Clinical Infectious Diseases

MAJOR ARTICLE

Immunogenicity and Safety of 2 Versus 3 Doses of 9-Valent Vaccine Against Human Papillomavirus in Women With Human Immunodeficiency Virus: The Papillon Randomized Trial

Deborah Konopnicki,[1] Christine Gilles,[2] Yannick Manigart,[2] Patricia Barlow,[2] Anca Reschner,[1] Coca Necsoi,[1] Marc Delforge,[1] Davy Vanden Broeck,[3] Nicolas Dauby,[1] and Stéphane De Wit[1]

[1]Infectious Diseases Department and HIV Reference Center, Saint-Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium; [2]Gynecology Department, Saint-Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium; and [3]Laboratory of Molecular Pathology Algemeen Medisch Laboratorium, Sonic Healthcare Belgium and Belgian National Reference Laboratory for Human Papillomavirus, Antwerp, Belgium

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Before the Papillon study

- Guidelines recommended to vaccinate persons with HIV (PWH) against HPV with 9-valent (9v) vaccine, given with a **3-doses** schedule (0, 2 and 6 months)(EACS, WHO, DHHS, ACIP, BHIVA, French guidelines)

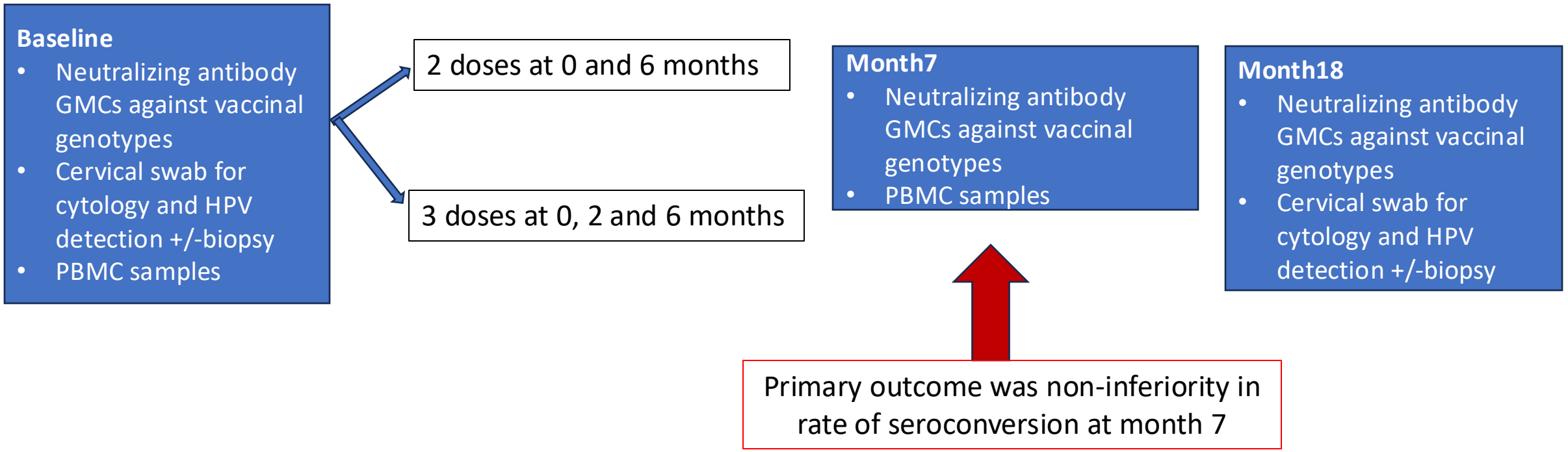
- Studies (n=18) on HPV vaccine in PWH, using the 2- or 4-valent vaccine given **in 3 doses**, had showed excellent immunogenicity with a seroconversion rate >90% for all vaccine genotypes and good safety.
- The 9v vaccine had only been tested in a single study including 100 PWH but only 15 women.

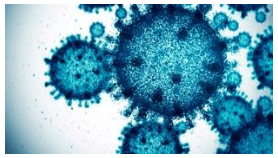
- **In persons without HIV** or other immunosuppression, **2 doses** of HPV vaccine provide similar immunogenicity than 3 doses but there were **no data on a 2-doses regimen** for PWH.

Single centre, prospective, non inferiority randomized-controlled study in Saint-Pierre University hospital

9-valent vaccine against HPV 6/11/16/18/31/33/45/52/58

not pregnant WWH 15-40 years-old with viral load < 400 cp/ml for at least 6 months





June 2018 to January 2019
Open-label phase
3 doses: n= 45

January 2019 to February 2021
Randomized phase n=100
2 doses: n= 50
3 doses: n= 50

February 2021 to October 2021
Last phase
2 doses: n= 22

Modified-ITT (mITT) at month 7

According to randomised arm
2 doses: n= 43
3 doses: n= 47

Per protocol at month 7
According to number of doses received
n=165
2 doses: n= 63
3 doses: n= 88

Table 1. Characteristics by Study Group in Modified Intention-to-Treat and Per Protocol Analyses at Baseline Except for Human Immunodeficiency Virus RNA and Median CD4 T-Lymphocyte Count at Baseline and Month 7

Characteristic	Total (n = 167)	mITT (Randomized to)			Per Protocol		
		2 Doses (n = 50)	3 Doses (n = 50)	*P* Value	2 Doses Received (n = 63)	3 Doses Received (n = 88)	*P* Value
Age at BL, y, median (IQR)	35.1 (31.2–38.3)	33.6 (31.6–38.4)	35 (31.2–37.9)	.86*	35.1 (30.9–38.4)	34.7 (31.2–38.3)	.88*
Region of origin				.29			.98
Sub-Saharan Africa	135 (81)	38 (76)	40 (80)		50 (79)	73 (83)	
North Africa	6 (3.59)	4 (8)	0		3 (4.8)	2 (2.3)	
Latin America	5 (3)	1 (2)	2 (4)		2 (3)	3 (3.4)	
Asia	3 (1.8)	1 (2)	2 (4)		1	2 (2.2)	
Europe (Central and East)	18 (11)	6 (12)	6 (12)		7 (11)	8 (9)	
HIV acquisition risk factor				.19			.36
Heterosexual	146 (87)	45 (90)	40 (80)		56 (89)	74 (84)	
Blood products, nosocomial, and IVDU	7 (4.2)	2 (4)	3 (6)		4 (6.3)	3 (3.4)	
Perinatal acquisition	7 (4.2)	2 (4)	1 (2)		2 (3.2)	5 (5.7)	
Unknown	7 (4.2)	1 (2)	6 (12)		1 (1.6)	6 (6.8)	
BMI at BL, kg/m^2, median (IQR)	28.1 (24–32.3)	28.9 (24.8–32.7)	28 (23.3–32)	.65	29 (24.2–32)	28 (23.7–31.3)	.92
HIV duration at BL, y, median (IQR)	8.1 (4.7–13.3)	7.6 (4.7–13.3)	9.1 (4.1–13.6)	.61*	7.3 (4.7–13)	9.4 (4.7–13.4)	.16*
Time on ART at BL, y, median (IQR)	5.7 (3.2–9.5)	5.6 (2.7–8)	5.7 (2.7–8.8)	.92*	5 (2.6–7.8)	5.7 (3.5–10)	.15*
Median CD4 T-lymphocytes/μL							***P****
Nadir	307 (229–478)	337.5 (229–489)	310 (224–480)	.53*	329 (234–518)	286.5 (212–426)	.12*
Baseline	649 (492–831)	611.5 (458–866)	654.5 (492–911)	.49*	641 (478–866)	654 (506–840)	.45*
Month 7 (n = 149)	661 (505–824)	635.5 (473–856)	670.5 (513–903)	.62*	601 (487–847)	699 (516–817)	.34*
Median CD4/CD8 ratio, %							
Baseline	1 (0.7–1.4)	1 (0.6–1.4)	1.1 (0.8–1.6)	.09*	1.1 (0.8–1.6)	0.9 (0.6–1.4)	.08*
Month 7 (n = 149)	1.1 (0.8–1.5)	1 (0.7–1.3)	1.3 (1–1.5)	.04*	1.1 (0.9–1.5)	1 (0.7–1.4)	.08*
HIV RNA <50 copies/mL							
Baseline	154 (92)[a]	43 (86)	48 (96)	.16	55 (87.3)	85 (96.6)	.053
Month 7 (n = 150)	139 (93)[a]	36 (85.7)	45 (93.8)	.13	51 (87.9)	88 (95.7)	.056
Cumulative time with HIV RNA <50 copies/mL, median (IQR)	4 (1.8–7.2)	3.8 (1.6–6.7)	4.1 (1–6.6)	.89*	3.6 (1.3–6.5)	4.9 (2.5–8)	.05*

Table 1. Continued

Baseline Characteristic	Total (n = 167)	mITT (Randomized to) 2 Doses (n = 50)	mITT (Randomized to) 3 Doses (n = 50)	*P* Value	Per Protocol 2 Doses Received (n = 63)	Per Protocol 3 Doses Received (n = 88)	*P* Value
Presence of HPV in cervical sample at baseline (n = 165)							
Any HPV	57 (34.5)	15 (31)	22 (44)	.21	19 (30)	31 (35)	.60
LR-HPV (HPV-6/11/53/66/67)	14 (8.5)	7	3	.20	8 (13)	5 (6)	.15
HPV-6	0	0	0		0	0	
HPV-11	0	0	0		0	0	
HR-HPV	50 (30)	11 (22.4)	21 (42)	.053	15 (24)	29 (33)	.28
No. of HR-HPV genotypes, median (range)	1 (1–2)	1 (1–2)	1 (1–1)	.29	1 (1–2)	1 (1–1)	
HPV-16	3 (1.8)	0	1	1	0	2	.51
HPV-18	4 (2.4)	2	1	.62	3	1	.31
HPV-31	4 (2.4)	0	3	.24	1	3	.64
HPV-33	6 (3.6)	0	5	.056	0	6	.04
HPV-35	10 (6)	2	4	.67	3	6	.74
HPV-39	1	0	0	.62	0	0	
HPV-45	7 (4.2)	1	3	.62	3	4	1
HPV-51	6 (3.6)	3	1	1	4	2	.23
HPV-52	7 (4.2)	2	3	1	3	2	.65
HPV-56	3 (1.8)	0	1	1	0	3	.27
HPV-58	3 (1.8)	1	0	.49	1	1	1
HPV-59	3 (1.8)	1	0	.50	1	2	1
HPV-68	10 (6)	4	4	1	4	5	1
Cervical cytology	n = 164	n = 50	n = 49	.58	n = 63	n = 85	.43
Normal	120 (72)	34	33		44 (69.8)	66 (76.7)	
ASCUS	21 (12.7)	6	8		8 (12.7)	11 (12.8)	
LSIL	22 (13)	10	6		11 (17.5)	8 (9.3)	
HSIL	1 (0.6)	0	1		0	0	
Cervical biopsy	n = 30	n = 9	n = 8	.46	n = 12	n = 13	.75
Normal	14 (47)	5	2		5	6	
CIN1	16 (53)	4	6		7	7	

Data are presented as No. (%) unless otherwise indicated. *P* values by Fisher exact test or *Kruskal–Wallis test.

Abbreviations: ART, antiretroviral therapy; ASCUS, atypical squamous cells of undetermined significance; BL, baseline; BMI, body mass index; CIN1, Cervical intraepithelial neoplasia; HIV, human immunodeficiency virus; HPV, human papillomavirus; HR, high-risk; HSIL, high-grade squamous intraepithelial lesions; IQR, interquartile range; IVDU, intravenous drug use; LR,

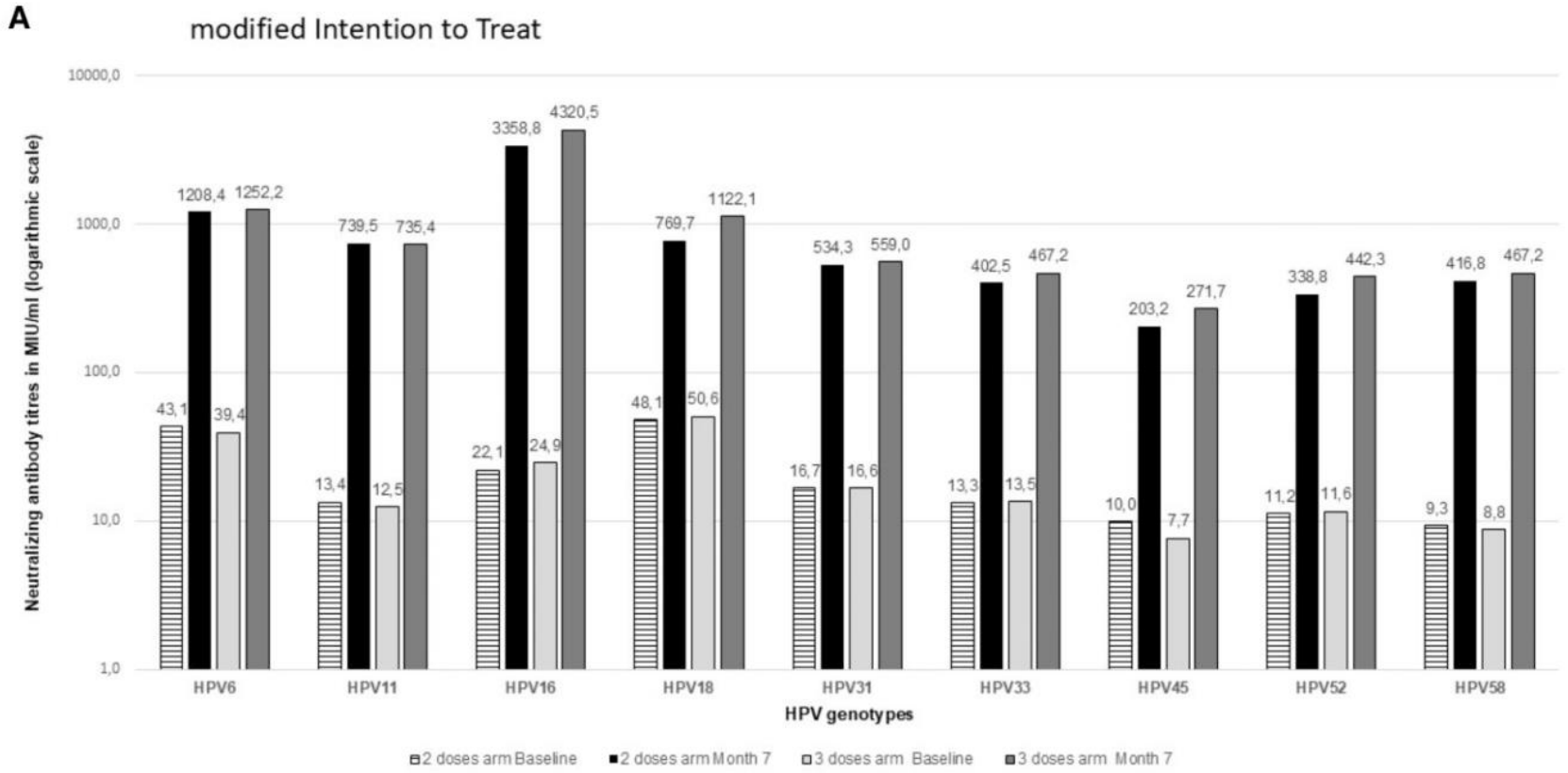
Baseline HPV seropositivity for HPV antibodies was present in <15% participant for most vaccine genotypes

Results at month 7: mITT

- Seroconversion 2 doses: 97.7%

  3 doses: 97.9%.

- Antibodies titers increased from baseline to M7 by 1.2–2.4 log10



Results at month 7: per protocol

- Seroconversion 2 doses: 96.8%

  3 doses: 98.9%.

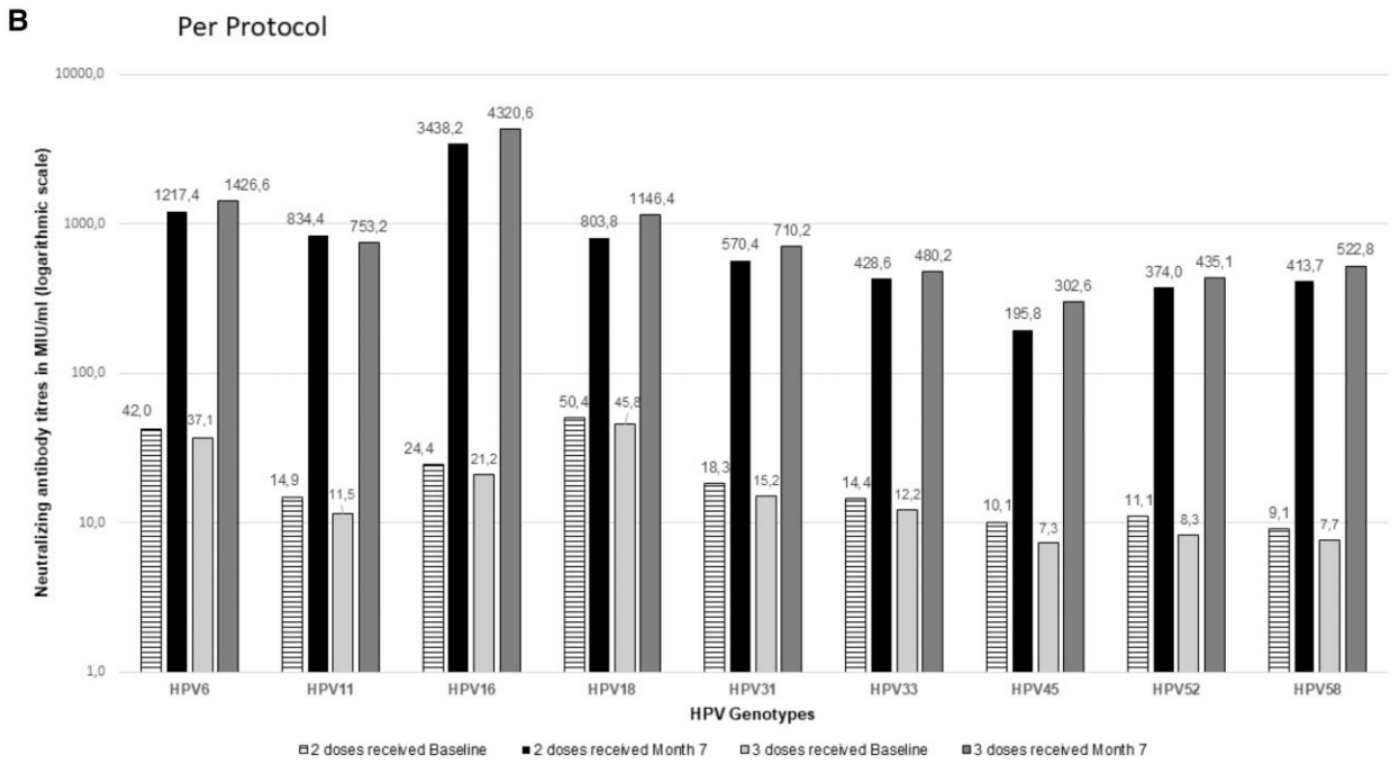


Figure 2. Neutralizing antibody titers (mIU/mL) at baseline and month 7 in modified intention-to-treat analysis according to the 2- vs 3-dose arm (*A*) and per protocol analysis according to 2 vs 3 doses received (*B*). Abbreviation: HPV, human papillomavirus.

Results: adverse event

There were no serious adverse events

Most reported AE were self-resulting mild local symptoms at injection site and of short duration.

Participants with 3 doses experienced local reactions more frequently (82% vs 60% for 2 doses, *P* = .027) with more symptoms and longer duration.

Table 3. Adverse Events During the Whole Course of Vaccination in Modified Intention-to-Treat and Per Protocol Analyses

	mITT			Per Protocol		
Adverse Event	2 Doses (n = 50)	3 Doses (n = 50)	*P* Value	2 Doses (n = 61)	3 Doses (n = 88)	*P* Value
Local reactions (pain, redness, swelling, pruritus, redness, other)						
Reported at least 1 AE, No. (%)	30 (60)	41 (82)	.027*	37 (61)	70 (80)	.016*
AEs, No., median (IQR)	1 (0–2)	2 (1–3)	.0045	1 (0–2)	2 (1–3)	.005
Duration of AEs, d, median (IQR)	0.3 (0–2)	2 (1–4)	.0007	1 (0–3)	2 (1–4)	.0003
Systemic reactions (fever, dizziness, nausea, fatigue, headache, other)						
Reported at least 1 AE, No. (%)	32 (64)	31 (62)	1*	40 (66)	47 (53)	.18*
AEs, No., median (IQR)	1 (0–1)	1 (0–2)	.23	1 (0–1)	1 (0–2)	.82
Duration of AEs, d, median (IQR)	1 (0–2)	1 (0–2)	.8	1 (0–2)	1 (0–2)	.53

P values by Kruskal–Wallis test or *Fisher exact test.

Abbreviations: AE adverse event; IQR, interquartile range; mITT, modified intention-to-treat.

Conclusion

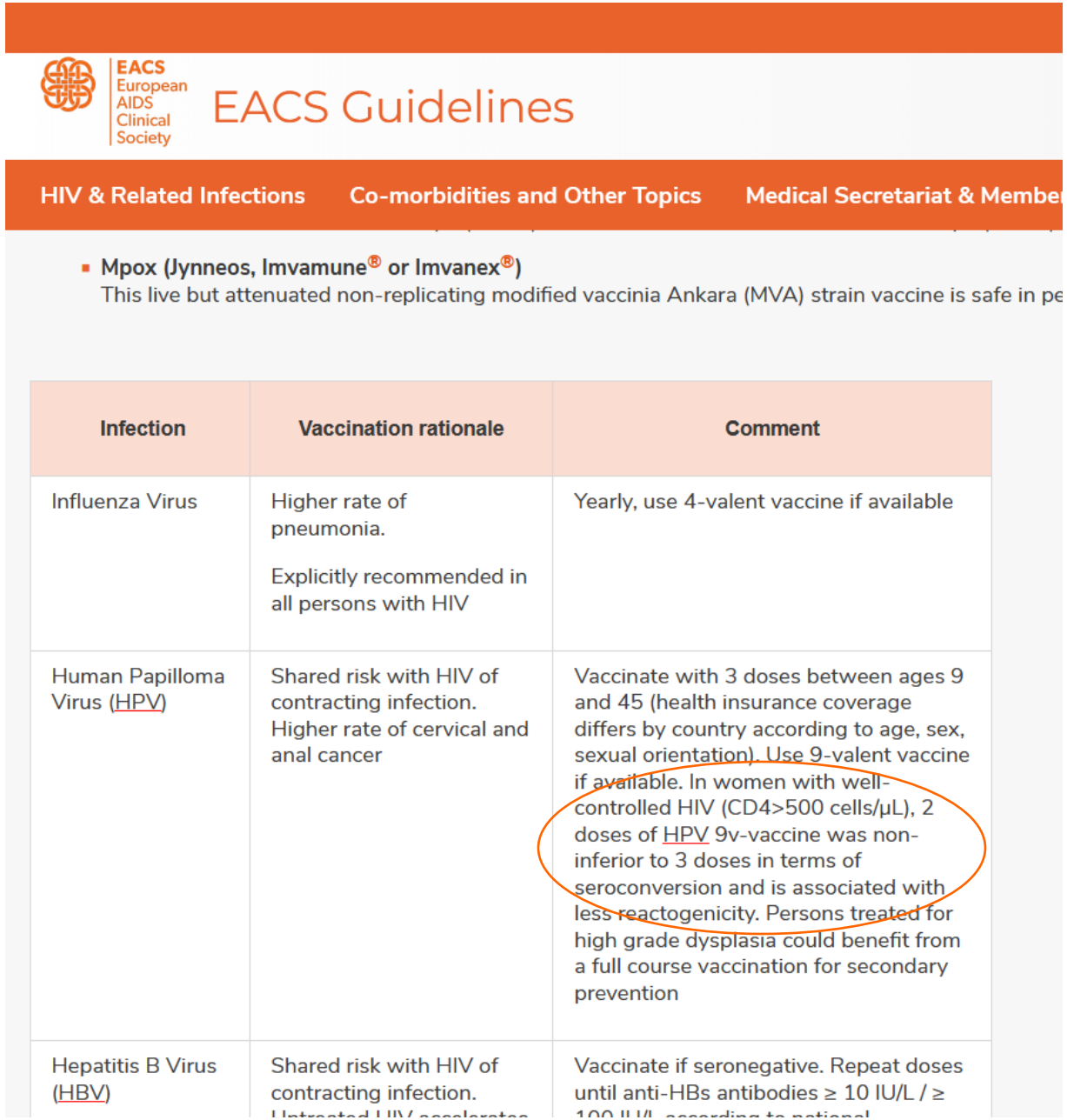
In women with well-controlled HIV infection, **2 doses** of 9vHPV vaccine given 6 months apart **are noninferior to 3 doses** in terms of immunogenicity with more than 95% of women vaccinated with 2 doses developing **high levels of neutralizing antibodies against the 9 vaccine genotypes.**

Safety was very good and 2-doses regimen was statistically significantly associated with less reactogenicity than 3 doses.

This study is the first to evaluate the 9v-vaccine safety and immunogenicity in a large cohort of WWH.

Implications

- Implications for women living with HIV but also for global health in terms of
  - ➢Lower cost
  - ➢Better compliance
  - ➢Health care management
  - ➢Immunization strategy policy.



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HIV & Related Infections | Co-morbidities and Other Topics | Medical Secretariat & Membe

- **Mpox (Jynneos, Imvamune® or Imvanex®)**
  This live but attenuated non-replicating modified vaccinia Ankara (MVA) strain vaccine is safe in pe

Infection	Vaccination rationale	Comment
Influenza Virus	Higher rate of pneumonia. Explicitly recommended in all persons with HIV	Yearly, use 4-valent vaccine if available
Human Papilloma Virus (HPV)	Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer	Vaccinate with 3 doses between ages 9 and 45 (health insurance coverage differs by country according to age, sex, sexual orientation). Use 9-valent vaccine if available. In women with well-controlled HIV (CD4>500 cells/µL), 2 doses of HPV 9v-vaccine was non-inferior to 3 doses in terms of seroconversion and is associated with less reactogenicity. Persons treated for high grade dysplasia could benefit from a full course vaccination for secondary prevention
Hepatitis B Virus (HBV)	Shared risk with HIV of contracting infection.	Vaccinate if seronegative. Repeat doses until anti-HBs antibodies ≥ 10 IU/L / ≥

Perspectives

Results of

- Antibody titles at month 18 are expected end of 2025
- Cellular immunity on PBMC samples

- Extension Dr Dauby and Nathalia Gorra

Antibody titles at month 24, 48 and 60

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- Dr Christine Gilles
- Dr Yannick Manigart

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