HPV vaccine controversies

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HPV vaccine challenging questions

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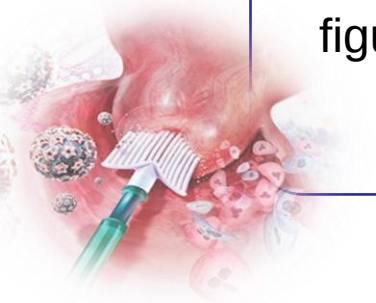
HPV vaccine development



1974: 1974-1976: HPV and cervical cancer relation

1976: 1976: coilocitic figures in cervical cytology

1983: 1983-1984: HPV 16 and 18
1985-1992: viral oncogenes activity

1987: First epidemiological study about HPV infection

1991: VLP production

1999: HPV is proposed as cervical cancer cause

2001: First studies about VLP vaccines security and immunogenicity

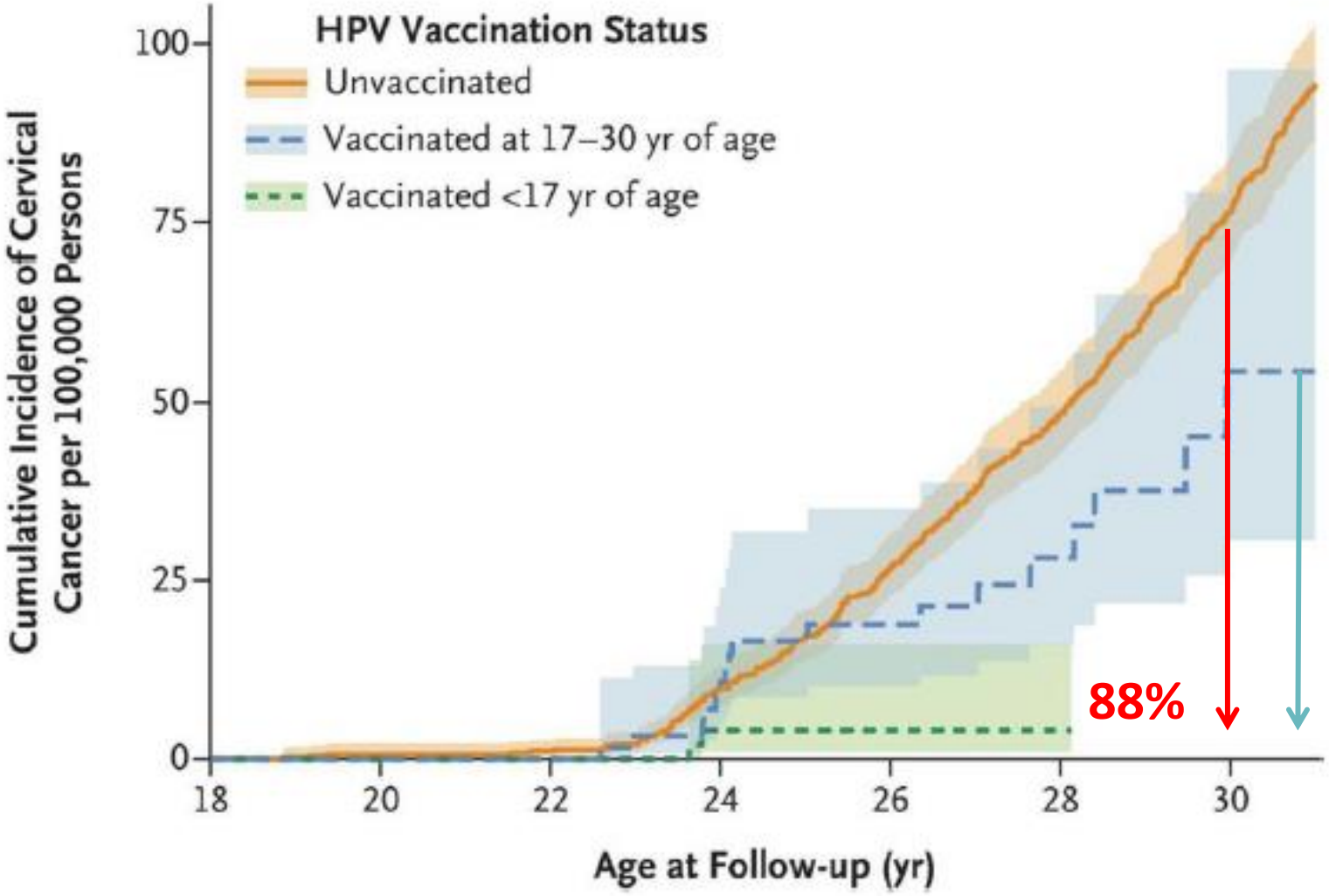
2006: Autorization of gardasil (2006), cervarix (2007) y gardasil 9 (2014)

Wang R et al. *Cancer Letters.* 2020

Firsts studies…

Study	Design	Study group	Control	n	Inclusion	Participants
FUTURE I	Phase III controlled randomized, double blinded, (1:1)	4v (3 dosis)	Placebo	5 455 ♀ (16–24 a)	January 2002- Match 2003	16 countries
FUTURE II		4v (3 dosis)	Placebo	12 167 ♀ (15–26 a)	June 2002- May 2003	13 countries
PATRICIA		2v (3 dosis)	Hepatitis A	18 644♀ (15–25 a)	May 2004- June 2005	14 countries
Costa Rica HPV-16/18 Vaccine Trial **(Guanacaste Study)**	Study communitarian, controlled randomized, double blinded, (1:1)	2v (3 dosis)	Hepatitis A	7 466 ♀ (18–25 a)	June 2004- December 2005	Costa Rica

HPV vaccine and cervical cancer reduction



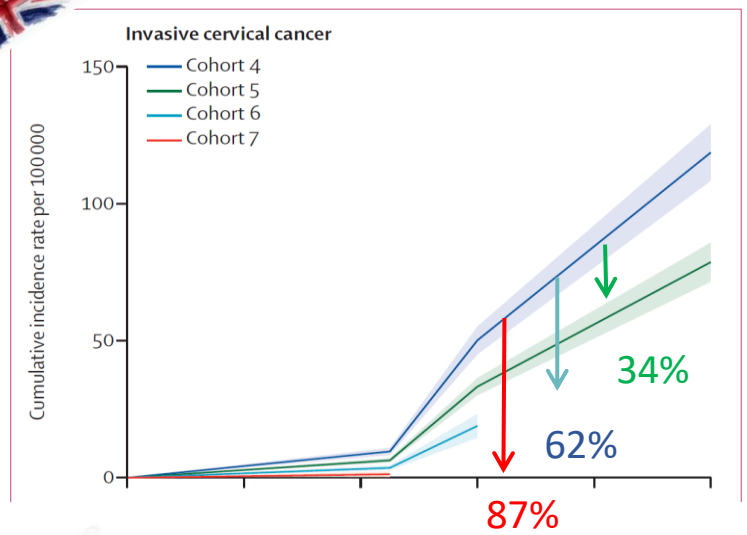
Cumulative incidence at 30s: **94/100.000**

Cumulative incidence at 30s : **54/100.000**

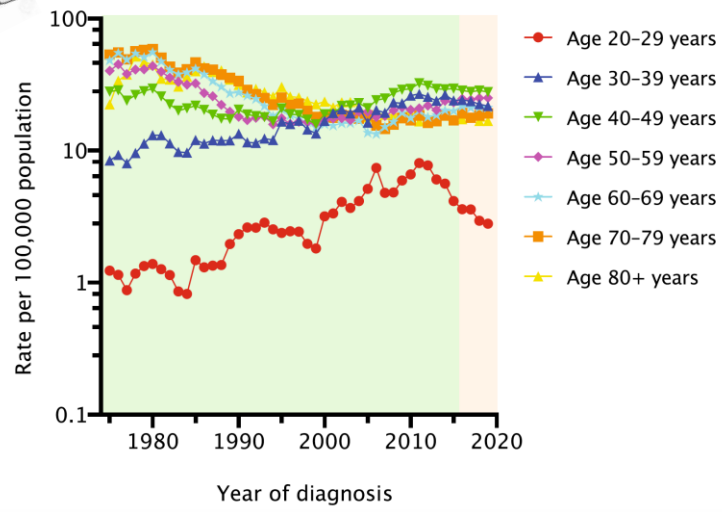
Cumulative incidence at 30s : **4/100.000**

Lei J, et al. N Engl J Med. 2020

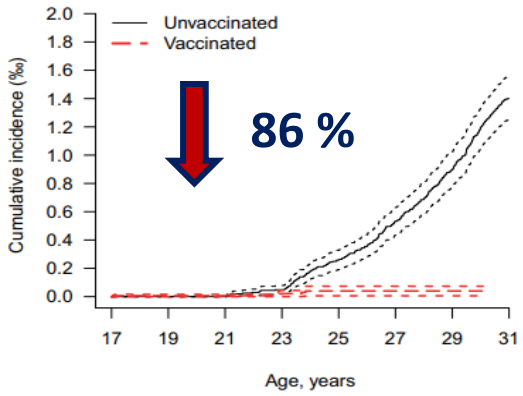
HPV vaccine and cervical cancer reduction



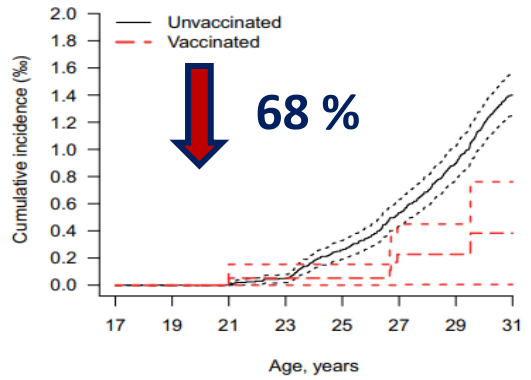
Conclusions: Since HPV vaccine introduction, both SCC and AC incidence rates declined among women aged 15–20 years, a group not typically screened for cervical cancer, which may suggest HPV vaccine impact.



Vaccinated at ≤ 16



Vaccinated at 17-19 years



Falcaro M et al. The lancet 2021
Mix JM et al. Cancer Epidemiol Biomarkers Prev 2021
Palmer TJ et al. JNCI 2024
Arbyn M at el. JNCI 2024

But… what happens in adults?

And what happens beyond the cervix?

Immunogenicity

HPV vaccine in adults: immunogenicity

n = 3253 women aged 27-45 years (FUTURE III study) + 150 men aged 27–45 years (MAM study)

	Women aged 27–45 years (Group A)		Women aged 16–26 years (Group B)		Group A/Group B	
Assay (cLIA)	n	GMT (mMU/mL)	n	GMT (mMU/mL)	GMT ratio	95% CI
Anti-HPV 6	1083	412.4	2800	536.2	0.77	0.72; 0.82
Anti-HPV 11	1083	538.2	2824	754.3	0.71	0.67; 0.76
Anti-HPV 16	1092	2212.0	2749	2297.6	0.96	0.89; 1.05
Anti-HPV 18	1223	348.4	3006	458.1	0.76	0.71; 0.82
	Men aged 27–45 years (Group C)		Men aged 16–26 years (Group D)		Group C/Group D	
Assay (cLIA)	n	GMT (mMU/mL)	n	GMT (mMU/mL)	GMT ratio	95% CI
Anti-HPV 6	115	364.9	1092	447.6	0.82	0.65; 1.03
Anti-HPV 11	136	489.9	1092	624.0	0.79	0.66; 0.93
Anti-HPV 16	111	2177.8	1135	2404.3	0.91	0.72; 1.13
Anti-HPV 18	135	296.2	1174	402.3	0.74	0.59; 0.92

Maldonado I. Hum Vaccin Immunother. 2022

HPV vaccine in men who have sex with men (MSM)

Immunogenicity in MSM

Anti-HPV GMT in MSW vs MSM

Response	Study time	Vaccinated HM (N = 1,726) n	Vaccinated HM (N = 1,726) GMT (mMU/ml)	Vaccinated MSM (N = 299) n	Vaccinated MSM (N = 299) GMT (mMU/ml)
Anti-HPV-6	Day 1	978	<7	114	<7
	Mo 7	978	473.9	114	274.3
	Mo 24	851	81.6	90	64.6
	Mo 36	792	73.4	55	49.2
Anti-HPV-11	Day 1	978	<8	114	<8
Anti-HPV-18	Day 1	1,032	<10	142	<10
	Mo 7	1,032	439.3	142	212.1
	Mo 24	897	39.4	114	31.4
	Mo 36	836	33.9	69	24.7

4v HPV vaccine

GMTs Comparison in MSM vs. women/MSW (7-m)

Assay	MSM/women GMT Ratio	MSM/women 95% CI
Anti-HPV 6	0.81	(0.70, 0.93)
Anti-HPV 11	0.77	(0.67, 0.89)
Anti-HPV 16	0.82	(0.72, 0.94)
Anti-HPV 18	0.89	(0.77, 1.04)
Anti-HPV 31	0.74	(0.64, 0.86)
Anti-HPV 33	0.78	(0.69, 0.89)
Anti-HPV 45	0.85	(0.72, 0.99)
Anti-HPV 52	0.70	(0.61, 0.80)
Anti-HPV 58	0.78	(0.68, 0.89)

MSM/♀

Antibody response was numerically lower in MSM than in HM and women

Anti-HPV 18	0.75	(0.64, 0.88)
Anti-HPV 31	0.59	(0.51, 0.69)
Anti-HPV 33	0.66	(0.57, 0.75)
Anti-HPV 45	0.67	(0.57, 0.79)
Anti-HPV 52	0.60	(0.52, 0.69)
Anti-HPV 58	0.63	(0.55, 0.72)

MSM/♂

9v HPV vaccine

Hillman RJ et al. CVI 2012
Castellsagué X et al. Vaccine 2016

HPV vaccine in people living with HIV

Immunogenicity in PLHIV

Review: 43 studies

4v HPV vaccine. Seropositivity 28 weeks post-3rd doses

- HPV 16: 0.99 (95% CI: 0.98-1.00, n=9)
- HPV 18: 0.94 (95% CI: 0.91-0.96, n=9)
- HPV 6: 0.99 (95% CI: 0.97-1.00, n=8)
- HPV 11: 0.98 (95% CI: 0.97-0.99, n=8)

9v HPV vaccine. Seropositivity 28 weeks post-3rd doses

- HPV 16: 1.00 (95% CI: 0.98-1.00)
- HPV 18: 1.00 (95% CI: 0.99-1.00)

High rate of seroconversion for all HPV vaccine types

2v HPV vaccine. Seropositivity 28 weeks post-3rd doses

- HPV 16: 0.99 (95% CI: 0.95-1.00)
- HPV 18: 0.99 (95% CI: 0.96-1.00)

Staadegaard E. et al. eClinicalMedicine 2022

HPV vaccine in people living with HIV

Implications of all the available evidence

PLHIV can develop a robust humoral immune response following HPV vaccination. The vaccine is safe and well tolerated, with few serious adverse events. Evidence of vaccine efficacy on biological outcomes following vaccination was generally of low quality. The evidence-base is lacking from well-designed studies that account for the underlying HPV infection status, timing of infection, and have a sample size and follow-up time that are appropriate for estimation of efficacy of HPV vaccine in PLHIV. The evidence of a robust immune response generated among all PLHIV who have received HPV vaccination supports cervical cancer elimination efforts to increase HPV vaccination coverage including in high HIV prevalence settings.

Staadegaard E. et al. eClinicalMedicine 2022

Efficacy/Effectiveness

HPV vaccine efficacy/effectiveness in the cervix (women)

n = 3253 women aged 50 years (LTFU FUTURE III study)

	m/n	Person-Years Follow-up	Incidence per 10,000 Person-Years Cases (95% CI)	m/n
HPV6/11/16/18-related CIN or condyloma				
Per-protocol population[b]				
Base study	0/528	1794.2	0.0 (0.0–20.6)	13/528
LTFU study	0/529	2946.7	0.0 (0.0–12.5)	—
ITP population[c]				
Base study	1/587	2308.8	4.3 (0.1–24.1)	17/573
LTFU study	0/586	3263.0	0.0 (0.0–11.3)	0/557
HPV16/18-related CIN2 or worse				
Per-protocol population[b]				
Base study	0/513	1694.2	0.0 (0.0–21.8)	3/518
LTFU study	0/482	2679.0	0.0 (0.0–13.8)	—
ITP population[c]				
Base study	1/578	2192.8	4.6 (0.1–25.4)	4/564
LTFU study	0/535	2976.8	0.0 (0.0–12.4)	0/511
HPV6/11-related condyloma				
Per-protocol population[b]				
Base study	0/443	1505.7	0.0 (0.0–24.5)	2/428
LTFU study	0/443	2460.4	0.0 (0.0–15.0)	—
ITP population[c]				
Base study	0/491	1937.3	0.0 (0.0–19.0)	4/468
LTFU study	0/491	2724.6	0.0 (0.0–13.5)	0/465

There were no cases of high-grade cervical dysplasia or genital warts caused by HPV vaccine types up to 10 years post-dose 3 in women vaccinated (4v) up to 50 years

*La vacuna 4v no está comercializada en España

Maldonado I. Hum Vaccin Immunother. 2022

HPV vaccine efficacy/effectiveness in the anus (adult)

Vaccine Efficacy/Effectiveness (VE) against vaccine-targeted **anal HPV infection** (14 studies)

Outcome	No. of Studies [References]	No. of Participants	VE (95% CI), %
Incident/prevalent anal HPV infection			
Age ≤26 y			
PPE in clinical trials	2 [16, 17]	2390	84 (77–90)
ITT in clinical trials	2 [16, 17]	4885	55 (39–67)
Real-world studies	4 [18–21]	2735	77 (40–91)
Age >26 y			
ITT in clinical trials	1 [22]	100	14 (−19 to 38)
Persistent anal HPV infection[b]			
Age ≤26 y			
PPE in clinical trials	2 [17, 23]	1345	98 (87–100)
ITT in clinical trials	1 [17]	551	59 (43–71)
Age >26 y			
PPE in clinical trials	1 [24]	554	31 (−82 to 74)
ITT in clinical trials	1 [24]	574	35 (−5 to 60)

6 studies (2 clinical trials and 4 real-world studies) in individuals (98% HIV-negative) ≤26 y

1 clinical trial in men having sex with men living with HIV >26 y

2 clinical trials that recruited HIV-negative men 16–26 y

1 clinical trial in people living with HIV >26 y

Wei F et al L, et al. JID. 2023

HPV vaccine efficacy/effectiveness in the anus (adults)

Vaccine Efficacy/Effectiveness (VE) against **anal intraepithelial neoplasia** and **anal condyloma** (14 studies)

Outcome	No. of Studies [References]	No. of Participants	VE (95% CI)
AIN1+			
Age ≤26 y			
PPE in clinical trials[a]	2 [17, 25]	668	82 (39–94)
ITT in clinical trials[a]	1 [17]	551	50 (26–67)
Age >26 y			
ITT in clinical trials[a]	1 [24]	262	17 (–6 to 35)
AIN2+			
Age ≤26 y			
PPE in clinical trials[a]	1 [17]	402	75 (14–93)
ITT in clinical trials[a]	1 [17]	551	54 (21–73)
Age >26 y			
ITT in clinical trials[a]	2 [22, 24]	702	–1 (–42 to 28)
Anal condyloma			
Age ≤26 y			
PPE in clinical trials[a]	1 [17]	402	100 (8–100)
ITT in clinical trials[a]	1 [17]	551	57 (16–80)
Age >26 y			
Real-world studies[b]	1 [26]	313	55 (8–78)

2 clinical trial in individuals (men having sex with men ; 81% HIV negative) ≤26 y

1 clinical trial in individuals (men having sex with men ; HIV negative) ≤26 y

1 clinical trials in individuals (82% men having sex with men 18% women; all living with HIV) >26 y

1 clinical trial in individuals (men having sex with men ; HIV negative) ≤26 y

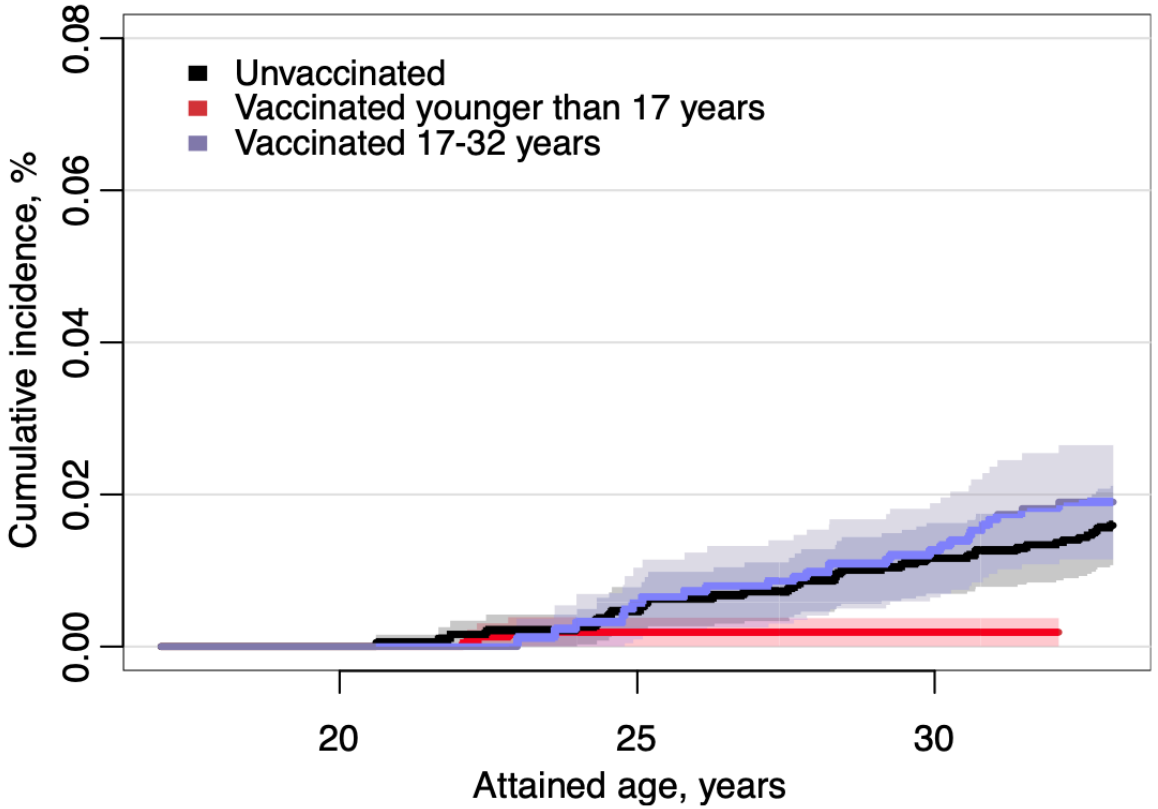
2 clinical trials in individuals (85% men having sex with men 15% women; all living with HIV) >26 y

1 clinical trial in individuals (men having sex with men HIV negative) ≤26 y

1 real world study in individuals (men having sex with men HIV negative) >26 y

Wei F et al L, et al. JID. 2023

HPV vaccine efficacy/effectiveness anal HSIL (women)



Vaccination status	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
Unvaccinated	Referent	Referent
Age at vaccination younger than 17 y	0.30 (0.10 to 0.89)	0.30 (0.10 to 0.87)
Age at vaccination 17-32 y	1.30 (0.78 to 2.15)	1.21 (0.73 to 2.03)

HSIL: high-grade squamous intraepithelial lesion

Baandrup L, et al. J Natl Cancer Inst. 2024

HPV vaccine efficacy/effectiveness in anogenital HSIL (men)

936 participants (827 heterosexual men and 109 MSM up to 26 years). Long term follow-up study (10 years)

	Early vaccination group (n=936)			Catch-up vaccination group (n=867)			reduction estimate (95% CI)*
	Participants	Person-years follow-up	Incidence per 10 000 person-years (95% CI)	Participants	Person-years follow-up	Incidence per 10 000 person-years (95% CI)	
External genital warts related to HPV6 or 11							
Per-protocol population							
Base study	2/640	1518·9	13·2 (1·6–47·6)	20/623	1456·5	137·3 (83·9–212·1)	90·4% (62·3 to 98·4)
Long-term follow-up study	0/639	4225·4	0·0 (0·0–8·7)	..	..	..	..
mITT population							
Base study	6/763	2203·9	27·2 (10·0–59·3)	31/725	2072·2	149·6 (101·6–212·3)	81·8% (55·9 to 92·6)
Long-term follow-up study	0/763	5054·1	0·0 (0·0–7·3)	0/567	2737·2	0·0 (0·0–13·5)	..
External genital lesions† related to HPV6, 11, 16, or 18							
Per-protocol population							
Base study	2/731	1728·4	11·6 (1·4–41·8)	23/704	1638·1	140·4 (89·0–210·7)	91·8% (69·4 to 98·6)
Long-term follow-up study	0/730	4798·4	0·0 (0·0–7·7)	..	..	..	..
mITT population							

The HPV vaccine provides durable protection against anogenital disease related to HPV6, 11, 16, and 18.

Goldstone I et al. Lancet Infect Dis 2022

HPV vaccine and disease in people living with HIV

Reference	N (age)	Study	Results
Women			
McClymont et al. 2019	279 (9-25a)	observational, cohorts prospective	Lower incidence of persistent infection (but higher rate of HPV vaccine failure.
Firnhaber et al. 2021	180 (35-45a)	randomized double-blinded clinical trial	Post treatment CIN2+ was similar between the vaccine and placebo arms BUT 73% showed positive margins for HSIL
MSM & Women			
Wilkin et al. 2018	575 (>27a)	randomized double-blinded clinical trial	No efficacy for prevention of anal HPV infection and disease. Stop studio BUT high level of current and prior HPV infection
MSM			
Hidalgo-Tenorio et al. 2021	129 (>26a)	randomized double-blinded clinical trial	No efficacy for prevention of anal disease BUT 74% showed prevalent high-risk HPV and 60% low-risk HPV infection
Palefsky et al. 2021	144 (18-26a)	phase II, open-label, multicenter trial	No incident qHPV type–associated anal lesions among men naive to that type
Gosens et al. 2021	126 (> 18a)	randomized, double-blind, multicentre trial	No efficacy for prevention of anal recurrence posttreatment BUT no HPV testing after treatment

HPV vaccine and guidelines for people living with HIV

	CDC/ACIP	EACS 2022	BHIVA 2015	WHO
Recommended age	11 or 12 (9–26)	9-45	12-13	9-14
Age limit for catch-up	26 (to 45 with shared decision making)	45	26 (to 40 for women and MSM)	Not specified
Number of doses	3	3	3	3 (preferred). Alternative 2-dose regimen >6-month interval
Preferred HPV vaccine	9vHPV (only vaccine currently distributed in US)	9vHPV	9vHPV	2vHPV, 4vHPV or 9vHPV
CD4 and VL at time of vaccination	No specific recommendation	Preferably when CD4>200 and suppressed VL	ART-naïve patients with CD4<200, vaccine may be deferred until ART establishment	No specific recommendation

CDC, Centers for Disease Control and Prevention; ACIP, Advisory Committee on Immunization Practices; EACS, European AIDS Clinical Society; BHIVA, British HIV association; WHO,World Health Organization

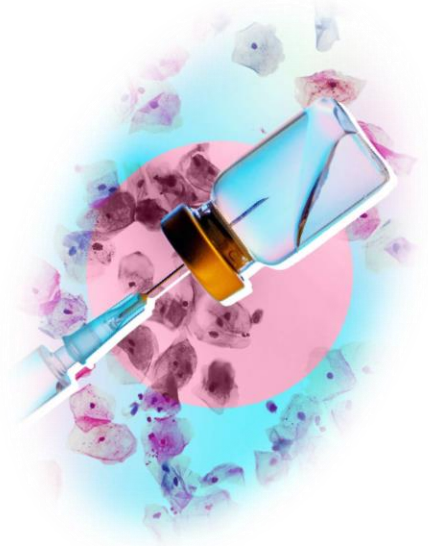
Losada C et al. Vaccines 2023

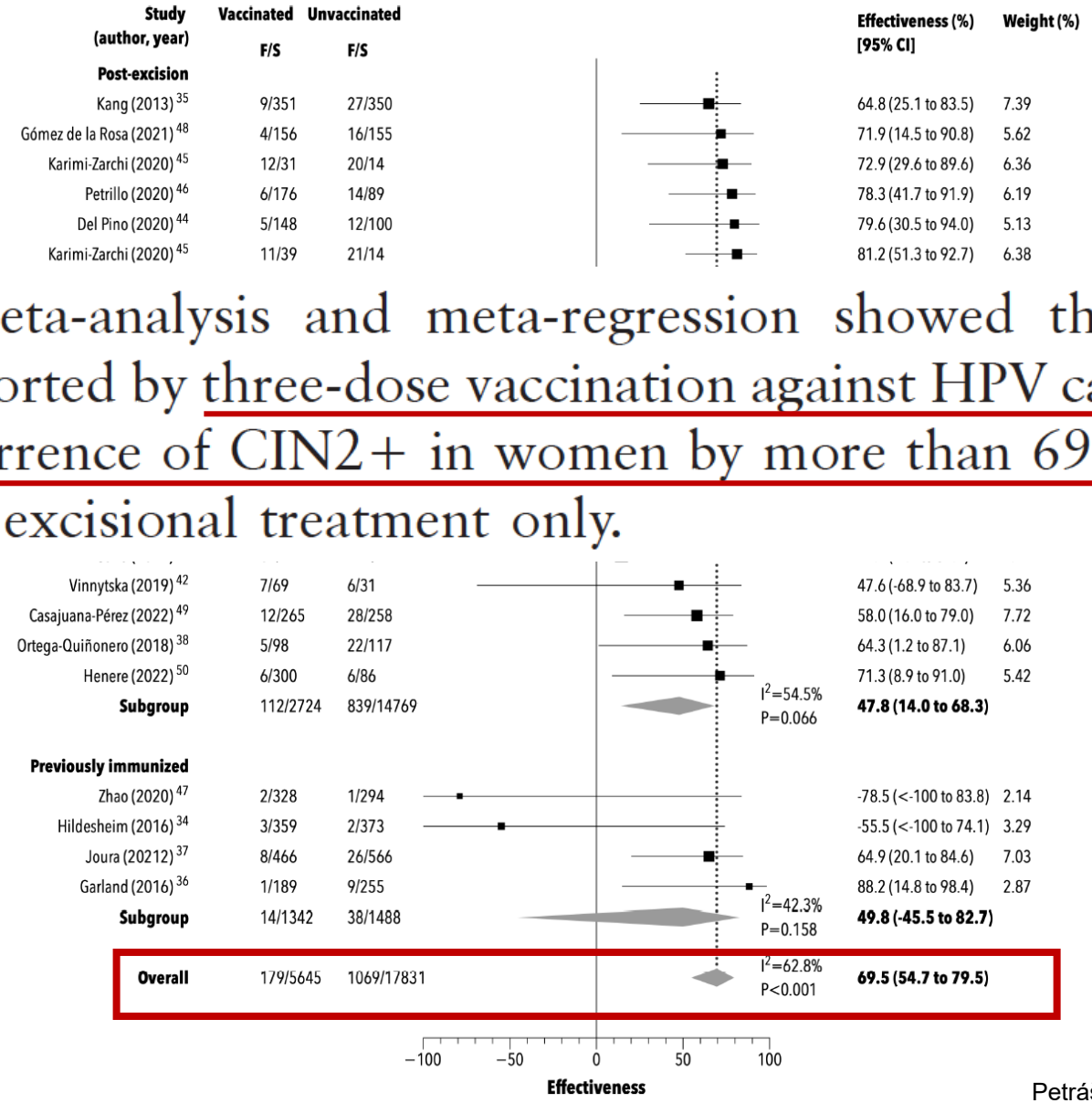
Efficacy/Effectiveness in recurrence

HPV vaccine and previous HPV/SIL history

PAVIVE Study (sistematic review):

20 studies (2011-2023)

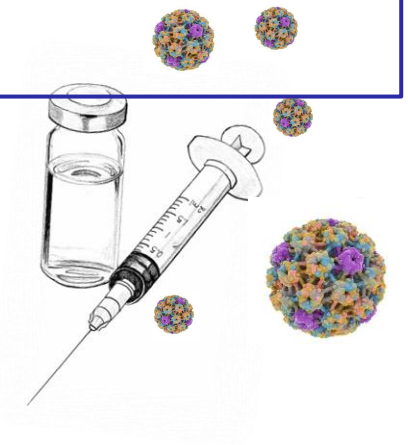




The present meta-analysis and meta-regression showed that conisation supported by three-dose vaccination against HPV can reduce the recurrence of CIN2+ in women by more than 69% compared with excisional treatment only.

Petráš M et al. Sex Transm Infect 2023

Re-activation and HPV-related disease



High quality evidence is coming….

1. NOVEL trial – UK (Finland, Sweden)

Nonavalent Prophylactic HPV Vaccine (GARDASIL9) After Local Conservative The NOVEL Trial - Full Text View - ClinicalTrials.gov

2. HOPE9 trial - Italy

Impact on Disease Relapse of HPV Vaccination in Women Treated With LEEP for Cervical Intraepithelial Neoplasia. HOPE9 - Full Text View - ClinicalTrials.gov

3. VACCIN study - Netherlands

Adjuvant VACcination against HPV in surgical treatment of Cervical Intra-epithelial Neoplasia (VACCIN study) a study protocol for a randomised controlled trial - PubMed (nih.gov)

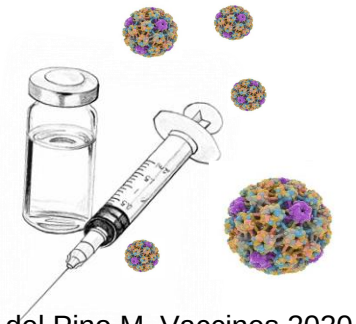
4. COVENANT trial - South Africa, HIV + women

HPV Vaccine Therapy in Reducing High-Grade Cervical Lesions in Patients With HIV and HPV - Full Text View - ClinicalTrials.gov

HPV vaccine and previous HPV/SIL history

Related to HPV status after the treatment

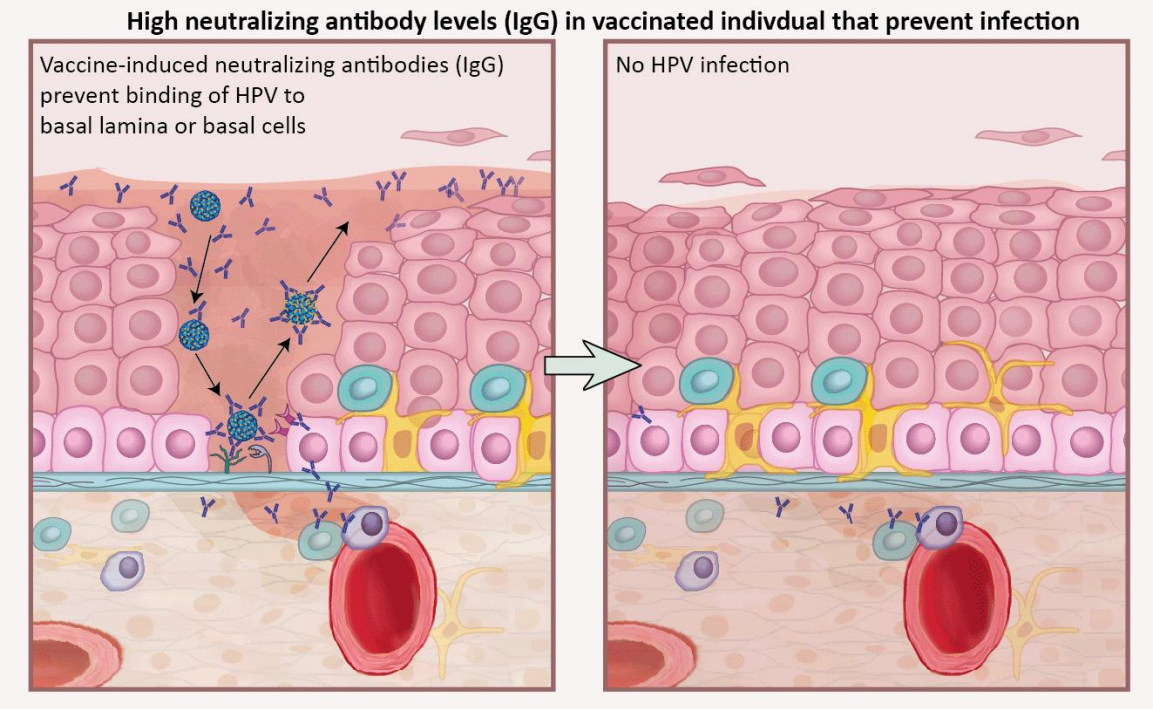
Status at the First Post-Conization Control (6 Months)		Clinical Outcome at the End of Follow-Up: No Disease	Persistent/Recurrent LSIL/HPV	Persistent/Recurrent HSIL	p *
	No disease (n = 153)				0.032
	Non-vaccinated	55 (83.3)	7 (10.7)	4 (6.1)	
	Vaccinated	78 (89.7)	9 (10.3)	0 (0.0)	
	Persistent LSIL/HPV (n = 101)				0.173
	Non-vaccinated	28 (65.1)	9 (20.9)	6 (14.0)	
	Vaccinated	33 (56.9)	21 (36.2)	4 (6.9)	
	Persistent HSIL/CIN2-3 (n = 11)				0.131
	Non-vaccinated	0 (0.0)	1 (33.3)	2 (66.7)	
	Vaccinated	3 (37.5)	4 (50.0)	1 (12.5)	



del Pino M. Vaccines 2020
Rykkelid M et al. Pathogens 2024

HPV vaccine and previous HPV/SIL history

HPV vaccination after exposure. Mechanism of action: Prophylactic HPV vaccine elicit production of antibodies that bind to L1 at the surface of viral particles, hindering their ability to infect host cells



Vaccination may **prevent new HPV infections** caused by a different HPV type **or re-infections** with the same HPV type coming from a new exposure (i.e. infected partner) or through autoinoculation from an adjacent infected site

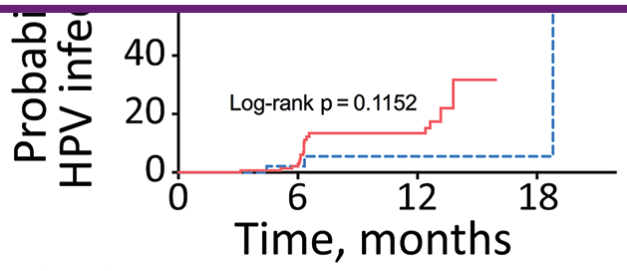
Reuschenbach M et al. Vaccines 2023
Schiffman M, et al.. Nat Rev Dis Primers 2016
Schiller JT, et al. Gynecologic oncology 2010

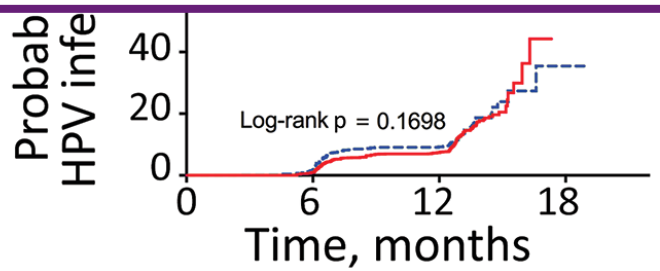
Autoinoculation and HPV-related disease

Sequential HPV acquisition between anal and genital sites (n=2022 women)

Risk of anal infection

In conclusion, men and women with previous HPV infection at the genital or anal site had a higher risk for sequentially acquiring a concordant HPV infection at the other site. For anogenital HPV infection, autoinoculation of HPV might play a major role, in addition to that of sexual intercourse, espe-

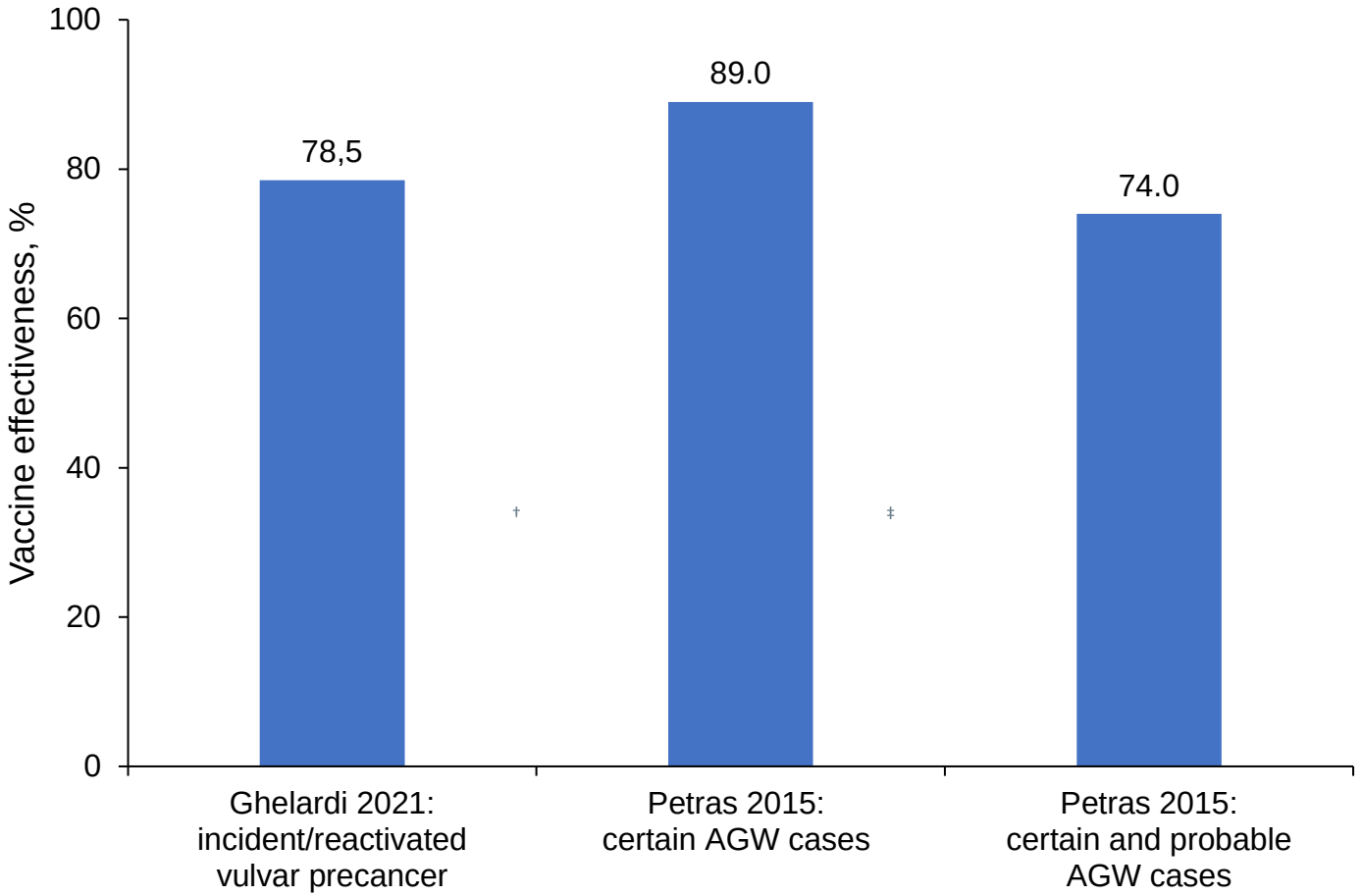




Wei F et al. Emerg Infect Dis. www.cdc.gov/eid 2020

HPV vaccine and vulva disease recurrence reduction

Woman with vulvar precancer or prior genital warts



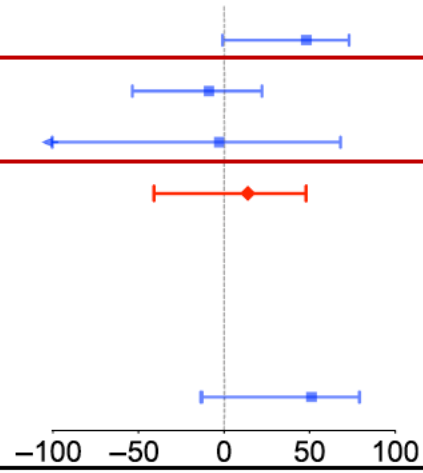
4vHPV/9vHPV was **effective in preventing subsequent vulvar HSIL** in women with pre-existing disease with high strength of evidence and low publication bias

Goodman E, et al. *Vaccines (Basel)* 2022;10:1543.

HPV vaccine and anal disease recurrence reduction over 17y

Vaccine Efficacy/Effectiveness (VE) against **anal intraepithelial lesion recurrence** (4 studies)

Study	Vaccine Group, No.		Nonvaccine Group, No.		VE (95% CI), %	Weight, %
	Event	Total	Event	Total		
Recurrence of AIN2+						
Swedish et al (2012) [27]	12	88	35	114	48 (−1 to 73)	31.9
Wilkin et al (2018) [24]	27	43	27	47	−9 (−53 to 22)	53.2
Gosens et al (2021) [29]	44	64	38	62	−3 (−234 to 68)	14.8
Random-effects model					**14 (−41 to 48)**	**100.0**
Heterogeneity: I^2 = 48%; P = .15						
Recurrence of anal condyloma						
Swedish et al (2014) [26]	6	40	19	62	51 (−13 to 79)	...



HIV positive

mean age 37–50 y

Wei F et al L, et al. JID. 2023

Conclusions: Watch out with the confounding factors

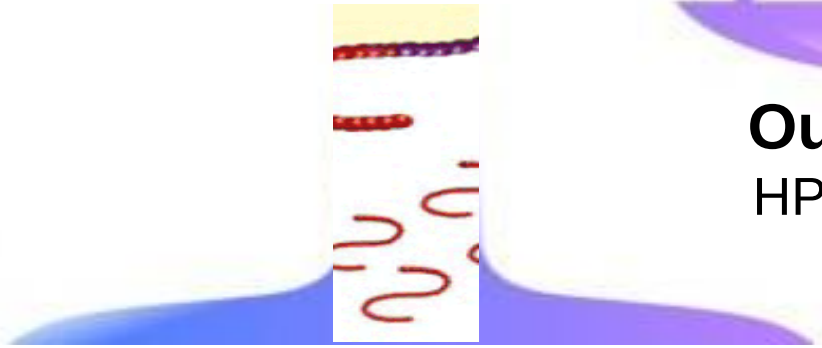
HPV vaccine

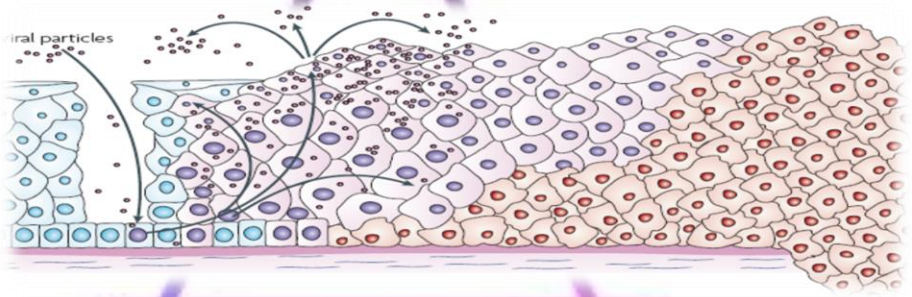
Age

HIV status

HPV status

SIL history





Outcomes:

HPV infection

LSIL

HSIL


Thanks for your attention