Use of Human Papillomavirus Vaccines in HIV-infected Adults

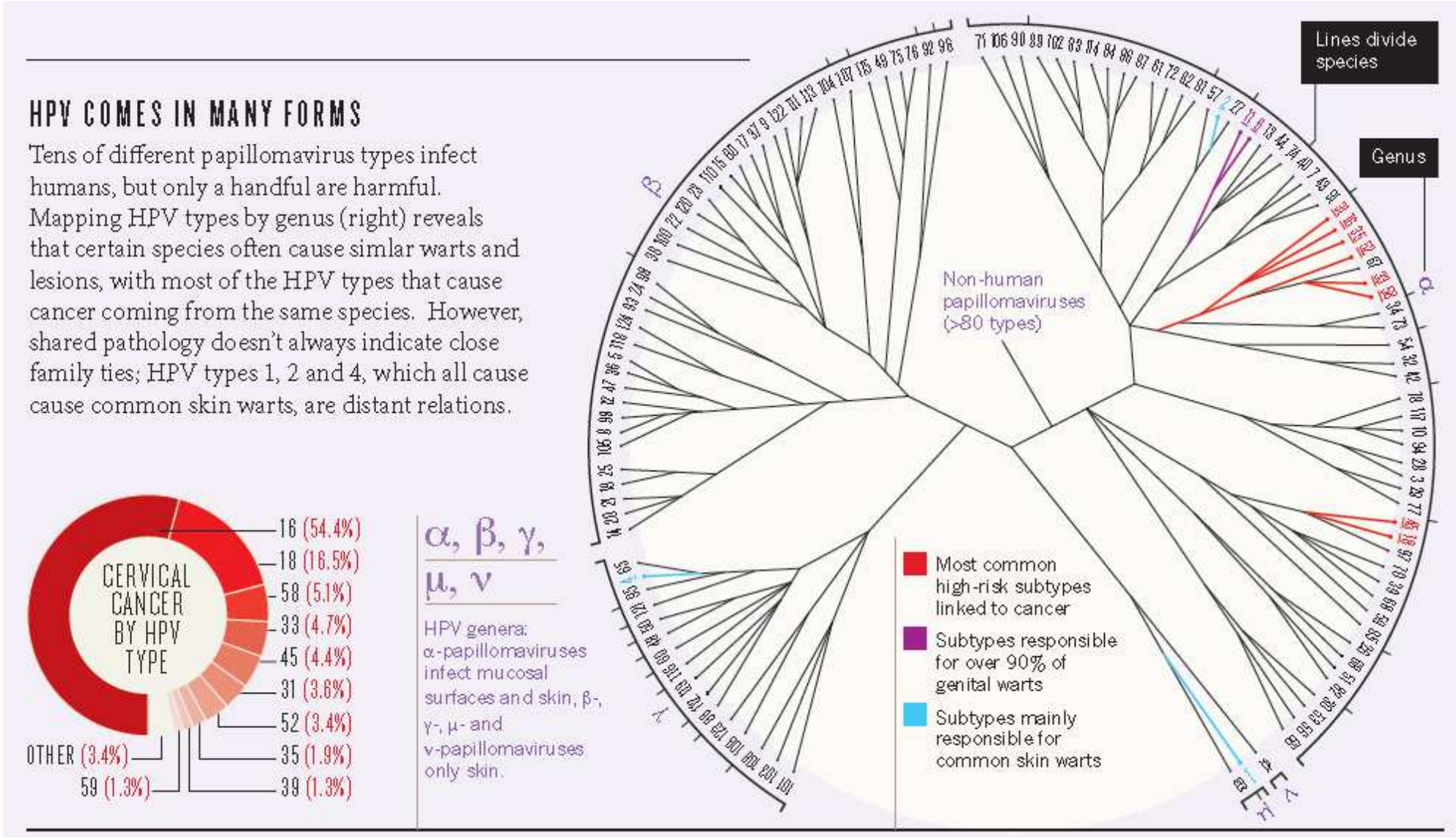
Christopher Mathews, M.D., MSPH

Professor of Clinical Medicine

UCSD Owen Clinic

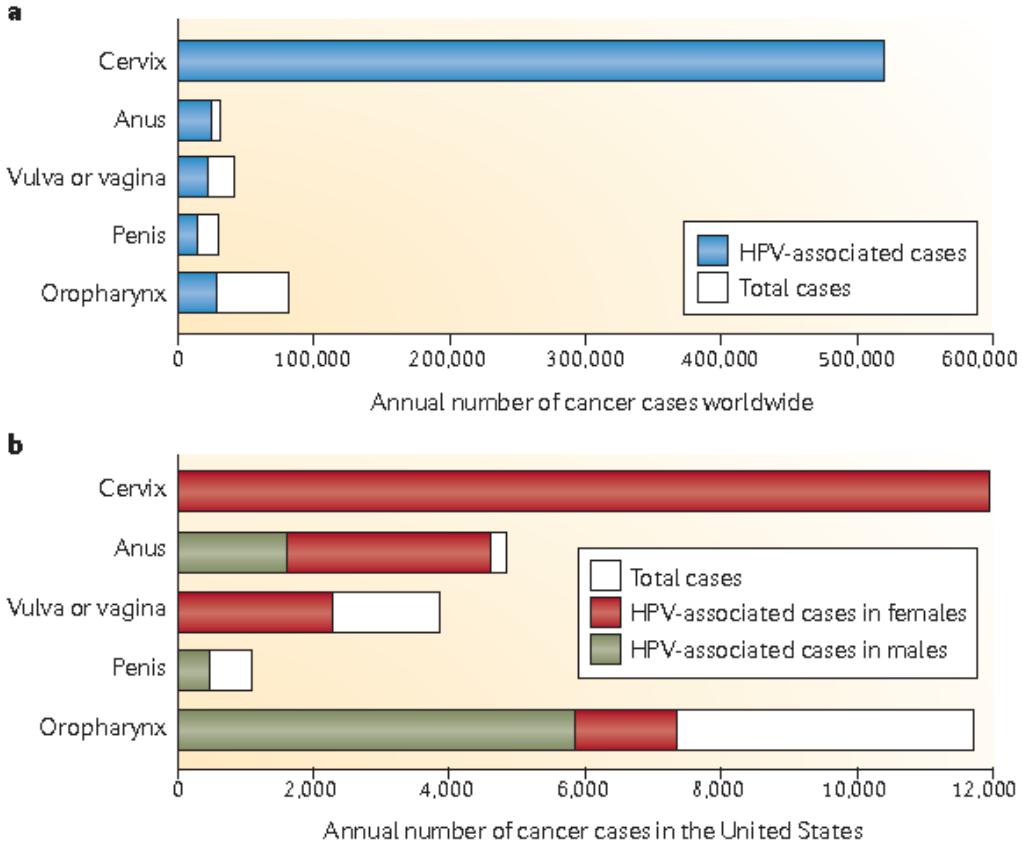
Outline

- HPV-associated cancer epidemiology
- Virus-like particle (VLP) HPV vaccines
  - Vaccine strain coverage and mechanisms of protection
- Key issues for HIV-infected populations
  - Cross protection against non-vaccine strains
  - Secondary prevention among those with prevalent HPV infections
- HPV-vaccine trials in HIV-infected populations
- Second generation VLP vaccines
- HPV therapeutic vaccines?



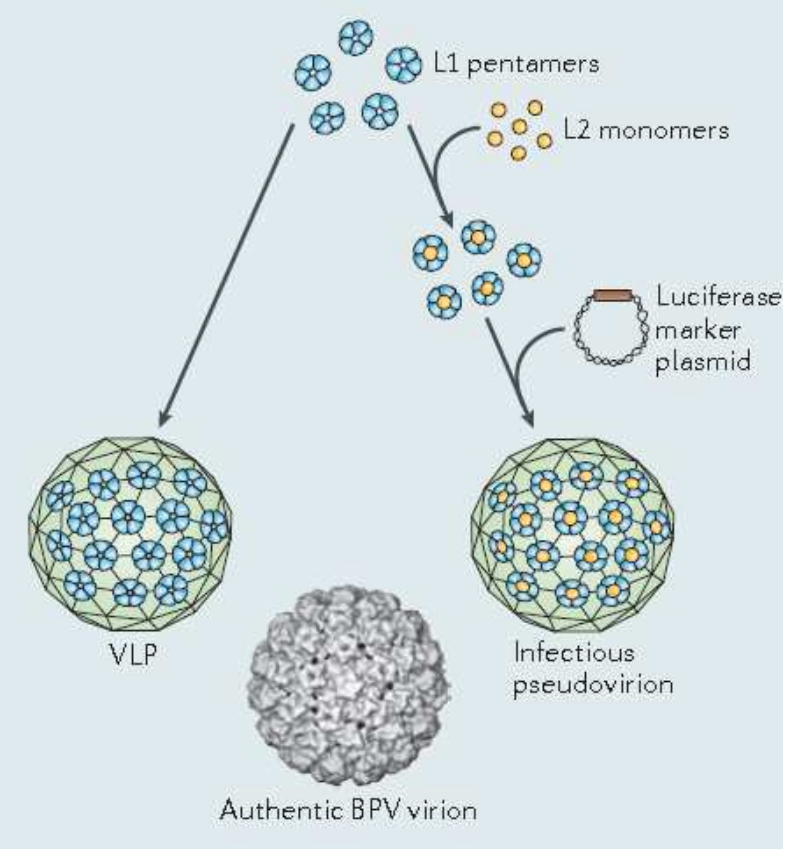
Crow. Nature. 2012 Aug 30;488(7413):S2-3

Prevalence of HPV-associated Cancers: Global & U.S.



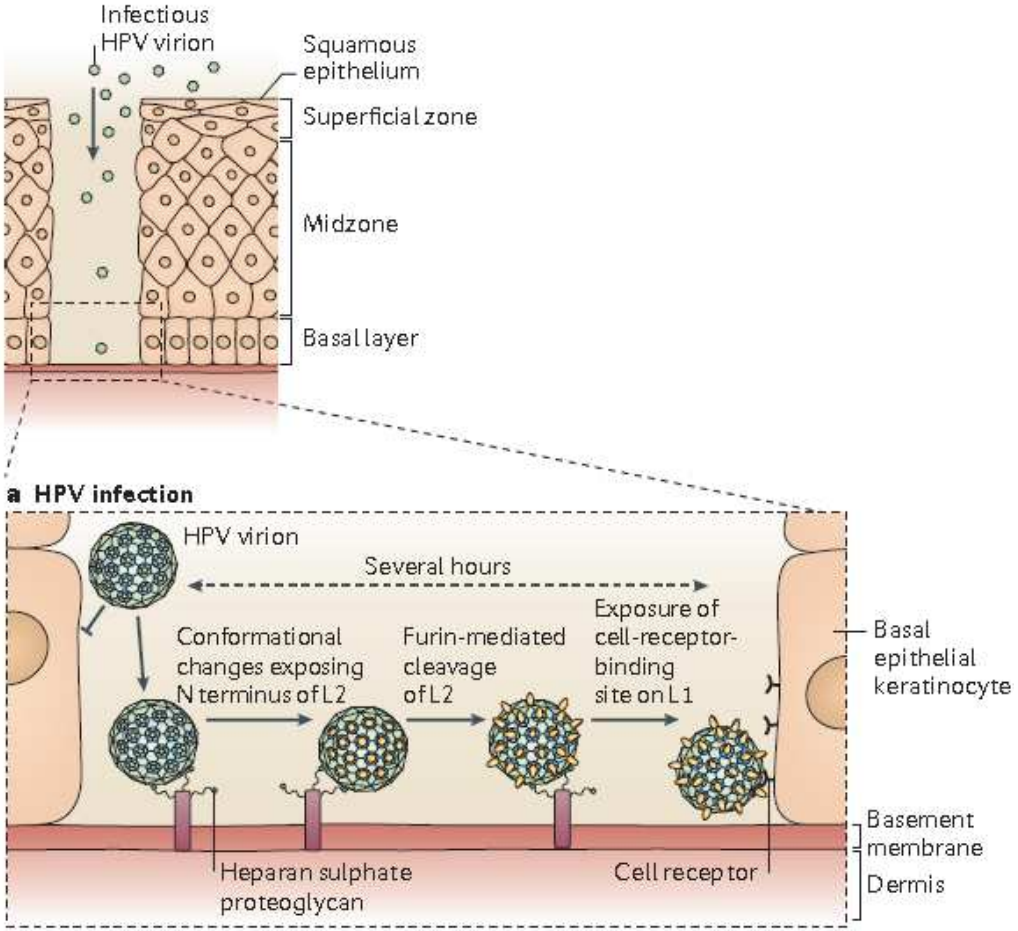
Schiller JT, Lowy DR. Nat Rev Microbiol. 2012 Oct;10(10):681-92

Papillomavirus Virion-related Structures



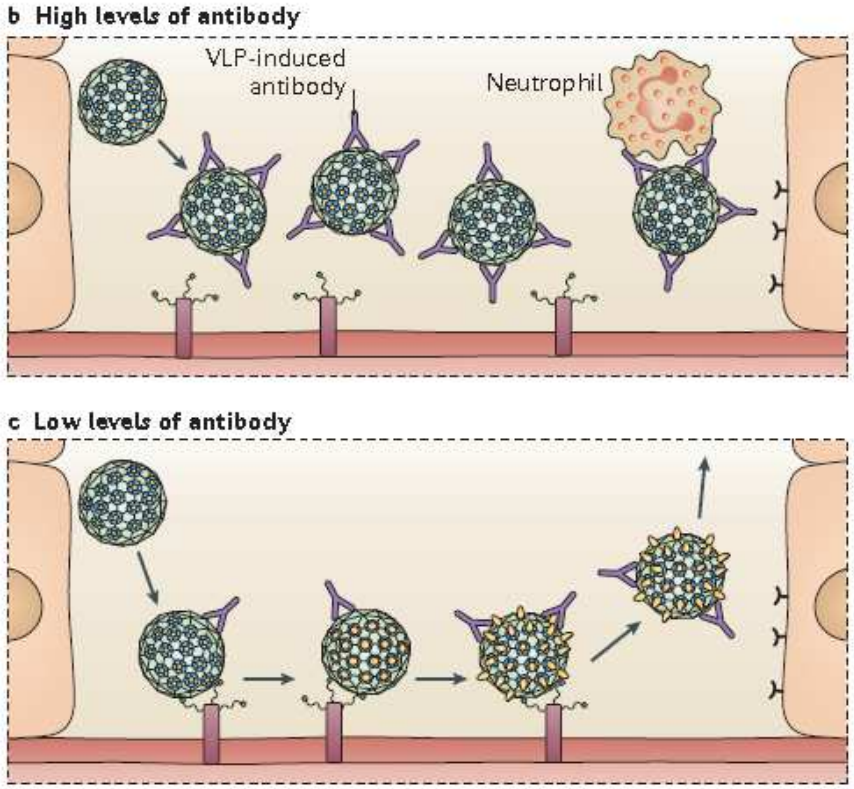
Schiller JT, Lowy DR. Nat Rev Microbiol. 2012 Oct;10(10):681-92

Mechanism of HPV Mucosal Infection



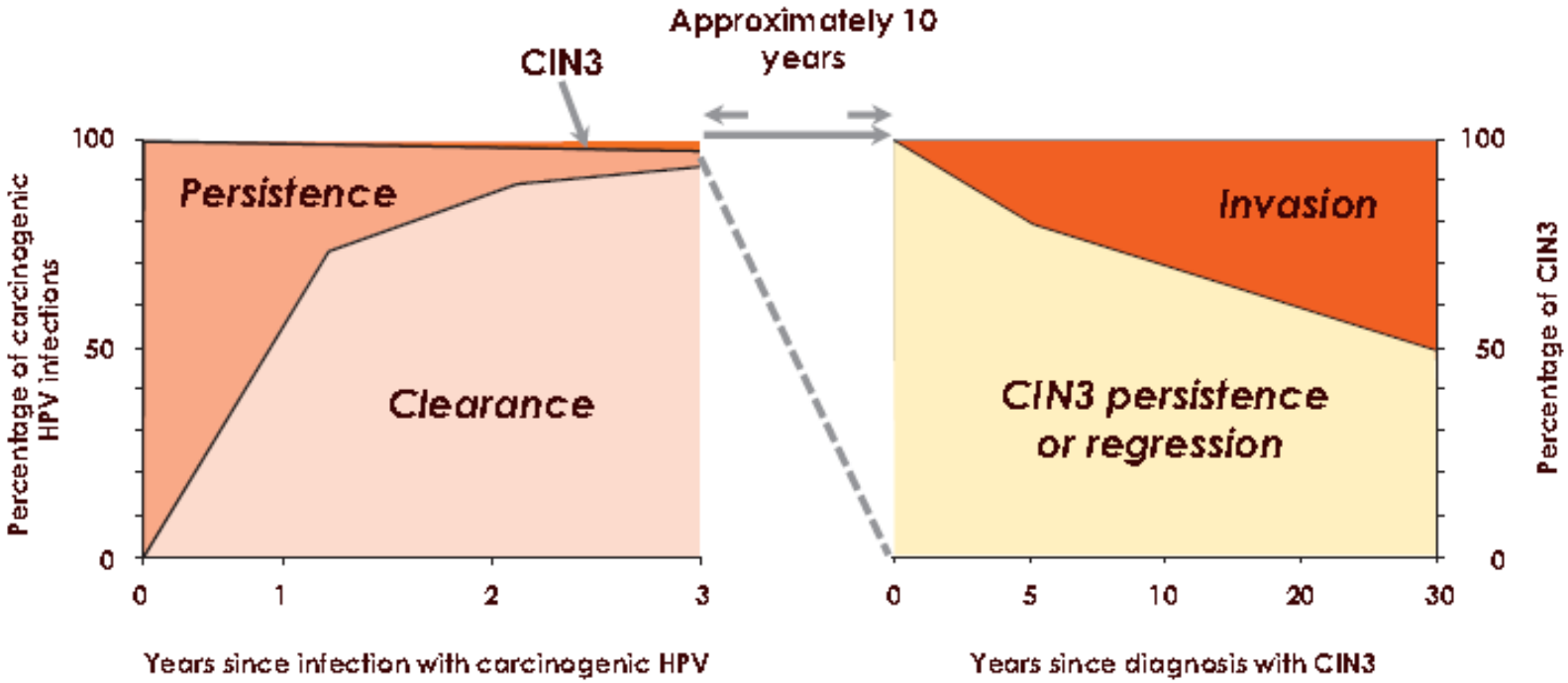
Schiller JT, Lowy DR. Nat Rev Microbiol. 2012 Oct;10(10):681-92

2 Mechanisms of Neutralizing Antibody-mediated Protection



Schiller JT, Lowy DR. Nat Rev Microbiol. 2012 Oct;10(10):681-92

Natural History of Cervical HPV Infection in Immunocompetent Women



Bosch FX et al. Vaccine. 2013 Nov 22;31 Suppl 8:I1-I31. doi: 10.1016/j.vaccine.2013.07.026.

High and Low Risk Human HPV Types

- Low Risk
  - **6, 11**, 40, 42, 43, 44, 53, 54, 61, 72, 73 and 81
- High Risk
  - **16, 18**, *31*, *33*, 35, 39, *45*, 51, *52*, 56, *58*, 59 and 68

Characteristics of Current L1-expressing VLP Vaccines

Table 1 | **Characteristics of commercial human papillomavirus virus-like particle-based vaccines**

	Cervarix	**Gardasil**
Manufacturer	GlaxoSmithKline Biologicals	Merck
VLP types included	HPV16 and HPV18	HPV6, HPV11, HPV16 and HPV18
Dose of L1 protein	20 μg from both types	20 μg (HPV6), 40 μg (HPV11), 40 μg (HPV16) and 20 μg (HPV18)
Producer cells	*Trichoplusia ni* (Hi 5) cell line infected with L1-recombinant baculovirus	*Saccharomyces cerevisiae* expressing L1
Adjuvant	500 μg aluminium hydroxide and 50 μg 3-*O*-deacylated-4′-monophosphoryl lipid A	225 μg aluminium hydroxyphosphate sulphate
Injection schedule	0, 1 and 6 months	0, 2 and 6 months

HPV, human papillomavirus; VLP, virus-like particle.

Schiller JT, Lowy DR. Nat Rev Microbiol. 2012 Oct;10(10):681-92

Efficacy of Current L1-expressing VLP Vaccines

Table 2 | **Efficacy of human papillomavirus virus-like particle-based vaccines***

End point‡	Sex of individuals	Age of individuals (years)	Vaccine	Trial requirement	Efficacy§ (95% CI)
CIN III	Female	15–25	Cervarix	ITT–naive‖	100% (90.5–100)
CIN III	Female	15–26	Gardasil	ITT–naive	100% (85.5–100)
Genital warts	Female	15–26	Gardasil	ITT–naive	96.4% (91.4–98.9)
AIN	Male	16–26	Gardasil	PPE¶	77.5% (39.6–93.3)
Genital warts	Male	16–26	Gardasil	PPE	89.4% (65.5–97.9)

Schiller JT, Lowy DR. Nat Rev Microbiol. 2012 Oct;10(10):681-92

Do VLP HPV Vaccines have a role in secondary prevention?

- qHPV vaccine did not clear pre-existing HPV infection or SIL in randomized controlled. (Hildesheim et al, JAMA 2007)
- HIV-infected MSM are infected with multiple strains of HPV, including oncogenic strains (Machalek et al, Lancet Oncol 2012)
- But 2 retrospective studies suggest VLP HPV vaccines may prevent recurrent cervical and anal disease after treatment
  - Joura BMJ 2012
  - Swedish CID 2012
- Not clear if patients with low levels of vaccine strain HPV antibodies who are HPV DNA negative may derive protection from HPV vaccines (Sadlier JID 2014)
- Clinical trials are needed

Effect of Quadrivalent HPV Vaccine on Pre-existing HPV Infection

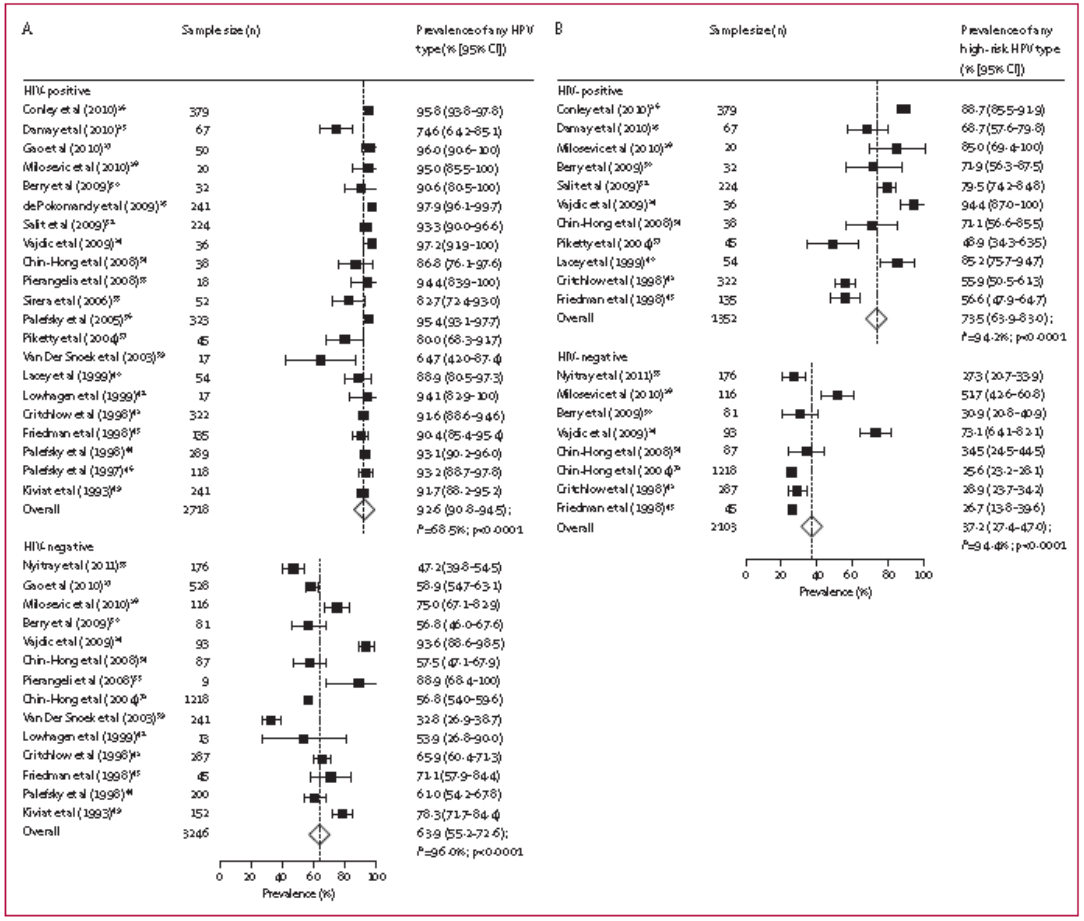
Table 2. Viral Clearance and Vaccine Efficacy for Viral Clearance for HPV-16 and HPV-18 by Study Group at 6 Months and 12 Months of Follow-up

Follow-up Time, mo	No. Cleared/Total Infections (%)[a]		Vaccine Efficacy for Viral Clearance, % (95% CI)
	HPV Vaccine Group	Control Group	
HPV-16			
6	47/172 (27.3)	61/222 (27.5)	−0.2 (−13.2 to 11.3)
12	54/123 (43.9)	73/159 (45.9)	−3.7 (−28.2 to 16.1)
HPV-18			
6	35/76 (46.1)	34/76 (44.7)	2.4 (−30.5 to 27.0)
12	32/54 (59.3)	37/61 (60.7)	−3.5 (−62.0 to 33.8)
HPV-16/18[b]			
6	82/248 (33.4)	95/298 (31.6)	2.5 (−9.8 to 13.5)
12	86/177 (48.8)	110/220 (49.8)	−2.0 (−24.3 to 16.3)
HPV-16/18 (restricted to women who received all vaccine doses)[c]			
6	81/241 (33.8)	93/288 (32.0)	2.6 (−10.1 to 13.8)
12	69/149 (46.5)	98/196 (50.0)	−7.0 (−31.7 to 13.0)
HPV-16/18 (restricted to women with single infections at entry)			
6	23/82 (28.0)	24/97 (24.7)	4.4 (−14.1 to 19.9)
12	28/63 (44.4)	37/79 (46.8)	−4.5 (−41.4 to 22.8)

Hildesheim et al. JAMA. 2007;298(7):743-753

Conclusion In women positive for HPV DNA, HPV-16/18 vaccination does not accelerate clearance of the virus and should not be used to treat prevalent infections.

Prevalence of PCR-detected Anal HPV among MSM, by HIV-status



Pooled Prevalence among HIV+ MSM:

Any HPV Genotype

92·6% (90·8–94·5)

Any high risk HPV Genotype

73·5% (63·9–83·0)

Machalek et al. Lancet Oncol. 2012 May;13(5):487-500 (Figure 2)

Prevalence of PCR-detected Anal HPV 16/18 among MSM, by HIV-status

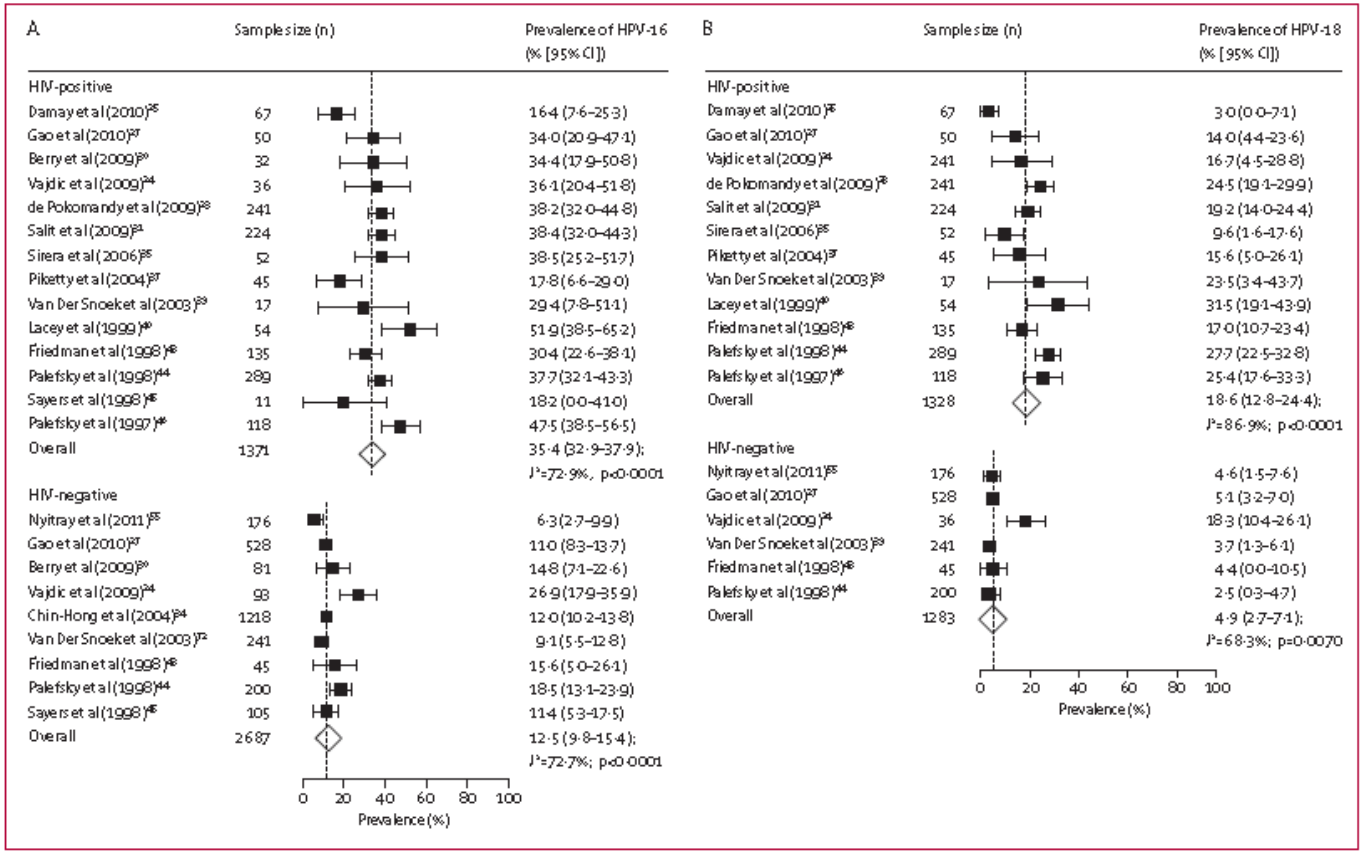


Figure 3: Prevalence of PCR-detected anal canal human papillomavirus (HPV)-16 (A) and HPV-18 (B) in men who have sex with men, by HIV status

Pooled Prevalence among HIV+ MSM:

HPV 16

35·4 (32·9–37·9)

HPV 18

18·6 (12·8–24·4)

Machalek et al. Lancet Oncol. 2012 May;13(5):487-500 (Figure 3)

Effect of Quadrivalent HPV Vaccine in Women Treated for Cervical or Vulvar HPV-related Disease

- Retrospective analysis of FUTURE I and FUTURE 2 Gardisil trials
- 2054 of 17 622 women underwent cervical surgery or were diagnosed with vaginal or vulvar intraepithelial neoplasia
- Of those who underwent cervical surgery, 587 received vaccine & 763 placebo
- The incidence of any subsequent HPV related disease was 6.6 and 12.2 in vaccine and placebo recipients respectively
  - 46.2% reduction (95% CI: 22.5% to 63.2% with vaccination)
- Vaccination was associated with a significant reduction in risk of any subsequent high grade disease of the cervix by 64.9% (20.1% to 86.3%).

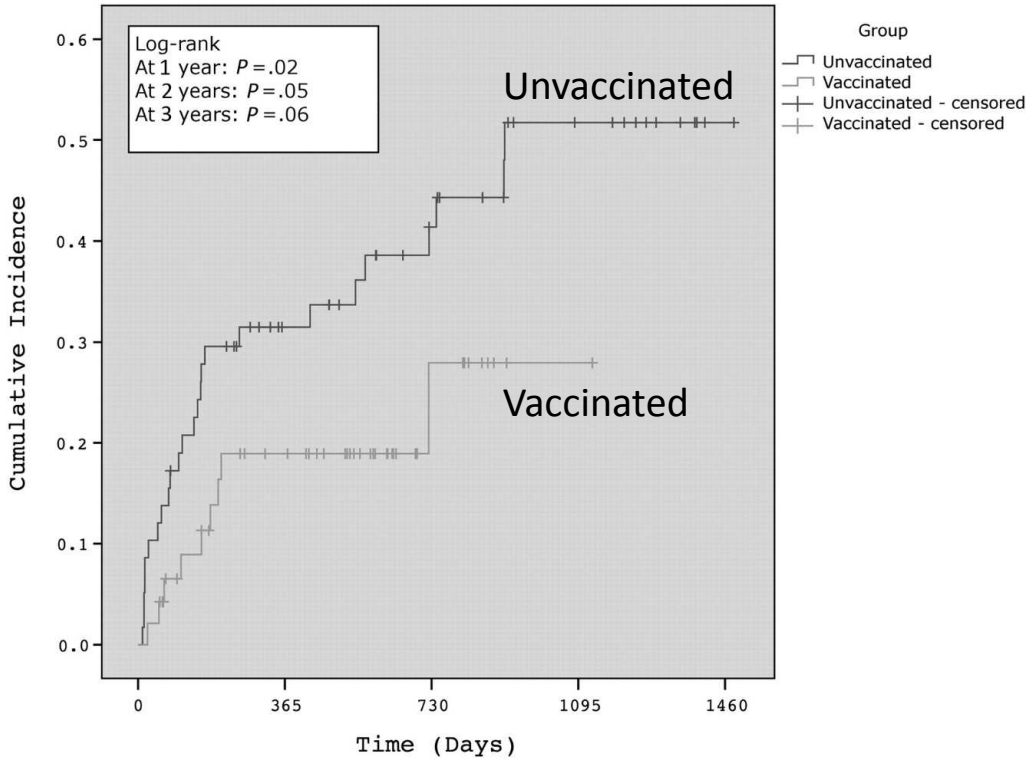
Joura et al. BMJ 2012 Mar 27;344:e1401.

Prevention of recurrent HGAIN with qHPV vaccination of MSM: a nonconcurrent cohort study

- 202 patients with a history of previously treated HGAIN.
  - One-third HIV-infected
  - 84 were vaccinated, and 114 were unvaccinated
- During 340.4 person-years follow-up, 12 (13.6%) vaccinated patients and 35 (30.7%) unvaccinated patients developed recurrent HGAIN.
- Testing positive for oncogenic HPV genotypes within 8 months before study entry was associated with increased risk of recurrent HGAIN at 2 years after study entry
  - HR 4.06; 95% CI: 1.58–10.40
- qHPV was associated with decreased risk of recurrent HGAIN
  - HR .50; 95% CI: 0.26–0.98

Swedish K A et al. Clin Infect Dis. 2012;54:891-898

Time to recurrence of high-grade anal neoplasia among vaccinated and unvaccinated oncogenic human papillomavirus–infected men who have sex with men with a history of high-grade anal neoplasia, New York City, April 2007–April 2011 (n = 105).



VACCINATED				
No. of cases	0	8	9	9
No. remaining	47	29	8	1
UNVACCINATED				
No. of cases	0	18	22	25
No. remaining	58	31	20	9

Swedish K A et al. Clin Infect Dis. 2012;54:891-898

Why would VLP HPV vaccination be effective in preventing recurrent HPV-related disease?

- VLP vaccine does not clear pre-existing HPV infection or treat pre-existing SIL (Hildesheim JAMA 2007)
- Possible mechanism of secondary preventive effect (Swedish CID 2012)
  - Antibody levels, much higher after vaccination than natural infection, prevent viral binding to the basement membrane and entry into basal cells
  - Mutated epithelial cells with integrated virus in the primary disease were removed at treatment,
    - but cells with free nuclear HPV were left behind.
  - qHPV antibodies prevent host reinfection.
  - Reinfection would increase risk of integration and neoplasia, but antibody response stops the cascade, reducing the risk of recurrent high-grade cervical and anal neoplasia.

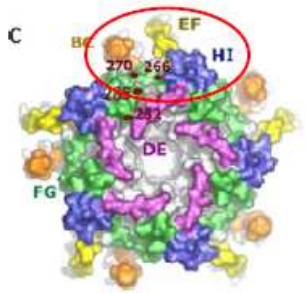
Is there cross-protection against non-vaccine strains with current VLP HPV vaccines?

- HPV type distribution in squamous cell cervical cancer[1]
  - HPV 16/18: 70%
  - HPV 16/18/45: 75%
  - HPV 31/33/35/52/58: 15%
- HPV type distribution in squamous cell anal cancer[2]
  - HPV 16: 73.4%
  - HPV 18: 5.2%
  - HPV 33: 4.8%
- So existing VLP HPV vaccines cover about 70% (cervical) and 79% (anal) strains associated with invasive SCC

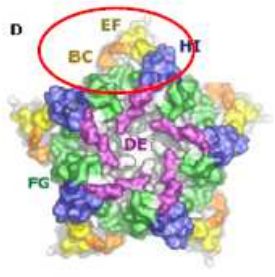
1. De Vincenzo et al. Gyn Oncol 2013; 130:642-651
2. De Vuyst et al. Int. J. Cancer 2009; 124: 1626–1636

Is there cross-protection against non-vaccine strains with current VLP HPV vaccines?

R. De Vincenzo et al. / Gynecologic Oncology 130 (2013) 642–651



HPV 16
Species A9



HPV 18
Species A7

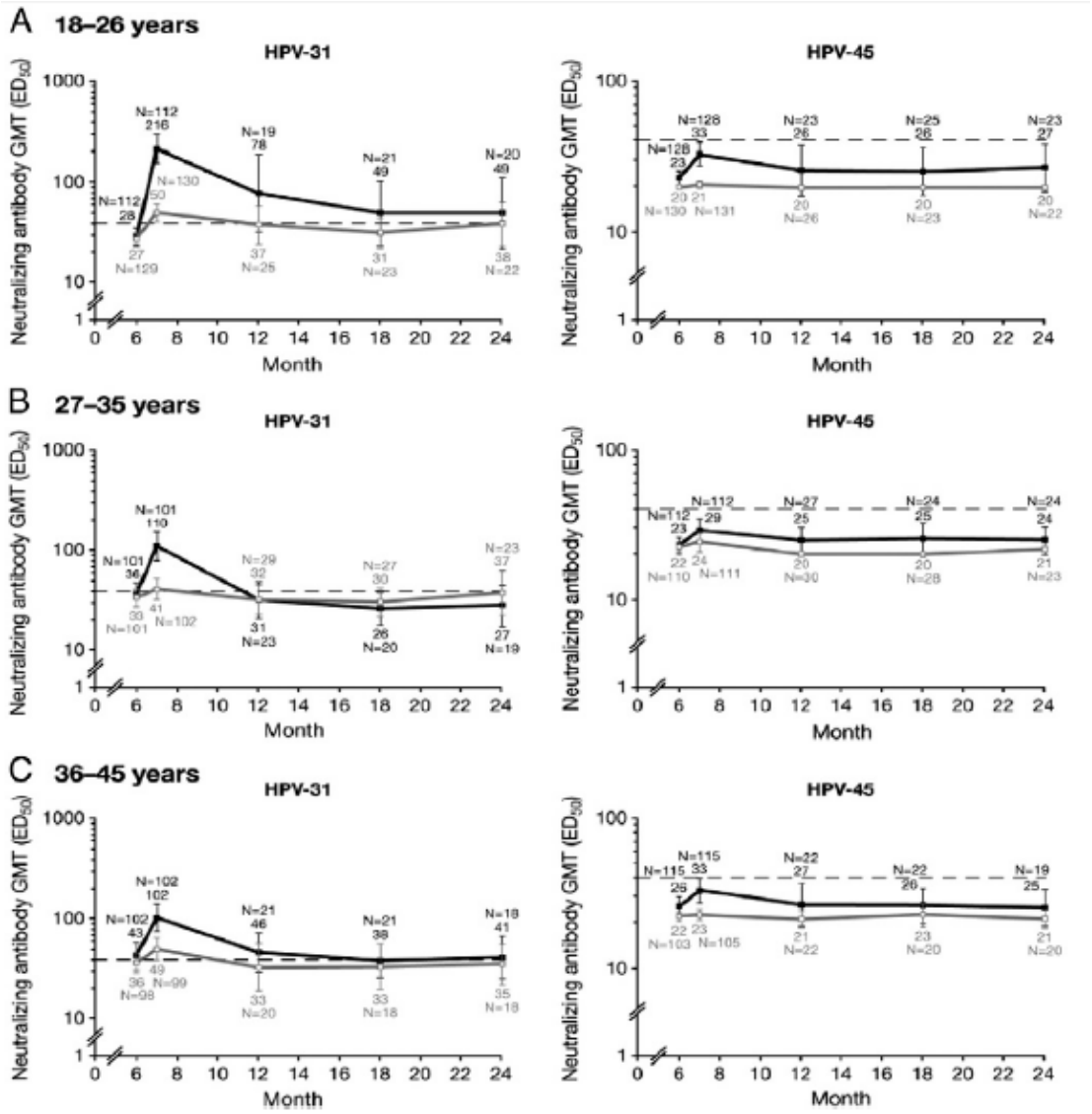
HPV Type	Species	L1 homology
HPV 16	**A9**	
HPV 45	*A7*	*67%*
HPV 31	**A9**	**83%**
HPV 33	**A9**	**81%**
HPV 52	**A9**	**80%**
HPV 58	**A9**	**80%**
HPV 35	**A9**	**82%**
HPV 59	*A7*	*65%*
HPV 39	*A7*	*64%*

HPV Type	Species	L1 homology
HPV 18	**A7**	
HPV 45	**A7**	**88%**
HPV 31	*A9*	*66%*
HPV 33	*A9*	*66%*
HPV 52	*A9*	*66%*
HPV 58	*A9*	*66%*
HPV 35	*A9*	*65%*
HPV 59	**A7**	**78%**
HPV 39	**A7**	**77%**

Fig. 1. Evaluation of analogies in amino acid structure of L1 protein.

Focus on L1 homology

De Vincenzo et al. Gyn Oncol 2013; 130:642-651



Einstein et al. Hum Vaccin. 2011;7(12):1359-73

HEAD to HEAD immunogenicity trial of qHPV & bHPV vaccines

- No difference between vaccine effects on nAb at 24 mo
- Higher T cell responses for bHPV vaccine
- Highest nAb titers for youngest age group
- Higher nAb titers for HPV-31 than HPV-45
- Titers peak at 6-8 mo and then plateau
- Non-vaccine titers 100-fold lower than vaccine strain titers

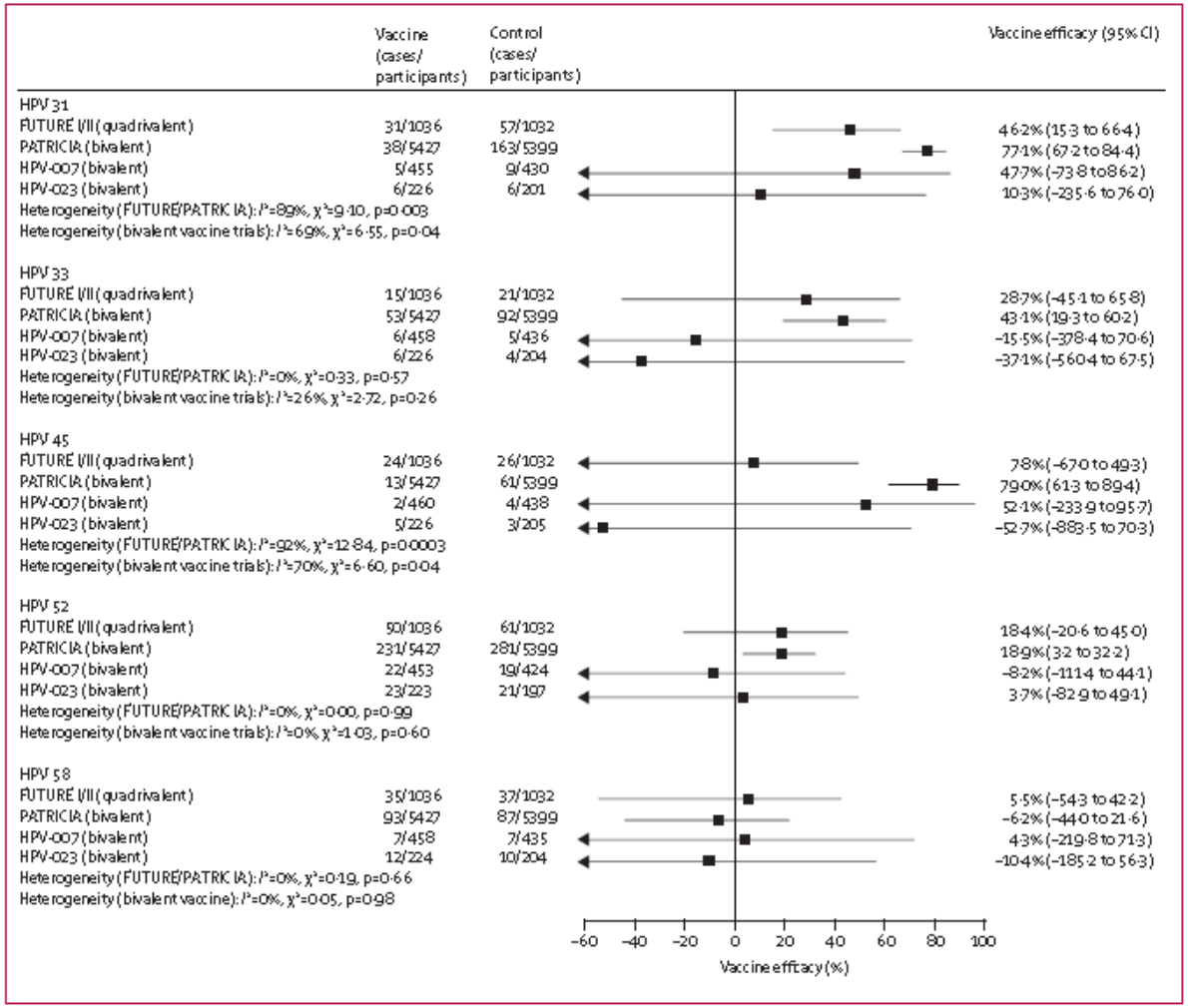


Figure 2: HPV vaccine efficacy against persistent infection (≥6 months) with individual non-vaccine type HPVs
HPV=human papillomavirus. NA=not available, not reported, or not assessable.

Meta-analysis examining vaccine efficacy for non-vaccine types (31, 33, 45, 52, 58) in HPV-naïve populations

- qHPV efficacious for outcomes against HPV 31
- bHPV efficacious for outcomes vs. HPV 31/33/45
- bHPV higher point estimates of vaccine efficacy vs. HPV 31/33/45, but not statistically significant
- Very little cross protection with either vaccine vs. HPV 31/45
- Possible waning of cross-protection vs. HPV 31/45 with bHPV in longer followup trials

Malagon et al. *Lancet Infect Dis* 2012;12: 781–89

What explains observed cross-protective effects?

- Differences in cross-protection between qHPV & bHPV vaccines
  - Could be due to differences in clinical trial characteristics
    - Type distributions, end points, assays, multiple infections, patient characteristics, post-hoc analysis, etc.
  - Could be due to different vaccine adjuvants (Schiller & Lowy, 2012)
    - Gardasil (quadrivalent)
      - Aluminium
      - Induces T_H2 response
    - Cervarix (bivalent)
      - Aluminium + MPL A
      - Induces T_H1 response
      - TLR4 agonist activates innate immune response

Clinical Trials of VLP HPV Vaccines in HIV-infected Patients

- Safety and immunogenicity of qHPV vaccine in HIV-infected children ages 7-12 [IMPAACT trial] (Levin et al, JAIDS 2010)
- Safety and immunogenicity of qHPV vaccine in HIV-infected men ([AMC 052] (Wilkin et al, JID 2010)
- Safety and immunogenicity of bHPV vaccine in HIV-infected women in South Africa (Denny et al, Vaccine 2013)

Quadrivalent VLP HPV Vaccine in HIV+ Pre-Adolescent Children

- HIV-infected children (N = 126)—age >7 to <12 years
  - with a CD4% ≥ 15—and on stable antiretroviral therapy if CD4% was ≤ 25
- Blindly assigned to receive a dose of QHPV or placebo (3:1 ratio) at 0, 8, and 24 weeks.
- QHPV did not alter the CD4% or plasma HIV RNA.
- Seroconversion to all 4 antigens occurred in > 96% of QHPV recipients and in no placebo recipients.
- Geometric mean titer was >27 to 262 times more seropositivity cutoff value, depending on the antigen (6,11,16,18)
  - but was 30%–50% lower against types 6 and 18 than those of age-similar historical controls.

Levin et al. J Acquir Immune Defic Syndr 2010;55:197–204

Safety and Immunogenicity of the QHPV Vaccine in HIV-1–Infected Men: Baseline Characteristics

- N=112 HIV+ men
- Median cells/mL (IQR) 517 (423–680)
- Nadir Median cells/mL (IQR) 226 (143–337)
- On ART: 84%
- Plasma HIV-1 RNA levela
  - <200 copies/mL 83%
  - 200–9,999 copies/mL 9%
  - ≥ 10,000 copies/mL 8%

Wilkin et al. J Infect Dis 2010 Oct 15;202(8):1246–53.

Safety and Immunogenicity of the QHPV Vaccine in HIV-1–Infected Men: Summary

- No grade 3 or greater adverse events attributable to vaccination
- Seroconversion was observed for all 4 types:
  - type 6: 59 [98%] of 60
  - type 11: 67 [99%] of 68
  - type 16: 62 [100%] of 62
  - type 18: 74 [95%] of 78
- No adverse effects on CD4 counts and plasma HIV-1 RNA levels were observed.
- Induced antibody levels 40-50% lower than in non-HIV+ vaccine trial participants
  - But still much higher than levels observed after natural HPV infection

Wilkin et al. J Infect Dis 2010 Oct 15;202(8):1246–53.

Bivalent HPV Vaccine in HIV+ Women

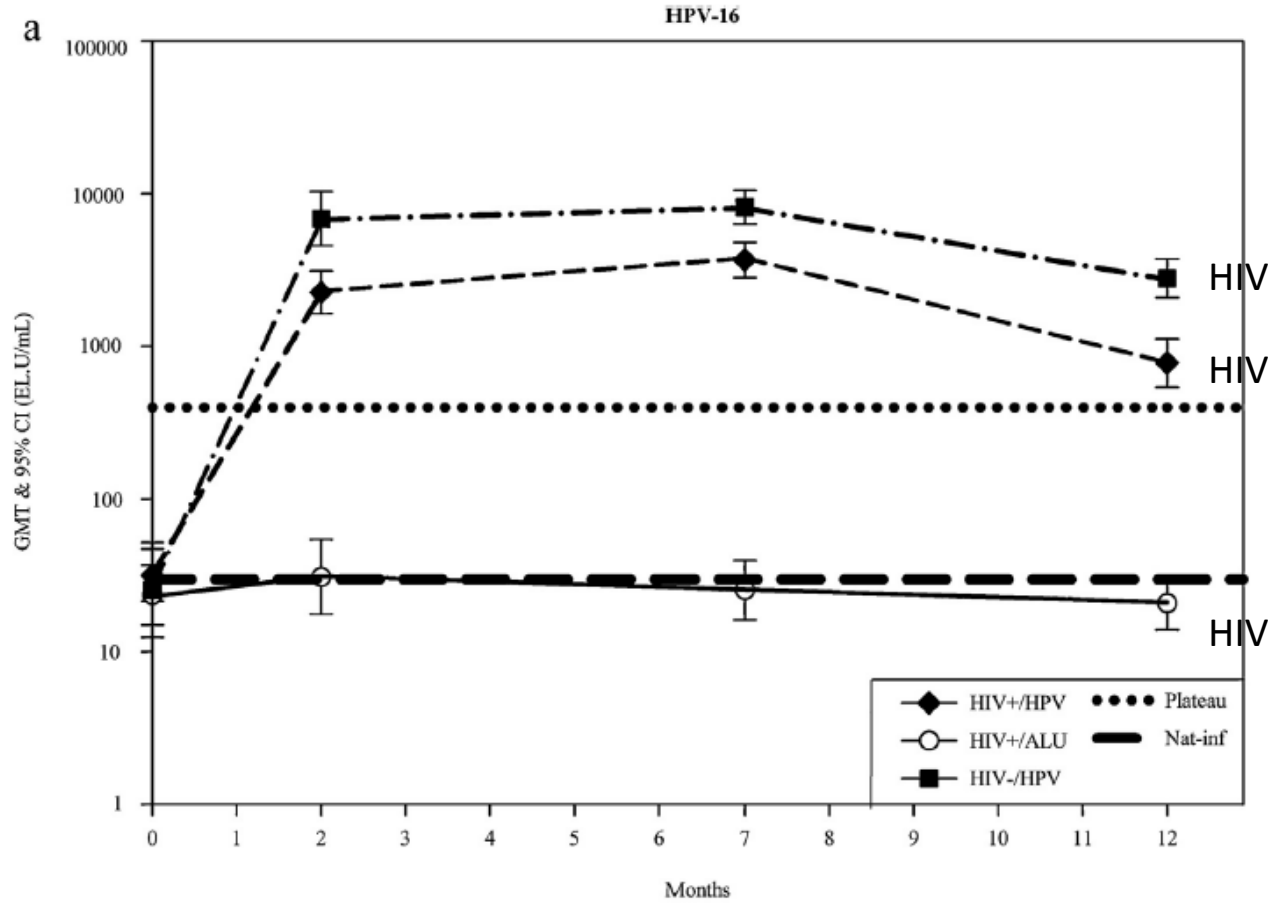
Table 1
Baseline demographics and HIV disease characteristics (TVC).

	HIV+/HPV ($N = 61$)	HIV+/ALU ($N = 59$)
Mean age, years (SD)	21.6 (2.21)	22.7 (1.70)
Mean weight, kg (SD)	67.9 (13.53)	67.6 (15.36)
Ethnicity, n (%) African	61 (100)	59 (100)
CD4+ T-cell count distribution, n (%)		
<200 cells/mm^3	2 (3.3)	1 (1.7)
200–500 cells/mm^3	35 (57.4)	37 (62.7)
>500 cells/mm^3	24 (39.3)	21 (35.6)
CD4+ T-cell count, cells/mm^3		
Median	451	458
Range	170–1314	156–1253
HIV viral load, copies/ml		
Median	23,310	23,100
Range	1–436316	136–531098
WHO Clinical Stage 1, n (%)	61 (100)	59 (100)
ART, n (%)	1 (1.6)	1 (1.7)

L. Denny et al. Vaccine *31 (2013) 5745– 5753*

Bivalent HPV Vaccine in HIV+ Women: HPV-16 Response

Geometric Mean Titer



HIV negative/bHPV vaccine

HIV positive/bHPV vaccine

Natural infection

HIV positive/Adjuvant only

L. Denny et al. Vaccine *31 (2013) 5745– 5753*

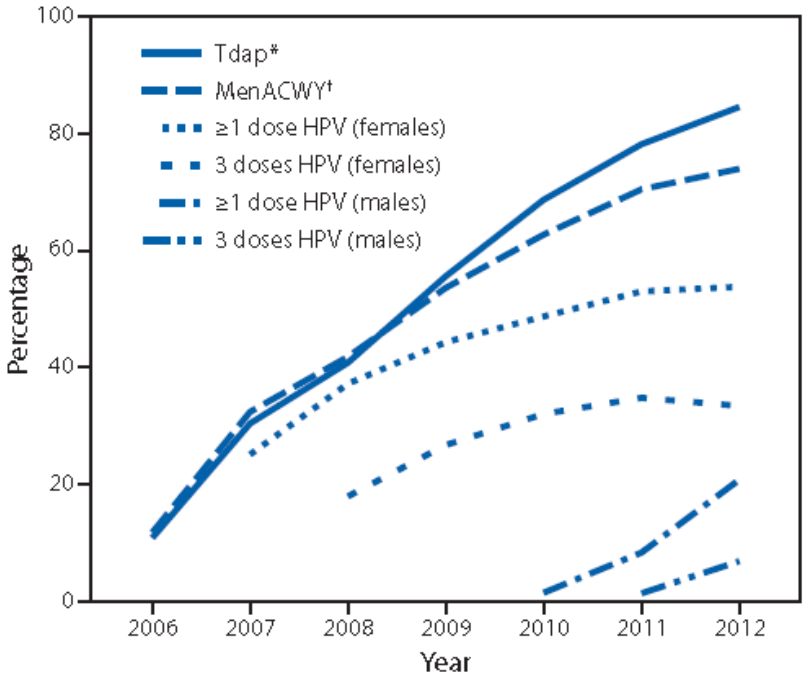
Bivalent HPV Vaccine in HIV+ Women

- The HPV-16/18 vaccine induced sustained *anti-HPV-16/18 CD4+T-cell responses* in both HIV-positive and HIV-negative women.
- No impact of baseline CD4+T-cell count or HIV viral load was observed on the magnitude of the immune response in HIV-positive women.
- In HIV-positive women,CD4+T-cell count, HIV viral load and HIV clinical stage were unaffected by HPV-16/18 vaccine administration.
- NOTE: <3% of participants had CD4<200 on enrollment although median CD4~450 cells/mm^3

L. Denny et al. Vaccine *31 (2013) 5745– 5753*

HPV Vaccine Coverage: USA and Spain

FIGURE. Estimated vaccination coverage with selected vaccines and doses among adolescents aged 13–17 years, by survey year — National Immunization Survey–Teen, United States, 2006–2012



MMWR 2014;63:69-72

- On the basis of the available data, the Spanish Ministry of Health estimated that coverage
  - for the first dose was 87.2% (range: 73.9–98.9%)
  - and 77.3% (range: 62.2–97.4%) for the third dose.

Limia et al. Euro Surveill. 2011;16(21):pii=19873

Second Generation Preventive HPV Vaccines

- Nonavalent VLP vaccine (Gardasil 9)
  - Phase III efficacy trial completed (Merck)
  - In addition to the four types in Gardasil., contains L1 VLPs of types 31, 33, 45, 52 and 58.
  - Even if the vaccine is entirely type-specific (no cross-protection)
    - would have the potential to prevent approximately 90% of cervical, vulvar, vaginal and anal cancer-associated HPV infections
  - Licensed by FDA in Dec 2014 for females (ages 9-26) & males (ages 9-15)
- L2 HPV vaccines
  - L2 contains broad cross-neutralizing epitopes
  - Antibody titers to L2 epitopes lower than homologous titers to VLP-based immunogens

Schiller JT, Lowy DR. *Nat Rev Microbiol*. 2012 Oct;10(10):681-92
Drolet et al. *International journal of cancer.* 2014;134(9):2264-2268.

IDSA Guideline Recommendations for HPV Vaccination of HIV-infected Patients

- Quadrivalent human papillomavirus (HPV4) vaccine in females and males aged 11–26 years (strong recommendation, very low quality evidence)
- HPV4 vaccine is recommended over bivalent human papillomavirus (HPV2) vaccine because HPV4 vaccine prevents genital warts (strong recommendation, low evidence)
  - although there are no data on differences between the vaccines for preventing cervical dysplasia in HIV-infected women.

Rubin et al. CID 2013 (available at: http://www.idsociety.org/Templates/Content.aspx?id=32212256011)

JCVI Recommendation to NHS UK (Nov 2014)

"The Committee has therefore concluded that a programme for the vaccination of MSM aged 16 to 40 years should be implemented in GUM and HIV clinics in the UK using the quadrivalent HPV vaccine, subject to the programme being commissioned and implemented at a cost-effective price."

https://www.gov.uk/government/publications/interim-statement-on-hpv-vaccination-of-men-who-have-sex-with-men

European AIDS Clinical Society (EACS) Statement on HPV Vaccine

Infection	Vaccination rationale in HIV+ persons	Comment
Human Papilloma Virus (HPV)	Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer	If HPV infection is established, efficacy of vaccine is questionable

EACS 7.1, Nov. 2014. Available at: http://www.eacsociety.org/files/guidelines_english_71_141204.pdf

Key unanswered questions re HPV vaccination of HIV infected adults

- Although HPV vaccination does not clear existing HPV infection or clear existing cancer precursors (Hildesheim JAMA 2007)
  - Is there a benefit in preventing new endogenous or exogenous re-infection?
  - Is there a benefit in preventing new or recurrent cancer precursors?
  - Is there a benefit in preventing invasive cancer?
- If there is a benefit in preventing re-infection, cancer precursors, or invasive cancer
  - Is vaccination with existing vaccines cost-effective given the high prevalence of pre-existing multiple HPV infections in HIV-infected adults (especially MSM)?
- Can diagnostic modalities (serology and site-specific PCR or antigen assays) play a role in identifying HIV-infected adults who could benefit from HPV vaccination?

What about HPV Therapeutic Vaccine Development?

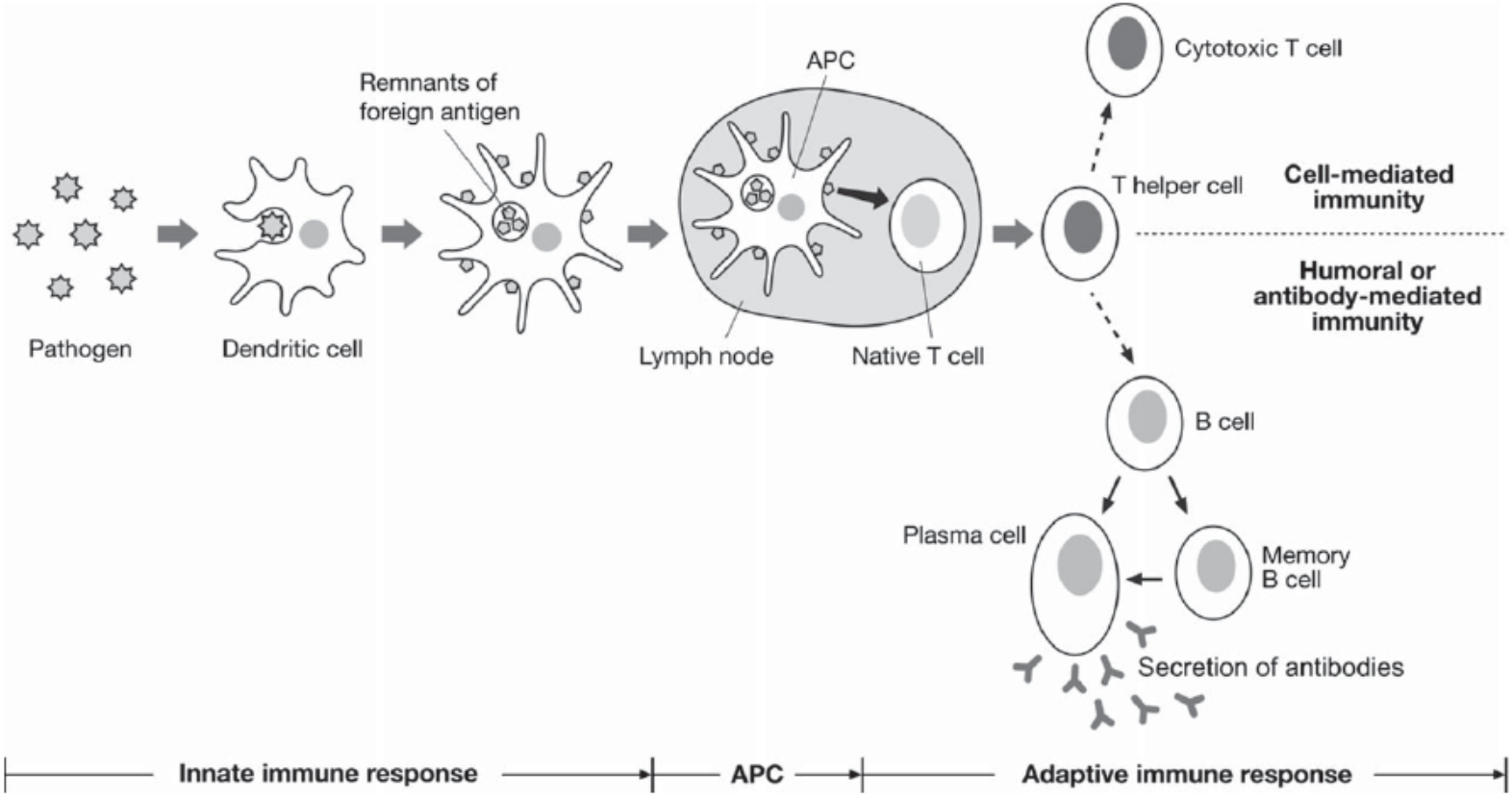


Figure 1. A summary of the innate and adaptive immune responses. APC, antigen-presenting cell.

Meyer et al. Acta Obstet Gynecol Scand 2014; DOI: 10.1111/aogs.12480

MHC-restriction of T-cell Responses

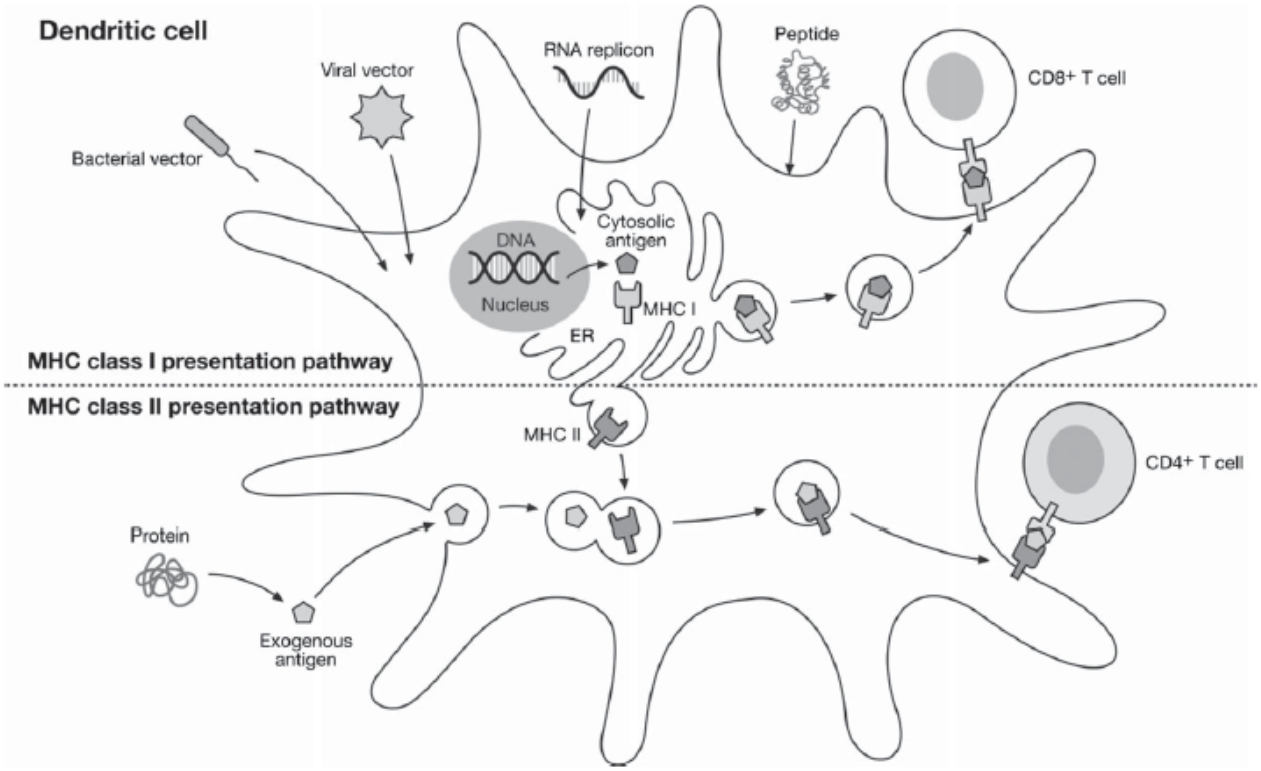


Figure 2. Therapeutic human papillomavirus (HPV) vaccine approaches to the dendritic cell. Peptide based, RNA replicon based, bacterial vector based and viral vector based vaccines deliver antigen for presentation via the MHC class I pathway to cytotoxic T cells ($CD8^+$). Protein based vaccines deliver proteins to be presented by the MHC class II pathway to activate T helper cells ($CD4^+$). CD, cluster of differentiation; MHC, major histocompatibility complex; RNA, ribonucleic acid.

Meyer et al. Acta Obstet Gynecol Scand 2014; DOI: 10.1111/aogs.12480

What about HPV Therapeutic Vaccine Development?

- The HPV nonstructural early proteins E6 and E7 are expressed in HPV-transformed neoplastic cells as well as throughout the life cycle of the virus in contrast to the structural capsid late proteins (L1 and L2) of HPV.
- L1 and L2 are expressed only in fully differentiated keratinocytes of the epithelium.
- Spontaneous regression of high grade CIN has been consistently associated with cellular immune responses to E-6 & E-7 peptides
- Hence, therapeutic vaccines targeting the early proteins E6 and E7 may provide the best opportunity to control HPV-associated premalignancies and malignancies already present.

Meyer et al. Acta Obstet Gynecol Scand 2014; DOI: 10.1111/aogs.12480

Selected References

1. Schiller JT, Lowy DR. Understanding and learning from the success of prophylactic human papillomavirus vaccines. *Nat Rev Microbiol.* Oct 2012;10(10):681-692.
2. Cachay ER, Mathews WC. Use of Human Papillomavirus Vaccine in HIV-infected Men for the Prevention of Anal Dysplasia and Cancer. *AIDS Reviews.* Apr-Jun 2014;16(2):90-100.
3. Meyer SI, Fuglsang K, Blaakaer J. Cell-mediated immune response: a clinical review of the therapeutic potential of human papillomavirus vaccination. *Acta Obstet Gynecol Scand.* Aug 21 2014.
4. Morrow MP, Yan J, Sardesai NY. Human papillomavirus therapeutic vaccines: targeting viral antigens as immunotherapy for precancerous disease and cancer. *Expert Rev Vaccines.* Mar 2013;12(3):271-283.

Backup Slides

Quadrivalent VLP HPV Vaccine in HIV+ Children: Baseline Characteristics

	All Groups	
Parameters (Categorical Levels)	**QHPV (95% CI)**	**Placebo (95% CI)**
n	96	30
Age (y)	10 (9.7 to 10.3)	9.9 (9.4 to 10.4)
CD4 count	868 (794 to 942)	1013 (843 to 1183)
CD4%	33.9 (32.3 to 35.5)	35.8 (32.6 to 39)
Ethnicity (%)		
White, non-Hispanic	4 (4)	2 (7)
Black, non-Hispanic	54 (56)	11 (37)
Hispanic	37 (39)	14 (47)
Others	1 (1)	3 (10)
Gender (%)		
Male	43 (45)	12 (40)
Female	53 (55)	18 (60)
Log_{10} (RNA)	2.7 (2.5 to 2.9)	2.6 (2.3 to 2.9)
RNA group (%)		
<400 copies/mL	65 (68)	22 (73)
401 to <5000 copies/mL	16 (17)	5 (17)
>5000 copies/mL	15 (16)	3 (10)

Levin et al. J Acquir Immune Defic Syndr 2010;55:197–204

Quadrivalent VLP HPV Vaccine in HIV+ Children: Seroconversion Results

TABLE 4. HPV Type–Specific Seroconversion: QHPV Vs Placebo*

	Group 1		Group 2		Group 3		All Groups†	
Serotype	QHPV	Placebo	QHPV	Placebo	QHPV	Placebo	QHPV	Placebo
6	100% (29/29)	0% (0/9)	100% (29/29)	0% (0/10)	100% (29/29)	0% (0/8)	100% (87/87)	0% (0/27)
11	100% (30/30)	0% (0/9)	100% (30/30)	0% (0/10)	100% (30/30)	0% (0/8)	100% (90/90)	0% (0/27)
16	100% (29/29)	0% (0/9)	100% (30/30)	10% (1/10)	100% (31/31)	0% (0/8)	100% (90/90)	4% (1/27)
18	90% (27/30)	0% (0/9)	100% (30/30)	0% (0/10)	100% (30/30)	0% (0/8)	97% (87/90)	0% (0/27)

*Seroconversion was measured at week 28 after beginning the vaccination series.
†The type-specific results shown in Table 4 represent the remaining subjects after exclusion of those with protocol violations, unevaluable specimens, or the presence of type-specific antibody at baseline.

Group 1: CD4% nadir <15 and CD4% ≥ 15 at screening;
Group 2: CD4% nadir ≥ 15 and CD4% between ≥ 15 and <25 at screening
Group 3: CD4% nadir ≥ 25 and CD4% ≥ 25 at screening

Levin et al. J Acquir Immune Defic Syndr 2010;55:197–204

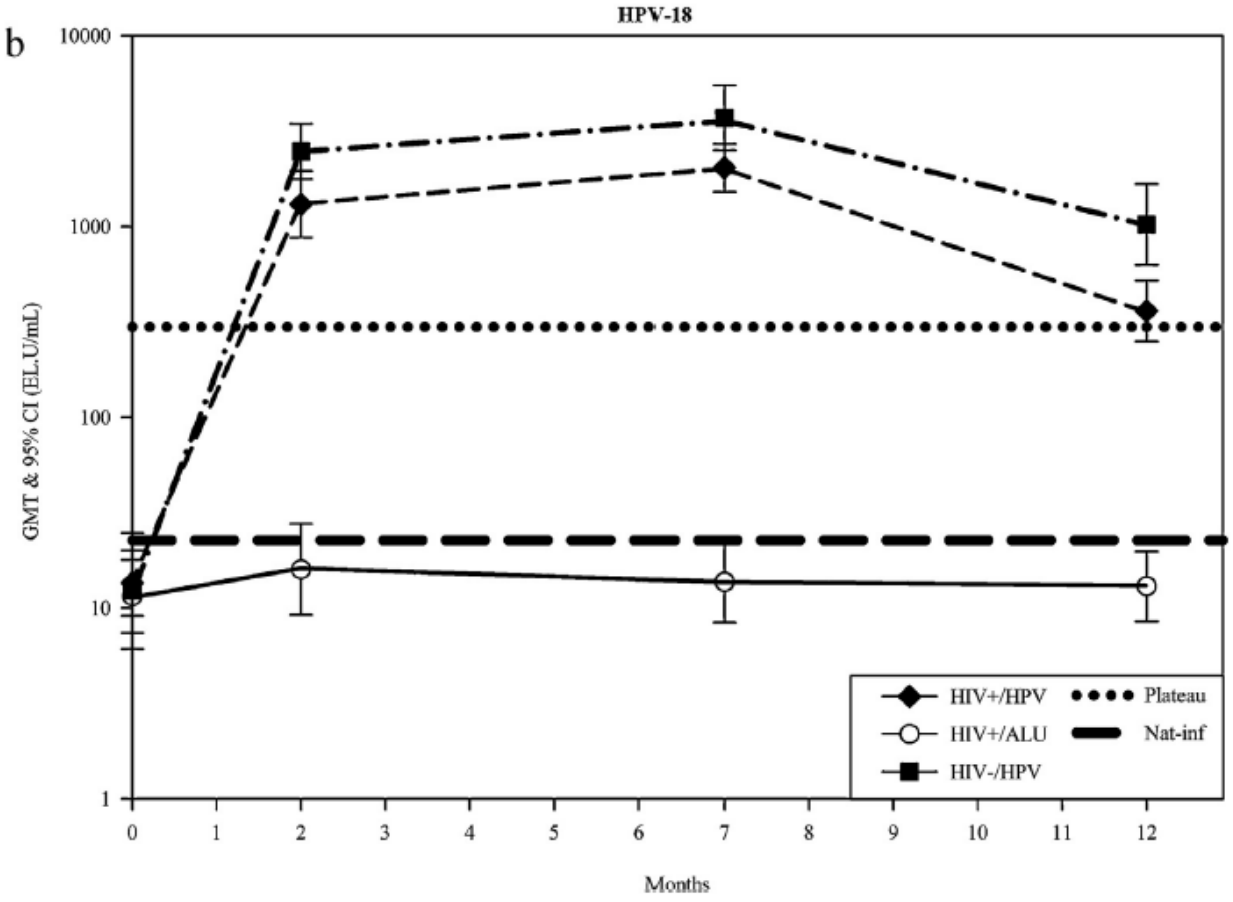
Immunogenicity Results of the QHPV Vaccine in HIV + Men

Table 2. Geometric Mean Antibody Concentrations according to Baseline Seropositivity and Anal Human Papillomavirus (HPV) DNA Detection

HPV type, anti-HPV serology	Anal HPV DNA detection	No. of participants	No. (%) of participants seropositive at week 28	Baseline GMC, mMU/mL	Week 28 GMC, mMU/mL (95% CI)
Type 6					
Negative	Negative	60	59 (98)	6	357 (256–497)
Negative	Positive	2	2 (100)	7	47[a]
Positive	Negative	32	30 (94)	75	1050 (514–2143)
Positive	Positive	6	6 (100)	86	531 (351–804)
Type 11					
Negative	Negative	68	67 (99)	5	525 (412–669)
Negative	Positive	3	2 (67)	6	177[a]
Positive	Negative	24	24 (100)	46	1804 (1263–2576)
Positive	Positive	5	5 (100)	90	617 (154–2472)
Type 16					
Negative	Negative	62	62 (100)	6	1139 (849–1529)
Negative	Positive	13	12 (92)	6	504 (177–1434)
Positive	Negative	19	19 (100)	74	2067 (1145–3733)
Positive	Positive	6	6 (100)	117	1480 (280–7831)
Type 18					
Negative	Negative	78	74 (95)	5	181 (136–241)
Negative	Positive	5	5 (100)	5	183 (27–1248)
Positive	Negative	14	14 (100)	54	819 (413–1623)
Positive	Positive	3	3 (100)	63	840[a]

Wilkin et al. J Infect Dis 2010 Oct 15;202(8):1246–53.

Bivalent HPV Vaccine in HIV+ Women: HPV-18 Response



L. Denny et al. Vaccine *31 (2013) 5745– 5753*