2 fold higher than women's

cLIA: chelated ligand internalization assay; ELISA: enzyme linked immunosorbent assay; GMT: geometric mean titer [12,26,27].
[a] According to protocol (ATP) analyses one month after 3rd vaccine dose.

Bivalent vaccine immunogenicity in adolescent boys and girls



GMTs at month 7 for HPV-16 and HPV-18 antibodies in initially seronegative boys and women (ATP immunogenicity cohort).

Petaja, T et al. Journal of Adol Health 2009; 44: 33-40

MERCK 020: EFFICACY OF THE QUADRIVALENT HPV VACCINE AGAINST HPV 6/11/16/18-RELATED EXTERNAL GENITAL LESIONS AND ANOGENITAL INFECTION IN YOUNG MEN

Protocol 020 objectives

Primary

- Safety
- Efficacy: Combined incidence of HPV 6/11/16/18-related external genital lesions:
    - Main study: HM + MSM
        - External genital warts
        - Penile/perianal/perineal intraepithelial neoplasia (PIN)
        - Penile, perianal, or perineal cancer
    - Sub-study: MSM
        - Anal intraepithelial neoplasia (AIN)
        - Anal Cancer
- Immunogenicity
    - Geometric mean titers, seroconversion

Secondary

- Efficacy:
    - Incidence of persistent HPV 6/11/16/18 infection*

Efficacy against HPV 6/11/16/18-related persistent infection

Per-protocol population

HPV Type	GARDASIL™			Placebo			% Efficacy	95% CI
	n	Cases	Inc. per 100 PY	n	Cases	Inc. per 100 PY		
HPV 6	1,239	4	0.2	1,238	33	1.4	88.0	66.3, 96.9
HPV 11	1,239	1	0.0	1,238	15	0.6	93.4	56.8, 99.8
HPV 16	1,290	9	0.4	1,264	41	1.8	78.7	55.5, 90.9
HPV 18	1,327	1	0.0	1,347	25	1.0	96.0	75.6, 99.9

Efficacy against external genital lesions (EGL)
Per-protocol population

Endpoint	GARDASIL™ (n = 1,397)		Placebo (n = 1,408)		% Efficacy	95% CI	p-value
	Cases	Inc. per 100 PY	Cases	Inc. per 100 PY			
All subjects	3	0.1	31	1.1	90.4	69.2, 98.1	<0.001

Efficacy against external genital lesions (EGL)
Per-protocol population

Severity	GARDASIL™ (n = 1,397)		Placebo (n = 1,408)		% Efficacy	95% CI
	Cases	Inc. per 100 PY	Cases	Inc. per 100 PY		
Condyloma	3*	0.1	28	1.0	89.4	65.5, 97.9
PIN 1	0	0.0	2	0.1	--	--
PIN 2/3	0	0.0	1	0.0	--	--
Penile/perineal/ perianal cancer	0	0.0	0	0.0	--	--

*Two cases related to HPV 6 alone, and one case related to HPV 6/11/35

Adverse experience summary; days 1-15 following any vaccination visit

	GARDASIL™		Placebo	
	n	%	n	%
Subjects in analysis population	2,020		2,029	
Subjects with follow-up	1,945		1,950	
Number of subjects:				
With one or more adverse experiences	1,345	69.2	1,244	63.8
injection-site adverse experience	1,169	60.1	1,047	53.7
systemic adverse experience	615	31.6	613	31.4
With vaccine-related adverse experiences	1,242	63.9	1,134	58.2
injection-site adverse experiences	1,169	60.1	1,046	53.6
systemic adverse experiences	274	14.1	284	14.6
With serious adverse experiences*	5	0.3	1	0.1
serious vaccine-related adverse experiences	0	0.0	0	0.0

Summary

- GARDASIL™ was highly efficacious in reducing the incidence of external genital lesions in men aged 16-26 years

- Based on these data GARDASIL™ was approved by the U.S. F.D.A. for use in boys aged 9-26 for prevention of genital warts
    - Covered by the Vaccines for Children program

Protocol 020 objectives

Primary

- Safety
- Efficacy: Combined incidence of HPV 6/11/16/18-related external genital lesions:

    - Main study: HM + MSM
        - External genital warts
        - Penile/perianal/perineal intraepithelial neoplasia (PIN)
        - Penile, perianal, or perineal cancer

    - Sub-study: MSM
        - Anal intraepithelial neoplasia (AIN)
        - Anal Cancer

- Immunogenicity
  - Geometric mean titers, seroconversion

Secondary

- Efficacy:
  - Incidence of persistent HPV 6/11/16/18 infection*
  - Incidence of HPV 6/11/16/18 DNA detection at one or more visits

Efficacy Against Persistent Anal Infection MSM

Per Protocol Population

Endpoint	GARDASILTM (N=299)		Placebo (N=299)		Efficacy (%) (95% CI)
	n	# of cases	n	# of cases	
HPV 6/11/16/18	193	2	208	39	94.9 (80.4, 99.4)
HPV 6	140	1	144	13	92.1 (47.2, 99.8)
HPV 11	140	0	144	5	100 (-15.5, 100)
HPV 16	166	1	170	16	93.8 (60.0, 99.9)
HPV 18	172	0	193	10	100 (51.5, 100)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Month 7.

Efficacy against HPC 6/11/16/18 related AIN and anal cancer in MSM

Per Protocol Population

	Quadrivalent HPV vaccine (N=299)		Placebo (N=299)			
	n	Cases	n	Cases	Efficacy (%)	CI
HPV 6/11/16/18 related AIN and anal cancer	194	5	208	24	**77.5**	(39.6 to 93.3)
By lesion type						
AIN 1	194	4	208	16	**73.0**	(16.3 to 93.4)
Condyloma acuminata	194	0	208	6	**100**	(8.2 to 100)
Non-acuminate	194	4	208	11	**60.4**	(-33.5 to 90.8)
AIN 2 or worse	194	3	208	13	**74.9**	(8.8 to 95.4)
AIN 2	194	2	208	9	**75.8**	(-16.9 to 97.5)
AIN 3	194	2	208	6	**63.7**	(-103.0 to 96.4)
Anal cancer	194	0	208	0	**NA**	NA

Palefsky J, for the Male Quadrivalent HPV Vaccine Efficacy Trial Team. Quadrivalent HPV vaccine efficacy against anal intraepithelial neoplasia in men having sex with men. Presented at: EUROGIN 2010 Congress; February 17-20, 2010; Monte Carlo, Monaco. Abstract SS 19-2.

Vaccination of HIV-positive populations

- Questions:
    - 2) Is the vaccine safe in HIV+ men?
    - 3) Can HIV+ men and women mount good antibody titers?

Vaccination of HIV-positive populations

- Questions:
    - 4) Does the response to the vaccine vary according to CD4 level or use of HAART?
    - 5) Does vaccination prevent disease in individuals naive to the HPV types in the vaccines?
    - 6) Have immunosuppressed adults had too much prior exposure to the HPV types in the vaccines to make vaccination ineffective?

HPV vaccination of HIV+ children: PACTG 1047

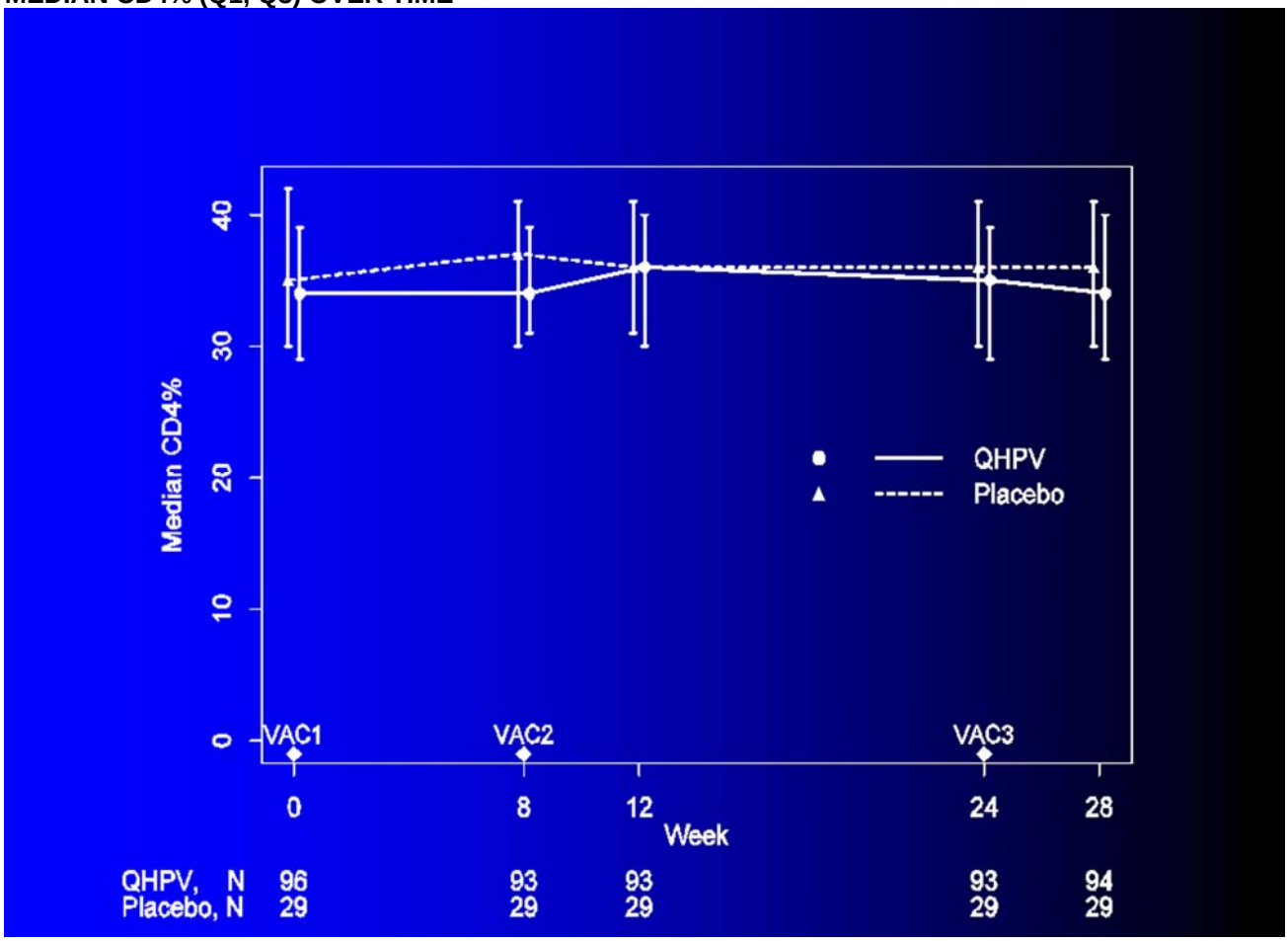
- 120 HIV+ children 7-12 years

- Safety
  - well-tolerated
- Immunogenicity
  - >99% seroconversion, titers for 11 and 16 same as historical controls, 6 and 18 lower

ADVERSE EVENTS WITHIN 14 DAYS AFTER FIRST VACCINATION: QHPV VS PLACEBO

	All Groups	
Adverse Event Categories	**QHPV**	**Placebo**
1: Ear & Eye & Respiratory System	1%	3%
2: Injection Site Reactions	7%	3%
3: Laboratory Abnormality	3%	3%
4: Systemic Reactions	2%	3%
5: Other	1%	3%
Number of Subjects	96	30

MEDIAN CD4% (Q1, Q3) OVER TIME



Safety in HIV-positive MSM AMC 052

- Vaccine did not change CD4 level or HIV viral load
- Vaccine was well-tolerated
    - No vaccine-related SAEs

Geometric mean titers among participants naïve to HPV 6, 11, 16, 18

	HPV 6 Month 7 (95% CI)	HPV 11 Month 7 (95% CI	HPV 16 Month 7 (95% CI)	HPV 18 Month 7 (95% CI)
Merck 020 HIV- HM	474 (447, 503)	652 (621, 684)	2622 (2485, 2767)	439 (416, 464)
AMC 052 HIV+ MSM	357 (256, 497)	525 (412, 669)	1139 (849, 1529)	181 (136, 241)

Geometric mean titers among participants naïve to HPV 6, 11, 16, 18

	HPV 6 Month 7 (95% CI)	HPV 11 Month 7 (95% CI	HPV 16 Month 7 (95% CI)	HPV 18 Month 7 (95% CI)
Merck 020 HIV- HM	474 (447, 503)	652 (621, 684)	2622 (2485, 2767)	439 (416, 464)
AMC 052 HIV+ MSM	357 (256, 497)	525 (412, 669)	1139 (849, 1529)	181 (136, 241)
Merck 020 HIV- MSM	274 (223, 338)	431 (348, 534)	1272 (996, 1623)	212 (170, 265)

Percentage of participants sero- and HPV DNA-negative to HPV 6/11/16/18

	Merck 020	AMC 052
	HIV-negative	HIV-positive
	Median age = 20 years	Median age= 44 years
	N= 602	N= 104
HPV 6	73	60
HPV 11	86	68
HPV 16	81	62
HPV 18	86	78

Summary- vaccination of HIV-positive individuals

- The vaccine appears to be safe in HIV-positive children and adult men
  - no evidence for perturbation of CD4 level or HIV viral load, other unexpected AEs.
- The vaccine appears to be immunogenic in this population although possibly not the same extent as HIV-negative historical controls.
- Vaccine efficacy is not known in this population.

Studies planned or in progress

- ACTG 5240 HIV+ women
- AMC 054- Indian HIV+ women
- AMC 052- HIV+ MSM, completed, fourth dose planned
- AMC 072/ATN - HIV+ MSM 13-26 years