HPV vaccination in people living with HIV

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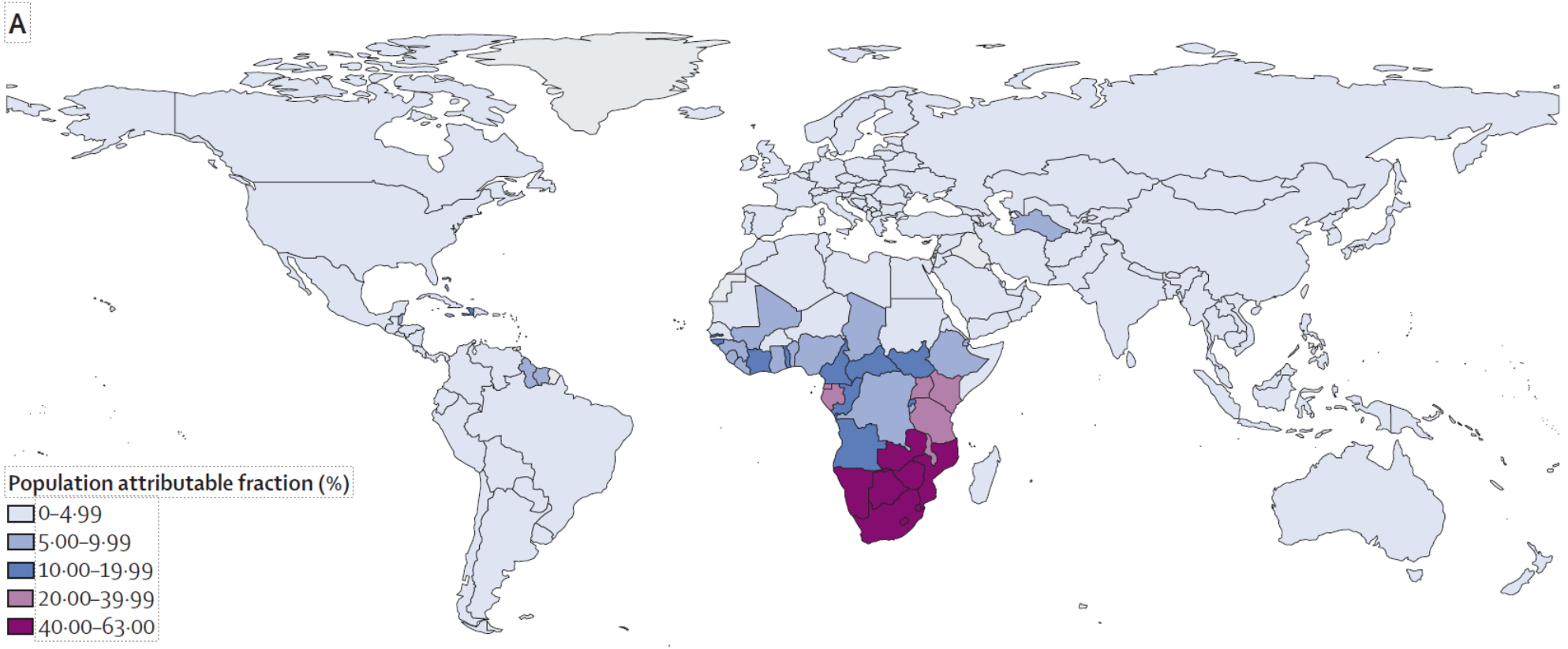
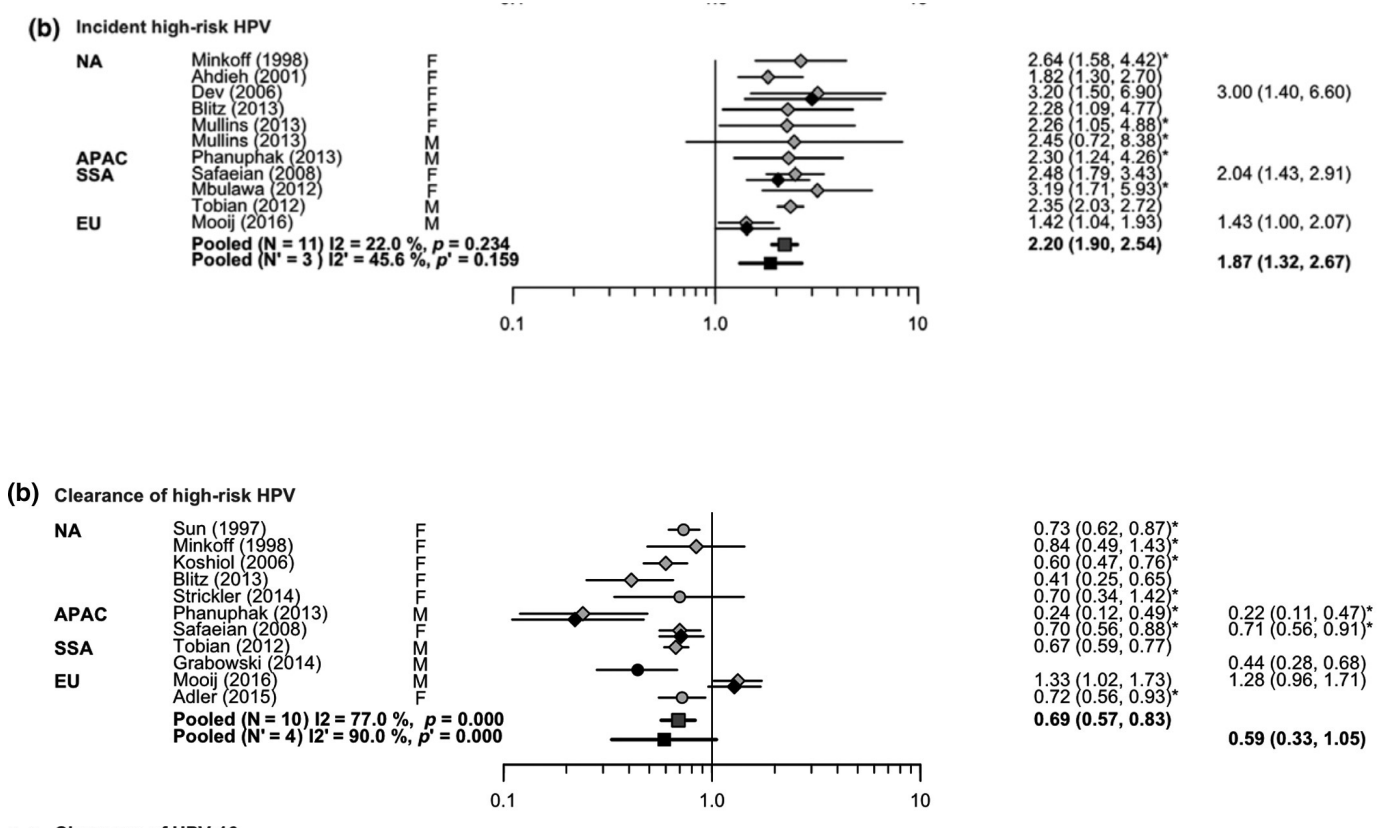
Women living with HIV have a 6-fold higher risk for cervical cancer



6 countries accounted for half of all women living with HIV who developed cervical cancer

Stelzle, Lancet Global Health 2021

HPV infection and HIV

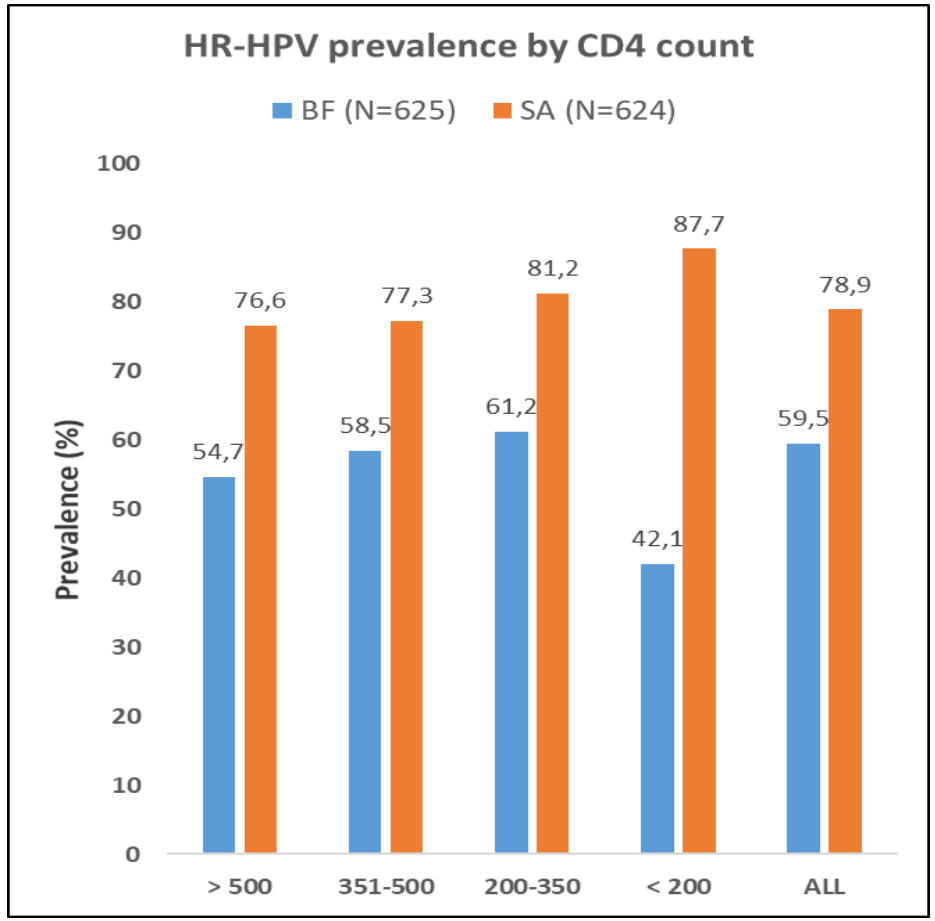


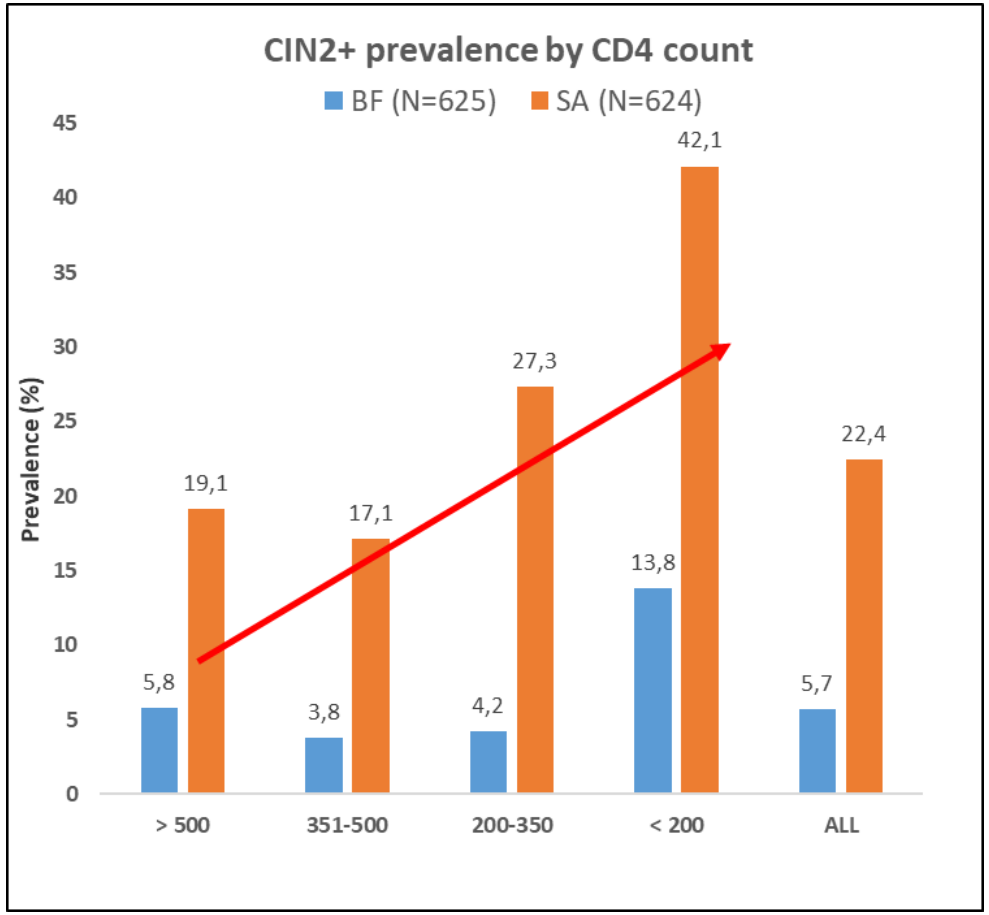
People living with HIV have

- ↑HR HPV incidence
- ↓HR HPV clearance
- Multiple HR HPV infections
- ↑progression to neoplasia
- Younger age at presentation
- ↑ recurrence

Looker, JIAS 2018; Stelzle Lancet Global Health 2021; Kelly, AIDS 2017

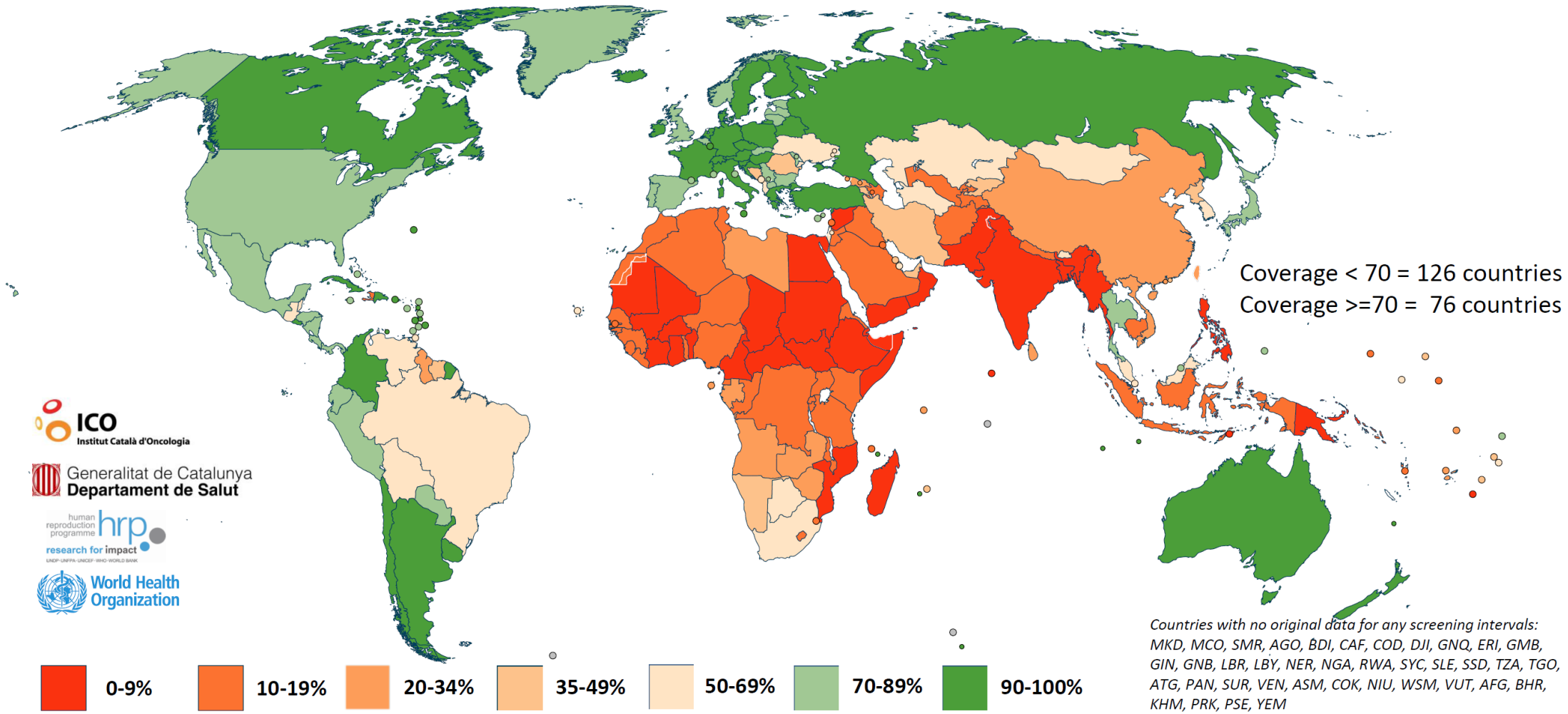
ART associated with lower risk of HPV infection and disease





Kelly, AIDS 2017; Chikandiwa, Plos One 2018

Ever in lifetime screening coverage (2019), women aged 30-49y by country



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human reproduction programme hrp research for impact UNDP-UNFPA-UNICEF-WHO-WORLD BANK

World Health Organization

Countries with no original data for any screening intervals: MKD, MCO, SMR, AGO, BDI, CAF, COD, DJI, GNQ, ERI, GMB, GIN, GNB, LBR, LBY, NER, NGA, RWA, SYC, SLE, SSD, TZA, TGO, ATG, PAN, SUR, VEN, ASM, COK, NIU, WSM, VUT, AFG, BHR, KHM, PRK, PSE, YEM

WHO recommendations for vaccination in women living with HIV

Vaccination of immunocompromised and/or HIV-infected individuals

Limited information is available about the immunogenicity of HPV vaccines in people who are immunocompromised and/or HIV-infected. Data on the use of HPV vaccines in a 3-dose schedule in HIV-infected females,[95, 96] males,[97] and children (aged 7–12 years)[98] are reassuring in terms of safety.[99]

Seroconversion against HPV types included in the vaccines, as well as non-vaccine types, was observed in HIV-infected children given HPV vaccines in a 3-dose schedule.[98, 100] In HIV-infected women, 3 doses of the bivalent vaccine induced lower GMTs than in HIV-uninfected women; however, the rate of seroconversion was the same in both groups.[101] The bivalent vaccine in a 3-dose schedule has similar immunogenicity to HPV-16 as the quadrivalent vaccine, but results in higher GMTs and higher rate of seroconversion to HPV-18 in HIV-infected adults.[102, 103, 104]

No data are available on use of the 2-dose schedule for bivalent, quadrivalent or nonavalent vaccines in persons infected with HIV.

WHO position paper, May 2017

Effectiveness of 7-Valent Pneumococcal Conjugate Vaccine Against Invasive Pneumococcal Disease in HIV-Infected and -Uninfected Children in South Africa: A Matched Case-Control Study

Cheryl Cohen,[1,2] Claire von Mollendorf,[1,2] Linda de Gouveia,[1] Nireshni Naidoo,[1,2] Susan Meiring,[3] Va

HIV often reduces responsiveness to vaccines and their effectiveness

Table 2. Effectiveness of 7-Valent Pneumococcal Conjugate Vaccine Against Invasive Pneumococcal Disease in HIV-Infected and -Uninfected Children by Pneumococcal Serotype

Outcome (No. of Cases/No. of Controls)	Unadjusted VE% (95% CI)	Adjusted VE% (95% CI)[a]
HIV-uninfected, ≥16 wk, ≥2 doses vs 0 doses		
PCV7 serotypes (48/194)	77 (40–91)	74 (25–91)
PCV7 serotypes plus 6A (71/289)	71 (35–87)	70 (28–88)
All serotypes (187/752)	35 (–13 to 63)	29 (–27 to 60)
Nonvaccine serotypes (101/403)	–56 (–315 to 41)	–76 (–384 to 36)
HIV-uninfected, ≥41 wk, ≥3 doses vs 0 doses		
PCV7 serotypes (23/86)	57 (–100 to 91)	90 (14 to 99)
PCV7 serotypes plus 6A (31/122)	47 (–109 to 87)	78 (–15 to 96)
All serotypes (89/353)	47 (–37 to 79)	63 (–1 to 87)
Nonvaccine serotypes (48/195)	2 (–433 to 82)	21 (–390 to 87)
HIV-infected, ≥16 wk, ≥2 doses vs 0 doses		
PCV7 serotypes (43/137)	15 (–145 to 71)	–12 (–449 to 77)
PCV7 serotypes plus 6A (60/188)	34 (–94 to 78)	29 (–174 to 81)
All serotypes (109/347)	31 (–42 to 67)	6 (–194 to 70)
Nonvaccine serotypes (44/136)	20 (–197 to 79)	–190 (–2997 to 73)
HIV-infected, ≥41 wk, ≥3 doses vs 0 doses		
PCV7 serotypes (28/86)	43 (–108 to 85)	57 (–371 to 96)
PCV7 serotypes + 6A (37/116)	53 (–49 to 85)	76 (–87 to 97)
All serotypes (68/223)	26 (–84 to 70)	46 (–122 to 87)
Nonvaccine serotypes (26/87)	–72 (–966 to 72)	76 (–166 to 318)

CID 2014

Safety and efficacy of human papillomavirus vaccination for people living with HIV: A systematic review and meta-analysis

Yongle Zhan, Xuan Liu, Yahui Feng, more...

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Article information

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REVIEW

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A systematic review of immunogenicity, clinical efficacy and safety of human papillomavirus vaccines in people living with the human immunodeficiency virus

Edison J. Mavundza [a], Alison B. Wiyeh[a], Phetole W. Mahasha[a], Gregory Halle-Ekane[b], and Charles S. Wiysonge[a,c,d]

Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males (Review)

Bergman H, Buckley BS, Villanueva G, Petkovic J, Garritty C, Lutje V, Riveros-Balta AX, Low N, Henschke N

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OPEN

Efficacy and safety of human papillomavirus vaccination in HIV-infected patients: a systematic review and meta-analysis

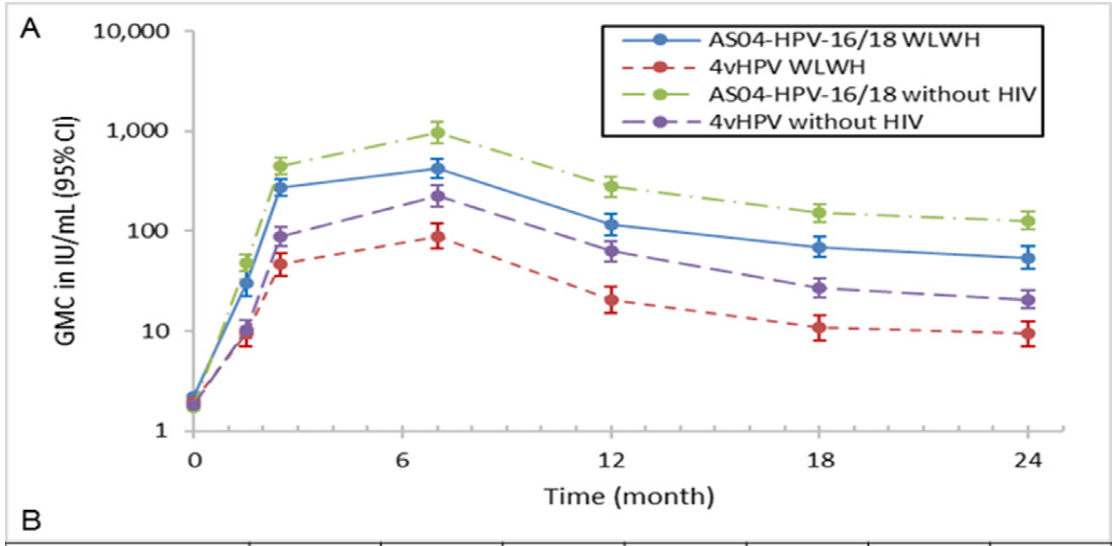
Antonella Zizza[1,11], Federico Banchelli[2,11], Marcello Guido[3,4,11]✉, Claudia Marotta[5,6], Francesco Di Gennaro[7], Walter Mazzucco[5,8,9], Vanna Pistotti[10] & Roberto D'Amico[2]

Safety and efficacy of HPV vaccination in PLWH

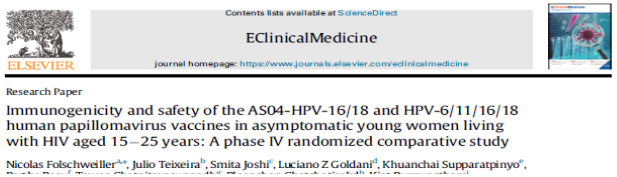
- 4-5 RCT included, 3-dose schedule
  - HIV-positive children 7-12 in USA; women 18-25 years in SA; women and men >27 years in Brazil and the US; >18 years in Denmark; MSM in Spain
- PLHIV show high seroconversion rate (>90%) for each vaccine with high antibody titres
- No differences in terms of severe adverse events
- Evidence of benefit of HPV vaccine in PLWH patients although efficacy on prevention of infection and prevention of neoplasm unknown
- Variations in CD4 counts and VL not observed
- Limited data on benefits for anogenital warts
- No RCT in PLHIV for 9vHPV vaccine

Zahn, 2019; Mavundza, 2019; Bergman, 2019; Zizza, 2021

Comparison of immunogenicity in q2 vs. q4, by HIV status (RCT in Brazil, Estonia, India and Thailand)



Seroconversion, % (n/N)	D0	W6	W10	M7	M12	M18	M24
AS04-HPV-16/18 WLWH	0 (0/96)	92·6 (88/95)	100 (95/95)	98·9 (88/89)	98·9 (89/90)	97·8 (87/89)	95·2 (80/84)
4vHPV WLWH	0 (0/105)	66·0 (68/103)	95·2 (99/104)	97·0 (96/99)	85·4 (82/96)	68·4 (65/95)	68·4 (65/95)
AS04-HPV-16/18 without HIV	0 (0/129)	100 (122/122)	100 (120/120)	100 (100/100)	100 (90/90)	100 (95/95)	100 (88/88)
4vHPV without HIV	0 (0/129)	89·7 (113/126)	98·4 (121/123)	98·2 (107/109)	99·0 (98/99)	98·1 (101/103)	98·0 (96/98)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EClinicalMedicine

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Research Paper

Immunogenicity and safety of the AS04-HPV-16/18 and HPV-6/11/16/18 human papillomavirus vaccines in asymptomatic young women living with HIV aged 15–25 years: A phase IV randomized comparative study

Nicolas Folschweiller[a,*], Julio Teixeira[b], Smita Joshi[c], Luciano Z Goldani[d], Khuanchai Supparatpinyo[e],

- Females 15-25 years, 257 HIV infected, 289 HIV uninfected
- Sizeable post-randomisation losses (546 enrolled, 448 analysed, 323 at M7)
- Higher HPV-18 seroconversion and titres with bivalent in HIV-infected women
- Similar findings in previous trial in Denmark (n=92; Toft 2014)

ACTG A5298: RCT of q4 in PLWH ≥ 27 years

Table 2. Vaccine Efficacy for Persistent Anal Infection, Persistent Oral Infection, Anal High-Grade Squamous Intraepithelial Lesions on Anal Biopsy, and Abnormal Anal Cytology

Endpoint	Vaccine Group		Control Group		Efficacy (95.1% Confidence Interval)
Persistent anal infection	n	Endpoint	n	Endpoint	
mITT-including single detection at final visit	286	27	283	33	22% (–31% to 53%)
mITT-persistent infection only	286	14	283	17	21% (–61% to 61%)
Per protocol analysis	276	7	277	10	31% (–82% to 74%)
Full ITT	288	28	286	41	35% (–5% to 60%)
Persistent oral infection					
mITT-including single detection at final visit	288	7	286	10	32% (–80% to 74%)
mITT-persistent infection only	288	1	286	8	88% (2% to 98%)
Per-protocol analysis	278	1	280	3	66% (–70% to 96%)
Full ITT	288	6	286	14	58% (–9% to 84%)
Improvement of anal high-grade squamous intraepithelial lesions on anal biopsy outcomes[a]					
Full ITT	288	46	286	45	0% (–44% to 31%)

Limited vaccine efficacy likely d/t high baseline HPV seropositivity and undetected infections at study entry

Wilkin, CID 2018

Efficacy of q4 in WLHIV

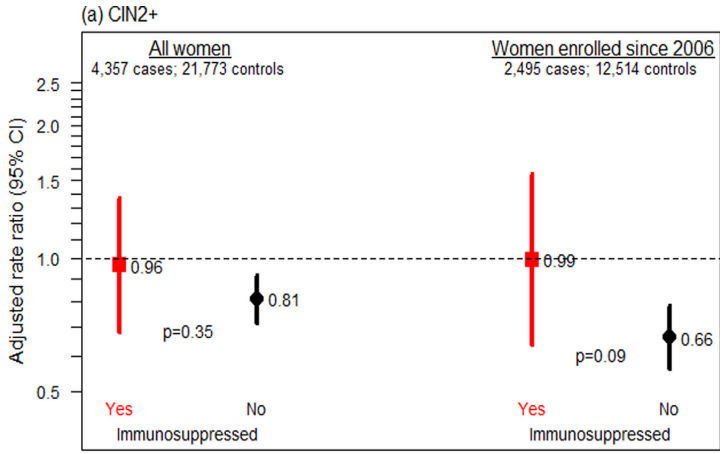
- 432 females, aged 9-65 years in Canada, 3-dose schedule
- ~ 270 included in 2 year outcome assessment
- No cases of CIN2+ during follow up
- Vaccine failures all d/t HPV 18, lower mean CD4 and nadir CD4
- Vaccine failures more common in WLH when compared to non-contemporary population

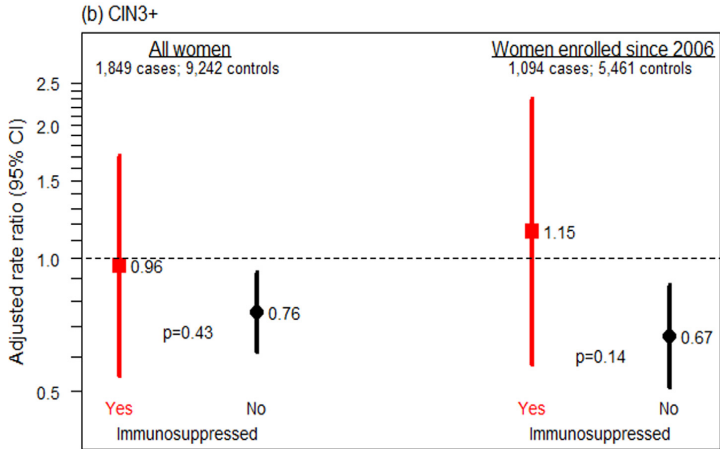
Table 3. Per-Protocol Efficacy Vaccine Failure Listing

Case Type	Baseline Age	Baseline CD4 Count (cells/mm^3)	CD4 Nadir (cells/mm^3)	Screening HIV Viral Load (copies/mL)	Baseline HIV Viral Load (copies/mL)	Time to Infection or Disease/Duration of Follow-up (years)	Log Peak HPV 18 GMT
qHPV	20	430	400	425	20027	2.0	5.37
qHPV	44	292	32	<50	<50	1.6	5.86
qHPV	49	320	33	<50	<50	1.8	6.95
qHPV	30	1570	767	<50	<50	2.0	6.03
Wart	47	130	40	<50	96952	1.6	NA
Wart	42	450	30	<50	NA	0.6	NA
Wart	42	346	244	<50	<50	0.6	NA
Wart	27	300	30	<50	71	1.5	NA
Median of Cases	42	333	37			1.6	5.95
Median of Non-Cases	39	513	240			2.0	5.87

McClymont, 2019

Influence of immune status on HPV vaccine effectiveness





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Vaccine

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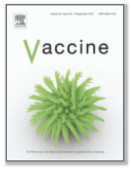
Short communication

Effectiveness of 'catch-up' human papillomavirus vaccination to prevent cervical neoplasia in immunosuppressed and non-immunosuppressed women

Michael J. Silverberg [a,*], Wendy A. Leyden [a], Jennifer O. Lam [a], Chun R. Chao [b], Steven E. Gregorich [c], Megan J. Huchko [d,e], Shalini Kulasingam [f], Miriam Kuppermann [d,g], Karen K. Smith-McCune [d], George F. Sawaya [d,g]

- HPV vaccination resulted in 19% reduction in CIN2+ for women without immunosuppression history but non-significant 4% reduction in women with immunosuppression history.
- More research needed on whether HPV vaccine effectiveness varies by immunosuppressive status.

Vaccine
Volume 34, Issue 40, 14 September 2016, Pages 4799-4806



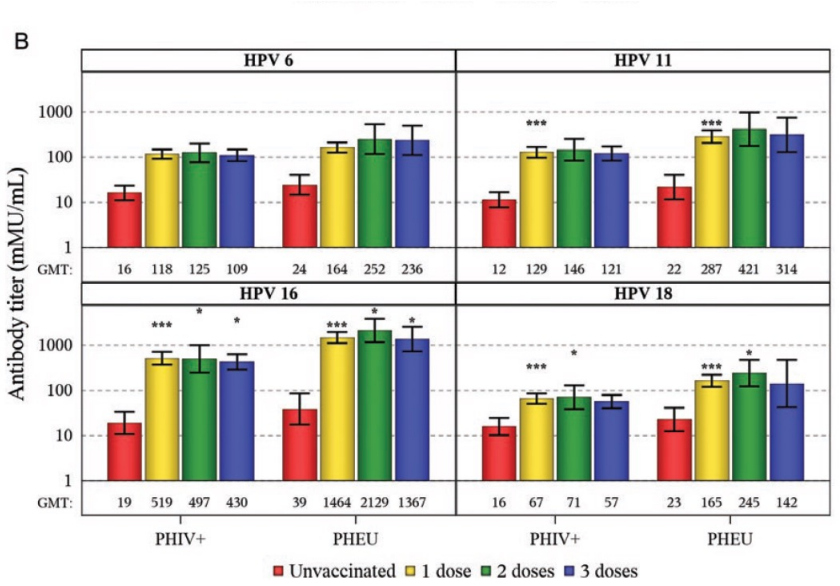
HIV viral suppression results in higher antibody responses in HIV-positive women vaccinated with the quadrivalent human papillomavirus vaccine

Deborah M. Money [a, b, c], Erin Moses [b], Sandra Blitz [d], Shannon M. Vandriel [a, b], Nancy Lipsky [b], Sharon L. Walmsley [c, d, e], Mona Loutfy [c, e, f], Sylvie Trottier [g], Fiona Smaill [h], Mark H. Yudin [i], Marina Klein [c, j], Marianne Harris [k, l], Jeffrey Cohen [m], Wendy Wobeser [n], Ari Bitnun [o, p], Normand Lapointe [q, r], Lindy Samson [s], Jason Brophy [s] ... Julie van Schalkwyk [a, b]

- 372 women, 18+ years
- q4 vaccine, 3-dose schedule (74%)
- M7 seroconversion rates >90% vaccine types
- Participants with HIV VLS at 1st dose had 1.74-3.05 higher peak antibody response ($p<0.0001$)

Clinical effectiveness in HIV infected or exposed pediatric populations

- 310 PLWH, 148 PHEU
- Observational
- Age at 1st vaccine dose 12-13 years
- GMTs similar for 1, 2 and 3 doses
- Higher GMTs associated with
  - Younger age and
  - Lower HIV RNA at first dose



- Clinical outcomes
  - Abnormal cytology incidence 18.3 per 100 py (restricted to vaccine pre-sexual debut)
  - Genital warts incidence low ~ 2 per 100py

Limited data on prevention of HPV infection

- Few data showing effectiveness vs. HPV infection or disease
- Concerns that protection is limited
- Immune status appears to influence effectiveness
  - Breakthrough infections at lower CD4+ counts and higher VL
  - ART appears to influence antibody titres
  - Younger age at first dose may be important
  - No differences in immunogenicity by 1, 2, 3 doses
- No data on q9 vaccines

Expected results for q9 vaccine

- Spain
  - Trial of immunogenicity and safety of 9vHPV vaccine in 158 adult HIV + women.
- USA
  - RCT in the USA is assessing the immunogenicity of the 9vHPV vaccine in MSM infected by HIV.
- COVENANT trial
  - is evaluating the effect of HPV vaccine in reducing lesions in HIV + women with high-grade cervical lesions.

Zizza, 2021

Other studies of HPV vaccine impact, by HIV status

Primary objectives

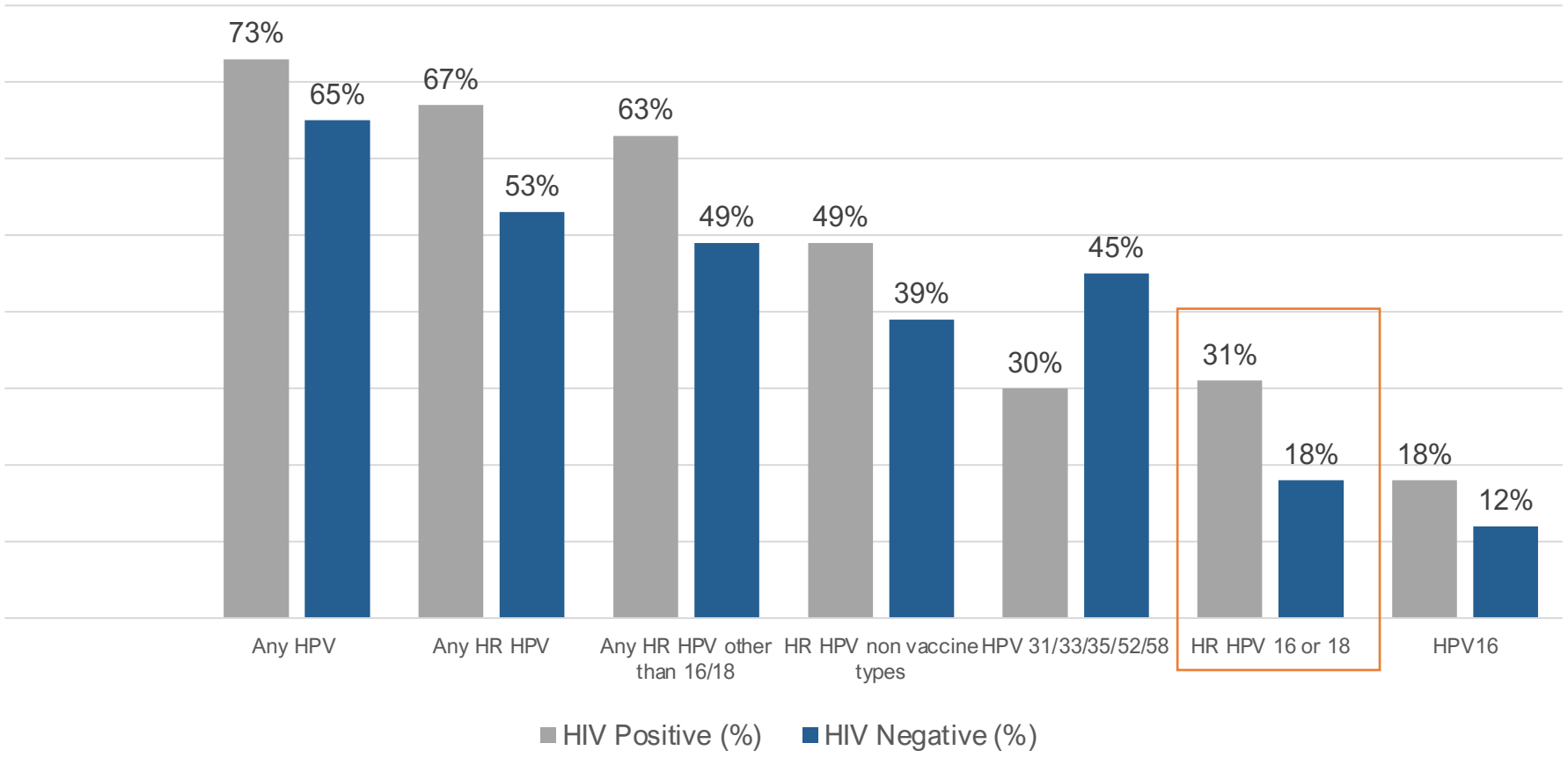
Measure the population impact of the **national 2-dose vaccine schedule**, delivered in Grade 4 to ≥9-year-old girls, in protecting against infection with HPV 16 and 18

Measure the population impact of a **1-dose vaccine schedule**, delivered as a catch-up, to AGYW in Grade 10 in one district, in protecting against infection with HPV 16 and 18

Secondary objective

Determine whether HIV infection status affects the impact of both HPV vaccine schedules.

HOPE Survey 1: HPV prevalence, by HIV status



HPV 16/18 infection associated with HIV status, 2 + partners

Programmatic considerations



What is the strategy for:

- Girls vaccinated with a 1-2 doses who are already HIV positive (around 1% resulting from PMTCT) either in the primary series or in catch-up cohorts
- Girls vaccinated with a 1-2 doses at age 9-12 years who subsequently become HIV positive by age 18 years (4-5% prevalence increasing to 25-30% by 30 years)

Do we continue with three doses for WLHIV knowing the challenges of getting two dose coverage?

Suggestions for next steps

- Ensure that future trials include populations of women living with HIV
- Consider data gaps on prevention of infection and look at opportunities to address
- Refocus on efforts to immunize WLHIV with HPV vaccines – catch up strategy
  - Importance of HIV testing, ARV access, retention in care and HIV viral suppression
  - Integrate HPV vaccination into HIV care
- Build surveillance platforms in LMIC that can monitor vaccine impact in HIV positive populations
- Other pending questions:
  - duration of protection
  - optimal schedules and booster options for WLH who are
    - HIV positive at time of initial vaccination
    - HIV negative but seroconvert post-vaccination

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