

19 September 2019

# HPV Vaccination in people living with HIV

Associate Professor Dr. Jason Ong  
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# Outline

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- **HPV**
- **HPV vaccination**
  - Immunogenicity
  - Safety
- **Should we vaccinate PLHIV (MSM)?**





# Audience question

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**Offering HPV vaccination to PLHIV should be implemented**

- Yes?**
- No?**
- Don't know...**

19 September 2019

# HPV

# Human papilloma virus

Most  
common viral  
STI

- Spread by direct, skin-to-skin contact during vaginal or anal sex
- Usually no symptoms and goes away by itself

40 genotypes  
infecting  
anogenital  
region

- Can cause genital warts (HPV 6, 11) and
- Squamous cell cancer (HPV 16, 18) - oropharyngeal, genital, cervical, anal

# Perfect storm for PLHIV (MSM)

- Increased life expectancy<sup>1</sup>
- Higher prevalence anal HPV<sup>2</sup>
  - High risk HPV ~74%
- Persistent HPV<sup>3</sup>
- Faster rates of progression

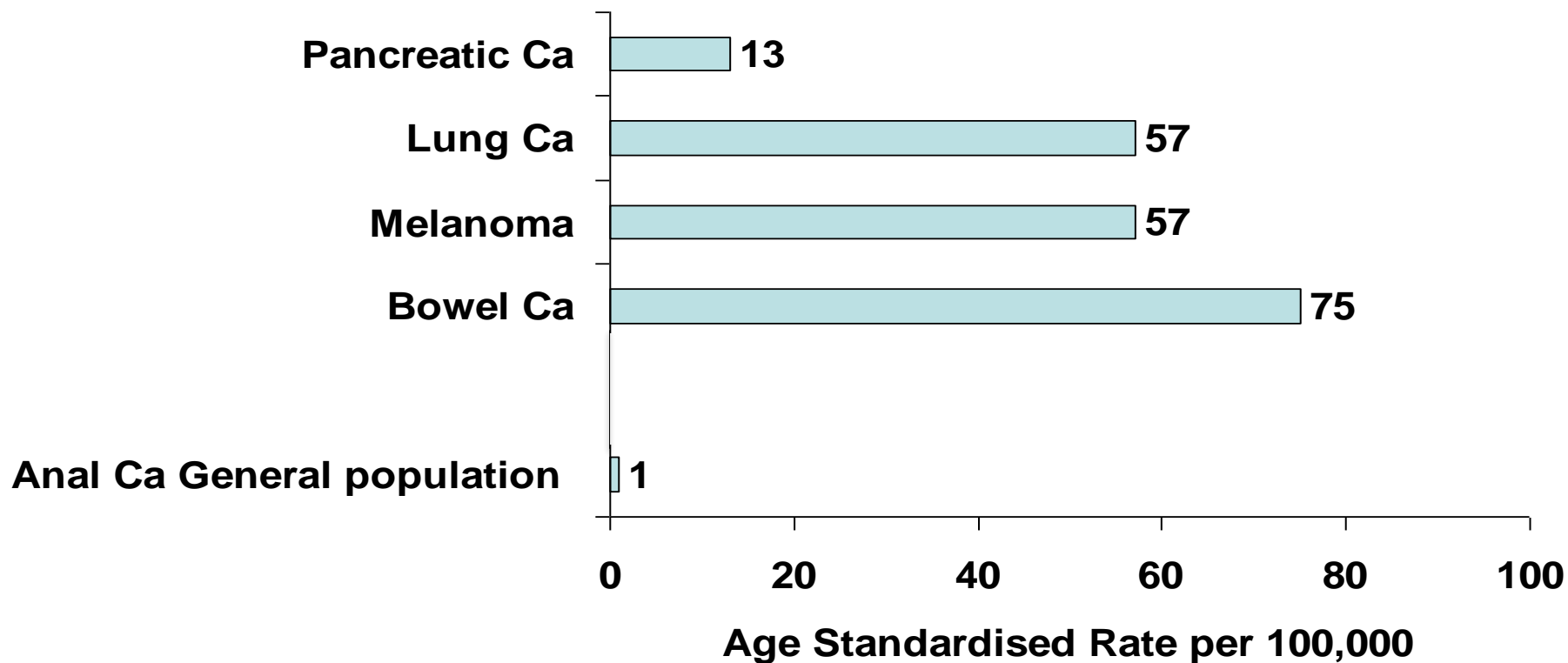
<sup>1</sup>Lancet 2008; 372(9635), 293-299

<sup>2</sup>Machalek. Lancet 2012; 13(5), 487-500

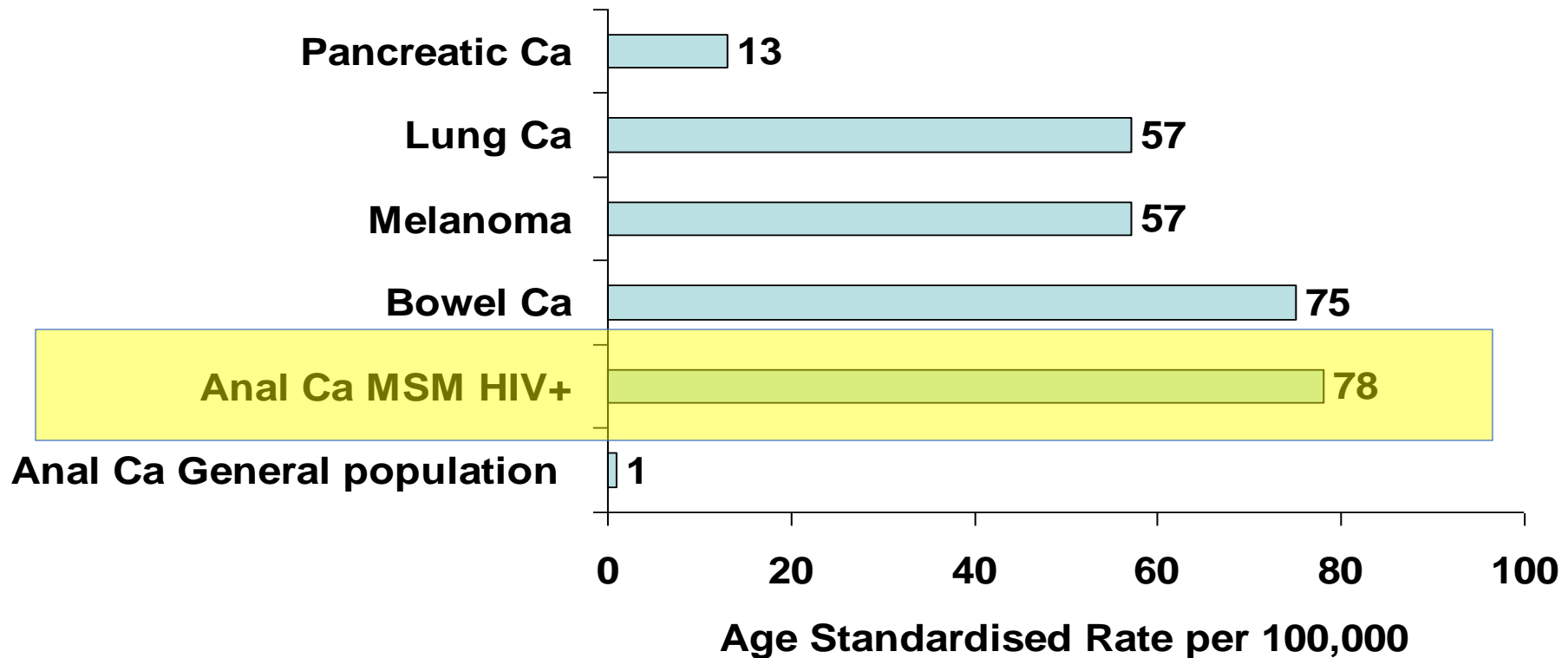
<sup>3</sup>de Pokomandy. JID; 199(7), 965-973



# Anal cancer in HIV positive MSM compared to cancers in men in the general community



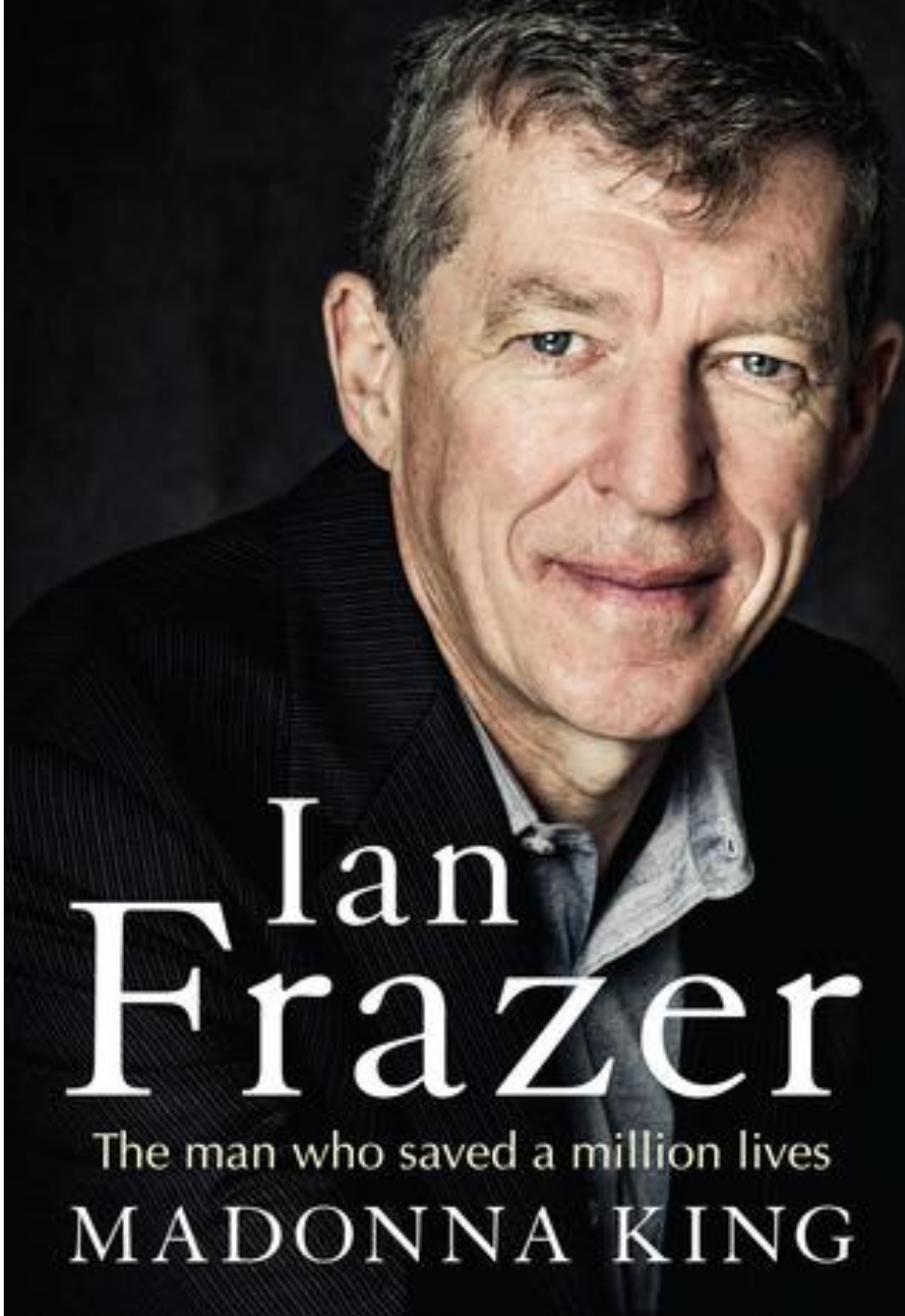
# Anal cancer in HIV positive MSM compared to cancers in men in the general community





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# HPV vaccine



# Ian Frazer

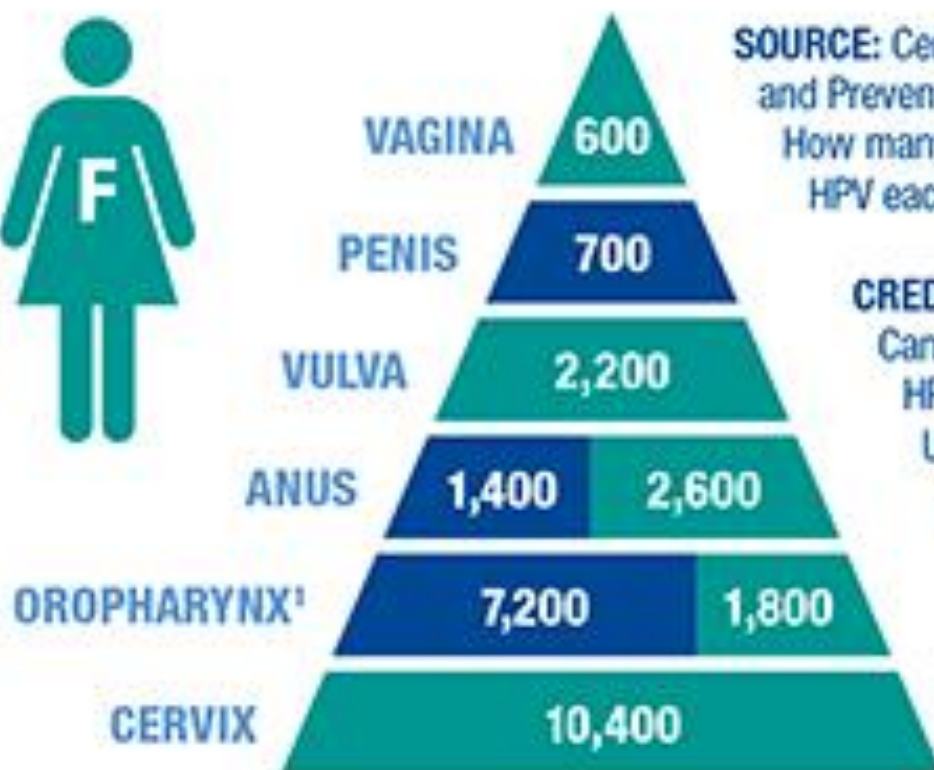
The man who saved a million lives  
MADONNA KING





# OF CANCERS

attributed to HPV infections in the U.S.



**SOURCE:** Centers for Disease Control and Prevention. HPV and cancer: How many cancers are linked with HPV each year? June 2014.

**CREDIT:** The President's Cancer Panel. Accelerating HPV vaccine uptake: Urgency for action to prevent cancer. 2014.

<sup>1</sup>Oropharyngeal cancers affect the throat, base of the tongue and tonsils.

# HPV vaccine

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## **An opportunity to do a lot of good**

- 4vHPV -> prevent 76% anal cancer / 71% cervical cancer
- 9vHPV -> prevent 83% anal cancer / 89% cervical cancer

Hoots 2009, Int J Cancer 124(10):2375-83.

# HPV vaccination in Australia

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- **National HPV vaccination program**
  - Girls (2007)
  - Boys (2013)
  - Patchy MSM catchup programs (up to 26 years old)

**BUT**

- Older individuals (esp. PLHIV) unlikely to benefit

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# Immunogenicity

# Immunogenicity

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Poor responses to standard vaccination series have been documented in HIV-infected patients.

- Hepatitis A / B
- VZV

How about for HPV?



# Immunogenicity

## At least 10 studies

Levin, 2010	Safety and Immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. <i>J Acquir Immune Defic Syndr.</i> 2010;55(2):197-204
Weinberg, 2012	Humoral, mucosal, and cell-mediated immunity against vaccine and nonvaccine genotypes after administration of quadrivalent human papillomavirus vaccine to HIV-infected children. <i>J Infect Dis.</i> 2012;206:1309-1318
Denny, 2013	Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. <i>Vaccine.</i> 2013;31:5745-5753
Toft, 2014	Comparison of the immunogenicity and reactogenicity of Cervarix and Gardasil human papillomavirus vaccines in HIV-infected adults: a randomized, double-blind clinical trial. <i>J Infect Dis.</i> 2014;209:1165-1173
Faust, 2016	Human papillomavirus neutralizing and cross-reactive antibodies induced in HIV-positive subjects after vaccination with quadrivalent and bivalent HPV vaccines. <i>Vaccine.</i> 2016;34:1559-1565
Wilkin, 2010	Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. <i>J Infect Dis.</i> 2010;202(8):1246-53.
Palefsky, 2014	AMC 054: safety and Immunogenicity of the Quadrivalent HPV Vaccine in Indian HIV-Infected Women. Conference on Retroviruses and Opportunistic Infections: 2014; Boston, MA. 2014.
Kojic, 2014	Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. <i>Clin Infect Dis.</i> 2014;59(1):127-135.
Giacomet, 2014	Safety and immunogenicity of a quadrivalent human papillomavirus vaccine in HIV-infected and HIV-negative adolescents and young adults. <i>Vaccine.</i> 2014;32(43):5657-5661.
Mosciki, 2019	Human papillomavirus antibody levels & quadrivalent vaccine clinical effectiveness in perinatally Human Immunodeficiency Virus-infected and exposed, uninfected youth. <i>Clin. Infect. Dis.</i> 2019;(Feb 21)
Cespedes, 2018	Anogenital human papillomavirus virus DNA and sustained response to the quadrivalent HPV vaccine in women living with HIV-1. <i>Papillomavirus Res.</i> 2018;6:15-21.



# Immunogenicity

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- Stronger immunogenicity in 9-15 year old males and females cf. 16-26 year old females
- Some reduction in HPV antibody levels in PLHIV and reduced persistence
  - **Clinical significance?**
- Better immunogenicity when viral load is controlled

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# Safety

# Safety

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- Levin J Acquir Immune Defic Syndr 2010; 55 : 197–204.
- Weinberg J Infect Dis 2012; 206: 1309–18.
- Kahn Clin Infect Dis 2013; 57: 735–44.
- Denny Vaccine 2013; 31: 745–53.
- Wilkin J Infect Dis 2010; 202: 1246–53.
- Giacomet Vaccine 2014; 32: 5657–61.
- Rainone AIDS 2015; 29: 739–43

# Safety

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- **Clinical trials, post-marketing surveillance of 2vHPV, 4vHPV (9vHPV)**
  - HPV vaccines are as safe in PLHIV compared with people without HIV
  - No adverse impact on CD4 / VL

*(BHIVA - If CD4 <200, wait till on ART)*

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# So, should we vaccinate PLHIV?



# Key facts

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- Immunogenic and safe in PLHIV
  - Licensed up to 45 years old
- Most efficacious when given to individuals naïve to the HPV types in the vaccine
  - Not a therapeutic vaccine
- Stronger immunogenic response in preadolescents compared with adults
  - HPV vaccine programs for 10-12 yo

# What is the hesitancy to vaccinate?

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- **How effective/cost-effective is vaccination?**
  - How likely are they to already be exposed?
  - How likely are they to acquire new infection?



# Question is not easy to answer

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- **Prevalence of HPV DNA in genital specimens does not measure cumulative exposure**
  - 70% of genital high-risk HPV (HR-HPV) infections in men clear by 12 month
  - HPV DNA is marker of current infection – no info on previous resolved episodes
  - HPV Abs in serum might give evidence of previous exposure – but low sensitivity because of low seroconversion rates





*Clinical Infectious Diseases*

MAJOR ARTICLE



OXFORD

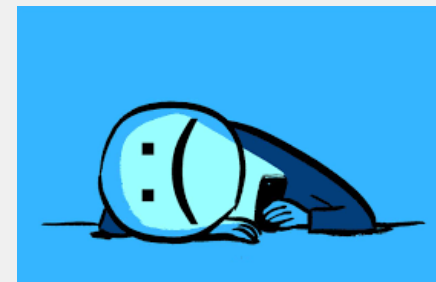
# A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298

Timothy J. Wilkin,<sup>1</sup> Huichao Chen,<sup>2</sup> Michelle S. Cespedes,<sup>3</sup> Jorge T. Leon-Cruz,<sup>2</sup> Catherine Godfrey,<sup>4</sup> Elizabeth Y. Chiao,<sup>5</sup> Barbara Bastow,<sup>6</sup> Jennifer Webster-Cyriaque,<sup>7</sup> Qinghua Feng,<sup>8</sup> Joan Dragavon,<sup>9</sup> Robert W. Coombs,<sup>9,10</sup> Rachel M. Presti,<sup>11</sup> Alfred Saah,<sup>12</sup> and Ross D. Cranston<sup>13</sup>

# HPV vaccination in PLHIV (MSM)

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- Placebo controlled RCT
- Quadrivalent HPV vaccine
- 575 adults, > 26 years old, USA
- 82% males, median age 47 (IQR 41-52)
- Median CD4 606, 88% HIV VL <200
- Endpoint = new persistent anal HPV
- Stopped early
  - No significant difference between vaccinated and placebo group



Characteristic	qHPV	Placebo
<b>Anal HPV infection</b>		
HPV 6 DNA detected	71 (25%)	70 (24%)
HPV 11 DNA detected	38 (13%)	37 (13%)
HPV 16 DNA detected	89 (31%)	95 (33%)
HPV 18 DNA detected	54 (19%)	49 (17%)
Missing	1 (0%)	0 (0%)
<b>HPV antibody status</b>		
HPV 6 seropositive	182 (64%)	174 (61%)
HPV 11 seropositive	128 (45%)	110 (38%)
HPV 16 seropositive	135 (47%)	135 (47%)
HPV 18 seropositive	89 (31%)	94 (33%)
Missing	3 (1%)	1 (0%)
<b>Oral HPV infection</b>		
HPV 6 DNA detected	7 (2%)	7 (2%)
HPV 11 DNA detected	6 (2%)	7 (2%)
HPV 16 DNA detected	18 (6%)	11 (4%)
HPV 18 DNA detected	10 (3%)	4 (1%)

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# HPV vaccination in PLHIV (MSM)

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- “Population level recommendation”
  - How about the patient in front of you?
  - No report on what proportion were seropositive to all 4 HPV types
- Trial stopped early
  - HPV vaccine trials showed benefit 2-3 years after vaccination – prevent recurrence HSIL?
- Only evaluated quadrivalent vaccine
  - Is there a value for nonavalent vaccine?

## HPV vaccines may reduce risk of HSIL recurrence

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- Observational studies only
- Exact mechanism?
  - Prevent new infections
  - Ab response may prevent cell reinfection
  - Additional cell-mediated immunity

Joura *BMJ*. 2012;344(3):e1401.

Kang *Gynecol Oncol*. 2013;130(2):264-268.

Swedish *Clin Infect Dis*. 2012;54(7):891-898.

Olsson *Hum Vaccin*. 2009;5(10):696-704.

**Original Investigation** | Infectious Diseases

# Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA)

## A Trial Protocol

Helen C. Stankiewicz Karita, MD; Kirsten Hauge, MPH; Amalia Magaret, PhD; Constance Mao, MD; Jeffrey Schouten, MD, JD; Verena Grieco, MD; Long Fu Xi, PhD; Denise A. Galloway, PhD; Margaret M. Madeleine, PhD; Anna Wald, MD, MPH

- Ongoing RCT (2017-2022)
- 345 participants age 27-69
- Anal/vulvar HSIL
- Outcome – recurrence of HSIL



# What is the hesitancy to vaccinate?

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- **How effective/cost-effective is vaccination?**
  - How likely are they to already be exposed?
  - **How likely are they to acquire new infection?**



In press

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# Incidence, Clearance, and Persistence of Anal Human Papillomavirus in Men Who Have Sex With Men Living With Human Immunodeficiency Virus: Implications for Human Papillomavirus Vaccination

*Jason J. Ong, PhD,\*†‡ Sandra Walker, DPsych,‡ Andrew Grulich, PhD,§ Jennifer Hoy, MBBS,¶  
 Tim R.H. Read, PhD,\*†‡ Catriona Bradshaw, PhD,\*†‡ Marcus Chen, PhD,\*†‡  
 Suzanne M. Garland, MD,\*\*†† Alyssa Cornall, PhD,\*\*†† Richard Hillman, MD,‡‡  
 David J. Templeton, PhD,§§§¶¶ Jane Hocking, PhD,\*\*\* Beng Eu, MBBS,††† BK Tee, MBBS,‡‡‡  
 Eric P.F. Chow, PhD,\*†‡ and Christopher K. Fairley, PhD\*†‡*

# HPV vaccination in PLHIV (MSM)

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- 279 MSM living with HIV
- Median age 50 (IQR 44-56)
- Median CD4 601 (IQR 450-778), 86% HIV VL <50
- Measure: anal HPV baseline and 2 years later
- Outcome: incidence of HPV vaccine types
  - i.e. 'opportunity lost' if we did not vaccinate

**TABLE 4.** Percentage of Men Who Could Potentially Benefit From Vaccination at Baseline and Proportion of Men Whose HRHPV Could Be Avoided if Actually Vaccinated, Stratified by Age Group

Age (Years)	No Vaccine-preventable HPV Types at Baseline, n/N (%)	Did Not Have all Vaccine-preventable HPV Types at Baseline, n/N (%)	Incident HRHPV at Follow-up 2 Years Later, n/N* (%)
For vaccines that protect against HRHPV 16/18			
35–39	15/27 (56)	26/27 (96)	3/26 (12)
40–44	33/43 (77)	42/43 (98)	5/42 (12)
45–49	34/52 (65)	51/52 (98)	7/51 (14)
50–54	44/62 (71)	60/62 (97)	6/60 (10)
55–59	24/32 (75)	31/32 (97)	2/31 (6)
60+	30/39 (77)	38/39 (97)	3/38 (8)
For vaccines that protect against HRHPV 16/18/31/33/45/52/58			
35–39	9/27 (33)	27/27 (100)	13/27 (48)
40–44	24/43 (56)	43/43 (100)	15/43 (35)
45–49	23/52 (44)	52/52 (100)	22/52 (42)
50–54	37/62 (60)	62/62 (100)	19/62 (31)
55–59	21/32 (66)	32/32 (100)	10/32 (31)
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**BJC**

British Journal of Cancer (2015) 112, 1585–1593 | doi: 10.1038/bjc.2015.90

**Keywords:** Human papillomavirus (HPV); MSM; sexual health clinic; genitourinary medicine clinic; immunisation; cross-sectional survey

# Human papillomavirus DNA in men who have sex with men: type-specific prevalence, risk factors and implications for vaccination strategies

E M King<sup>1</sup>, R Gilson<sup>\*,1,2</sup>, S Beddows<sup>3</sup>, K Soldan<sup>4</sup>, K Panwar<sup>3</sup>, C Young<sup>1,2</sup>, P Prah<sup>1</sup>, M Jit<sup>5,6</sup>, W J Edmunds<sup>6</sup> and P Sonnenberg<sup>1</sup>



# HPV vaccination in PLHIV (MSM)

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- 500 MSM London GUM clinic
- 2010-2012
- 68% no quadrivalent vaccine-types detectable
- 25% one type
- 7% 2/3 types

# National HPV program for MSM (UK)

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- Joint Committee on Vaccination and Immunisation recommended vaccinating HIV+/- MSM up to 45 through GUM clinics
- Started April 2018
- Awaiting evaluation...



# Take home messages

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Responsibility to  
the **patient** in front  
of you

Responsibility to  
the health of the  
**public**

# Take home messages

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- **HPV vaccines are largely immunogenic and safe for PLHIV**
- **Patient**
  - Informed consent
  - How likely are they to already be exposed?
  - How likely are they to acquire new infection?
  - Spare \$460 – do it.

## Australian Technical Advisory Group on Immunisation

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- Advices Minister of Health
- Recommends 9vHPV vaccine can be given to
  - males aged >26 years in high-risk groups, such as men who have sex with men, and people of any age who are immunocompromised

# Take home messages

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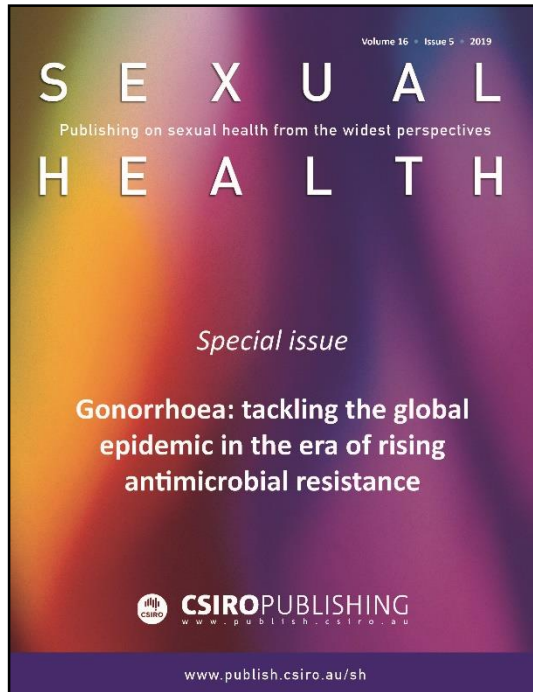
- **Population**
  - Probably not going to be cost-effective unless:
    - Vaccine price drops
    - Partial therapeutic effect
    - Lifelong immunity

# Useful resources

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- European CDC guidelines
  - <https://ecdc.europa.eu/sites/portal/files/documents/hpv-public-consultation-1-April-2019.pdf>
- BHIVA guidelines
  - <https://www.bhiva.org/file/NriBJHDVKGwzZ/2015-Vaccination-Guidelines.pdf>
- Australian Immunization handbook
  - <https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/human-papillomavirus-hpv>

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Guest editors: Jason J. Ong, Teodora Wi, Gwenda Hughes, Deborah Williamson, Philippe Mayaud and Eric Chow

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