

# Neutralizing antibody levels to human papillomavirus following bi- and quadrivalent vaccination

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Tumorvirus-specific Vaccination Strategies (F035)

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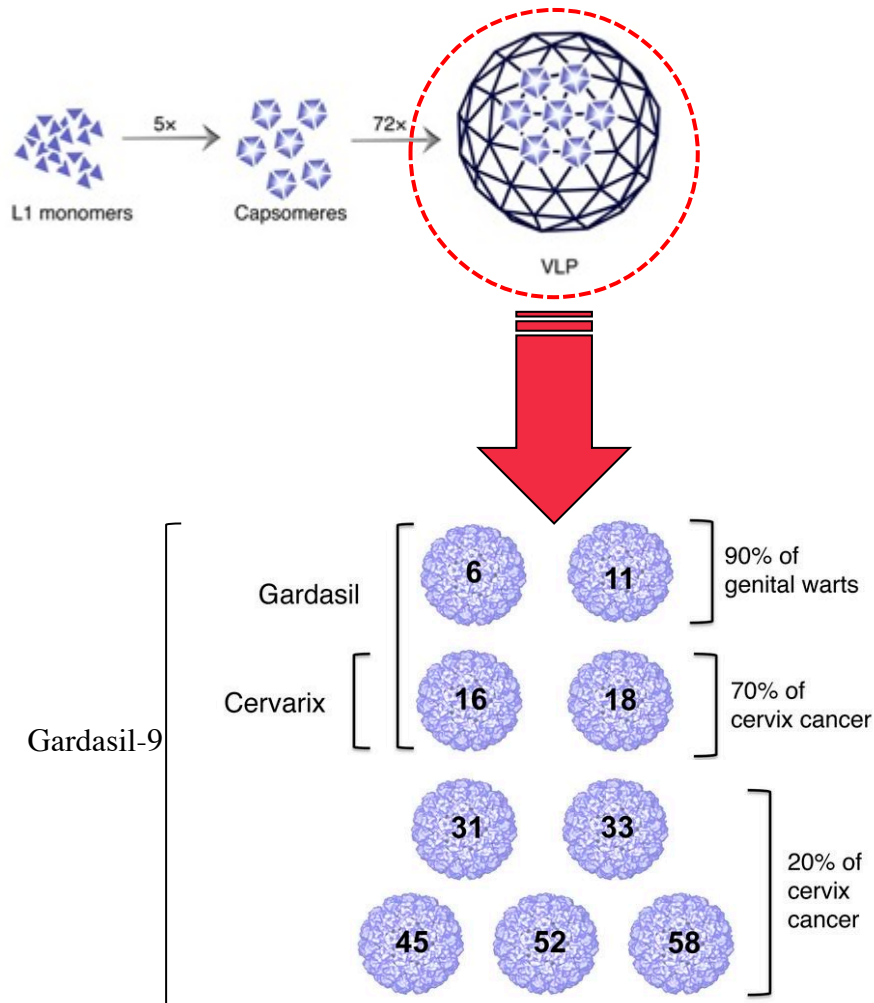
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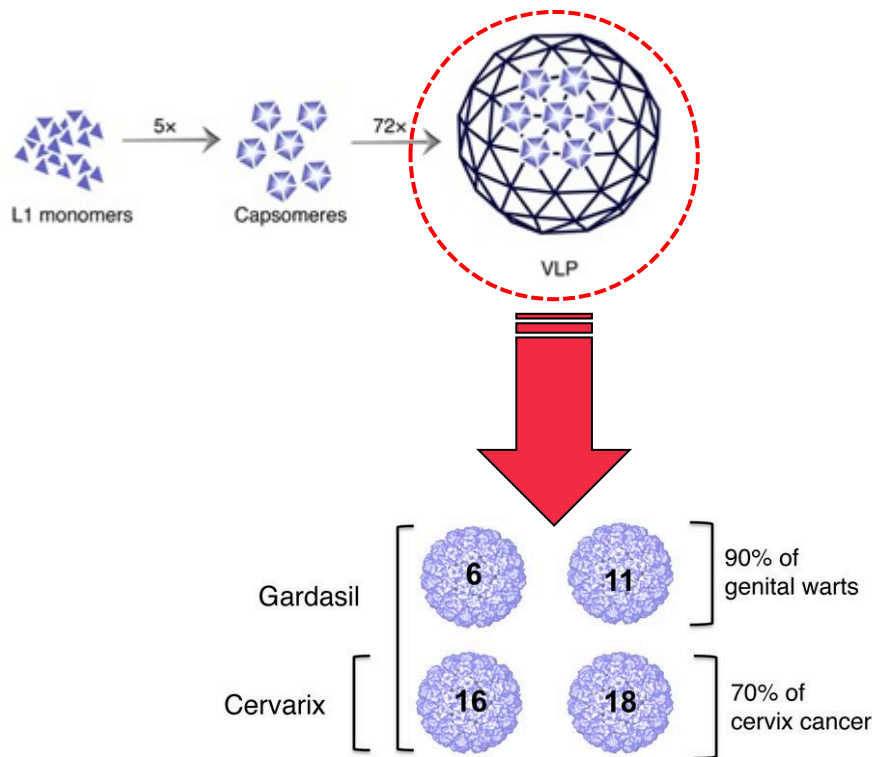
Research for a Life without Cancer

# bi- and quadrivalent HPV prophylactic vaccines



Modified from Schiller & Müller., (2015) Lancet Oncol 16(5)

# bi- and quadrivalent HPV prophylactic vaccines



bi- and quadrivalent HPV vaccines confer:

- Strong type-specific humoral responses;
- Different cross-reactive responses mainly against alpha-9 HPV types (HPV31/33/52/58), and alpha-7 HPV45.

Modified from Schiller & Müller., (2015) Lancet Oncol 16(5)

# Neutralizing antibodies (nAb) as predictor of protection against HPV-related cancers

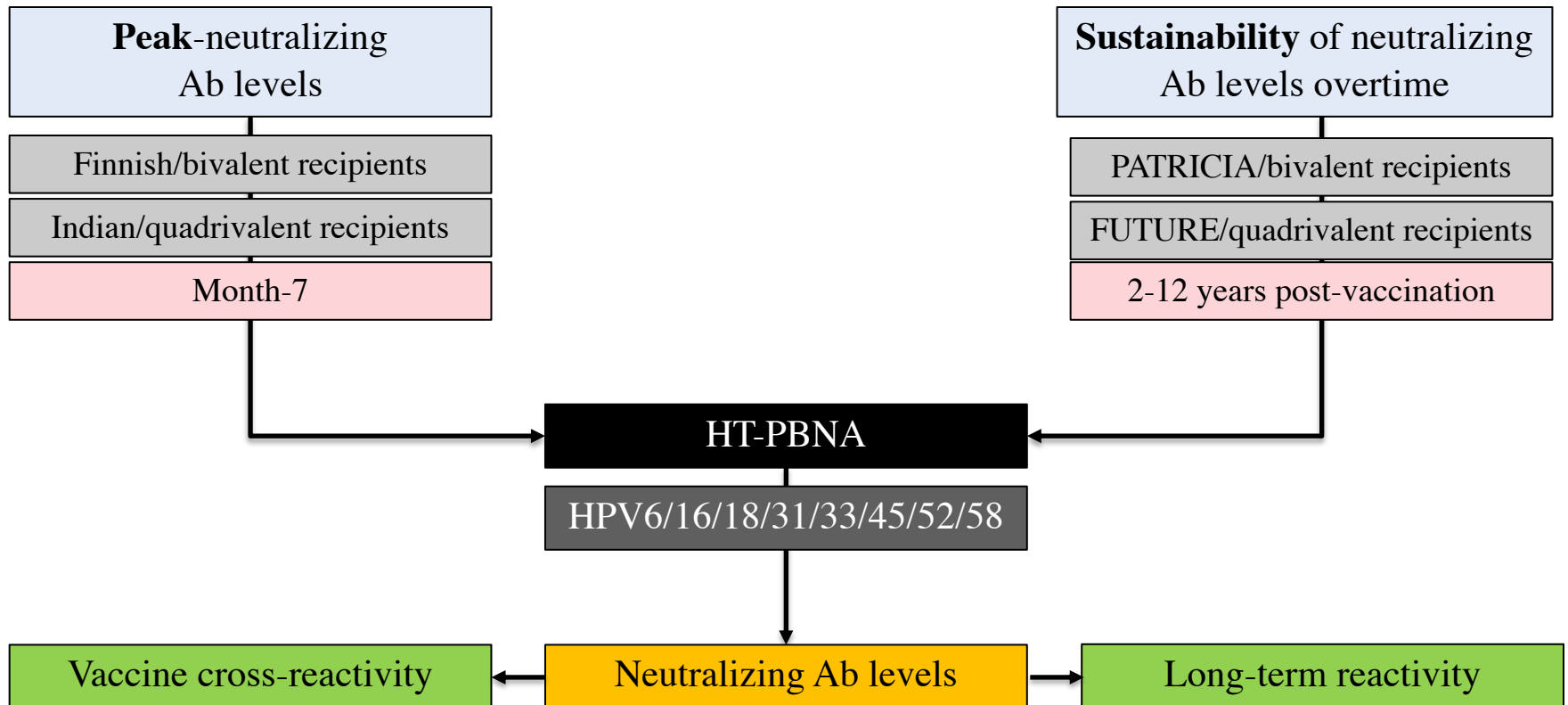
Pre-clinical animal models support the role of anti-L1 nAb responses in protection against experimental HPV infection and related lesions;

Vaccine correlates of protection:

- Prevention against pre-malignant lesions
- Prevention against persistent infection (>6-months)
- **Neutralizing antibodies, unknown protective levels**

**How sustainable and cross-reactive are the vaccine-induced Ab levels?**

# Study design and rationale

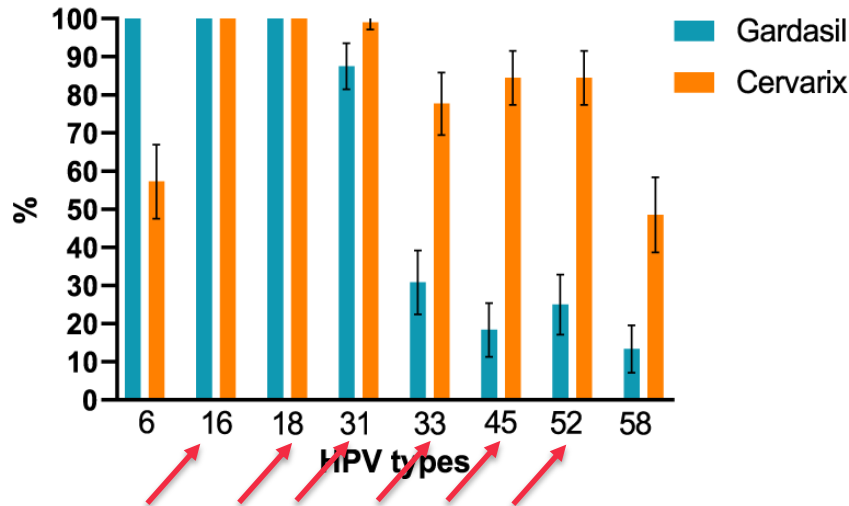


Mariz et al., (2020) *npj Vaccines* 5(14); Mariz et al., (in-press) *Lancet Infect Dis*

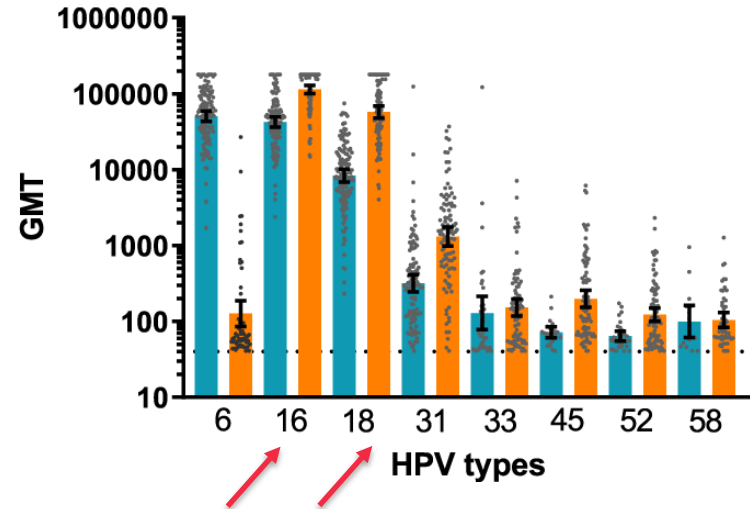
# Peak-antibody levels cross-neutralize phylogenetically related non-vaccine types

	Bivalent (Cervarix)	Quadrivalent (Gardasil)
Cohort age (vaccination)	16-17y (recipients of three doses)	15-18y (recipients of three doses)
n	103	120

**a Seroprevalence**

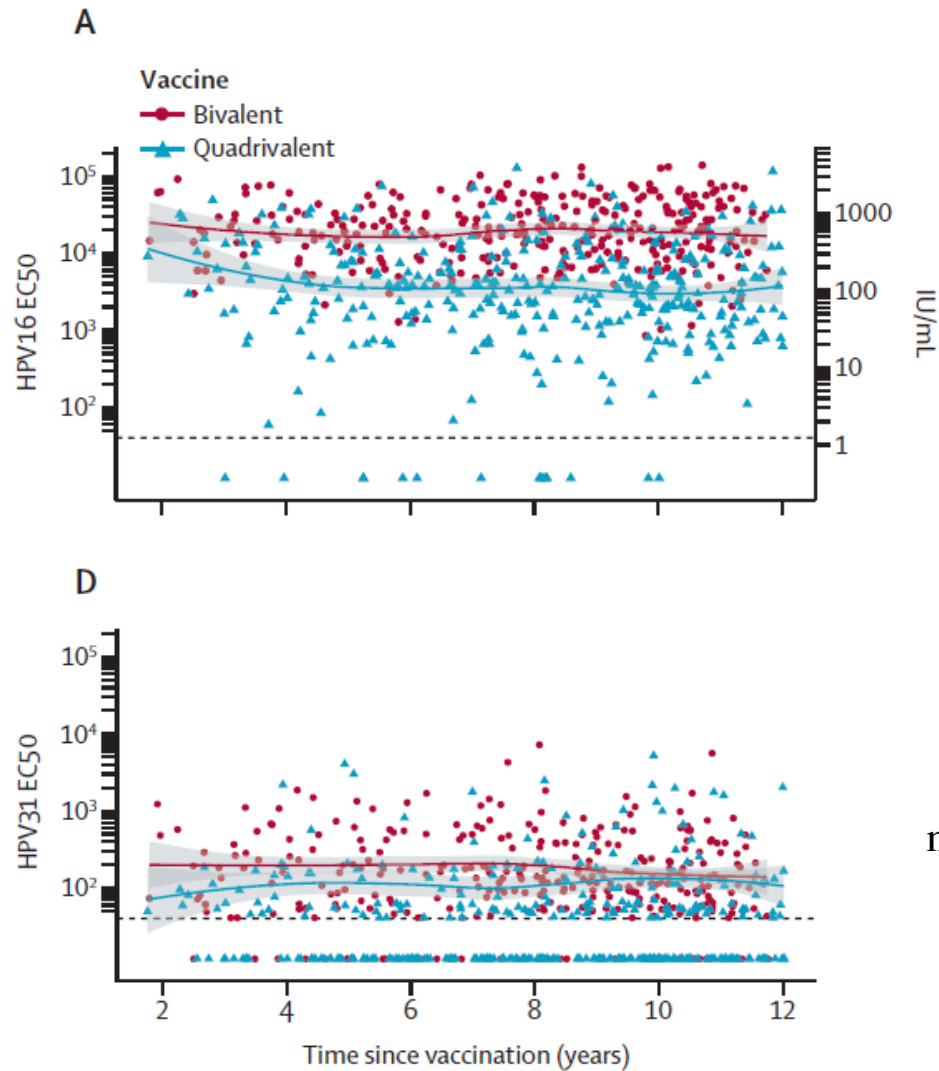


**b Neutralization titer**



Mariz et al., (2020) *npj Vaccines* 5(14)

# Vaccine-induced neutralizing and cross-neutralizing antibody levels are sustainable for up to 12 years



Similar findings for vaccine HPV types 6, 11 and 18

Similar findings for non-vaccine HPV types 33, 52 and 58

Mariz et al., (2021) Lancet Infect Dis S1473-3099(20)30873-2.

# Vaccine-induced cross-neutralizing antibody seroprevalence is sustained for 12 years

	Bivalent vaccine			Quadrivalent vaccine		
	Seroprevalence (95% CI)	Median titre (95% CI)	GMT (95% CI)	Seroprevalence (95% CI)	Median titre (95% CI)	GMT (95% CI)
<b>HPV31</b>						
2-4 years	90.0 (73.4-97.8)	183 (73-290)	205 (134-313)	65.5 (45.6-82.0)	53 (25-93)	102 (66-157)
5-7 years	80.7 (70.2-88.8)	129 (62-192)	189 (144-249)	45.7 (34.7-57.0)	<40	114 (77-169)
8-10 years	85.3 (78.4-90.6)	117 (93-138)	179 (149-216)	46.3 (37.7-55.0)	<40	120 (90-160)
11-12 years	83.5 (74.2-90.4)	97 (63-128)	147 (117-185)	53.8 (43.0-64.3)	44 (25-53)	121 (87-168)
5-12 years	→ 83.6 (79.0-88.3)	110 (92-133)	171 (151-195)	→ 48.4 (42.7-54.1)	<40	119 (98-143)
<b>HPV33</b>						

Similar findings for non-vaccine HPV types 33, 52 and 58

Modified from Mariz et al., (2021) Lancet Infect Dis S1473-3099(20)30873-2.



# Vaccine-induced cross-neutralizing antibody seroprevalence is sustained for 12 years

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Similar findings for non-vaccine HPV types 33, 52 and 58

<b>HPV45</b>						
	Seroprevalence (95% CI)	Median titre (95% CI)	GMT (95% CI)	Seroprevalence (95% CI)	Median titre (95% CI)	GMT (95% CI)
2-4 years	46.6 (28.3-65.6)	<40	124 (80-192)	10.3 (2.1-27.3)	<40	53 (25-112)
5-7 years	48.7 (37.2-60.3)	<40	88 (72-108)	13.2 (6.8-22.4)	<40	97 (53-175)
8-10 years	46.1 (37.7-54.6)	<40	79 (68-92)	13.9 (8.6-20.9)	<40	89 (62-129)
11-12 years	40.6 (30.4-51.4)	<40	74 (60-90)	18.6 (11.2-28.2)	<40	117 (64-216)
5-12 years	→ 45.1 (39.5-50.9)	<40	80 (72-88)	15.1 (11.3-19.6)	<40	101 (76-133)

Modified from Mariz et al., (2021) Lancet Infect Dis S1473-3099(20)30873-2.

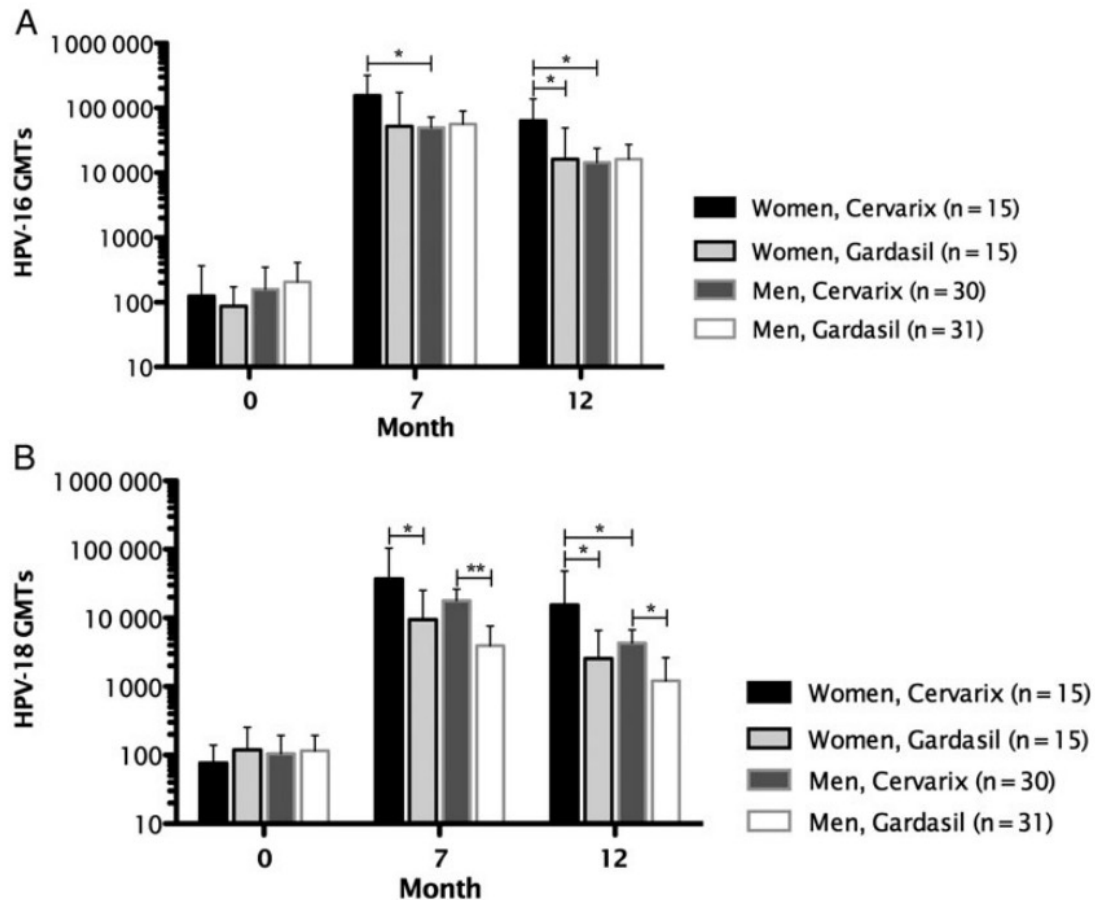
# Outlook #1

- In the general, HIV-uninfected population:
  - bi- and quadrivalent HPV vaccines induce sustainable nAb levels to vaccine HPV types for up to 12-years;
  - nAb levels to non-vaccine types HPV31/33/45/52/58 are, when measurable, as sustainable as nAb to vaccine HPV types;
  - nAb seroprevalence rates to HPV types 16, 18, 31, 33, 52 and 58 significantly correlated with reported VE against persistent infections (not shown).

**How sustainable and cross-reactive are the vaccine-induced Ab levels in people living with HIV?**

# Peak-neutralizing antibody levels at Month-7 are induced in HIV+ patients following vaccination

Toft et al 2014 reported on a randomized, double-blind study conducted with **adults living with HIV**, recipients or not of ART



Toft et al., (2014) JID 209:1165-73.

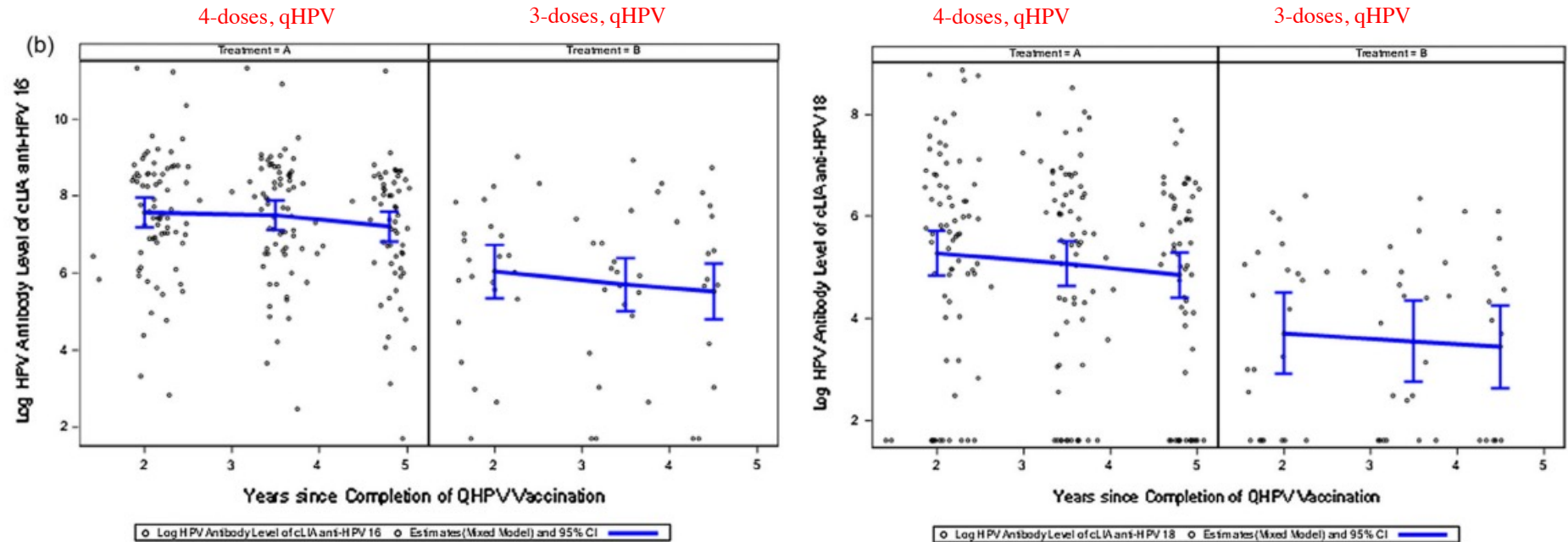
# Vaccine-induced cross-reactivity is more restricted in HIV-infected subjects

(B) Antibodies detected with neutralization assays

HPV type	Baseline seroprevalence %			Seroconversion total%			Seroconversion Gardasil™%			Seroconversion Cervarix™%		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
6	42	32	38	80	69	75 <sup>#</sup>	100	90	95 ←	0	0	0
11	27	32	29	84	85	84 <sup>#</sup>	100	100	100 ←	0	0	0
16	38	33	36	100	95	98	100	90	96 ←	100	100	100 ←
18	28	27	27	86	86	86 <sup>#</sup>	71	78	73 ←	100	92	97 ←
31	28	30	29	34	50	39	24	44	29	47	55	50 ←
33	17	30	21	18	35	23	17	22	18	18	45	27
45	22	17	20	19	8	15	24	8	18	13	8	11

Modified from Faust et al., (2016) Vaccine 34:1559-65.

# Vaccine-induced neutralizing antibody responses are sustained for 4 years in HIV+ patients



## Seroprevalence rates 4-years post-vaccination:

3-doses: 86-93% for HPV types 6, 11 and 16; 64% for HPV18

4-doses: >95% for HPV types 6, 11 and 16; 75% for HPV18

Modified from Levin et al., (2017) Vaccine 35(13):1712-20.

## Outlook #2

- In the people living with HIV:
  - bi- and quadrivalent HPV vaccines induce **high rates of seroconversion**;
  - Vaccine-induced **cross-reactivity** is **diminished**, as compared to the general, HIV-uninfected population;
  - Vaccine-induced nAb responses are **sustained for 4 years**;
  - Amplitude and sustainability of vaccine-induced nAb levels also depend on **HIV RNA load and CD4 counts** at first dose (Moscicki et al 2019 Clin Infec Dis; Cespedes et al 2018, Papillomavirus Res)
- **estimation of VE in adults living with HIV is challenging** due to the seropositivity rates at baseline.

# Acknowledgments



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Research for a Life without Cancer

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