



# Immunogenicity of the Quadrivalent HPV Vaccine in HIV Positive Women

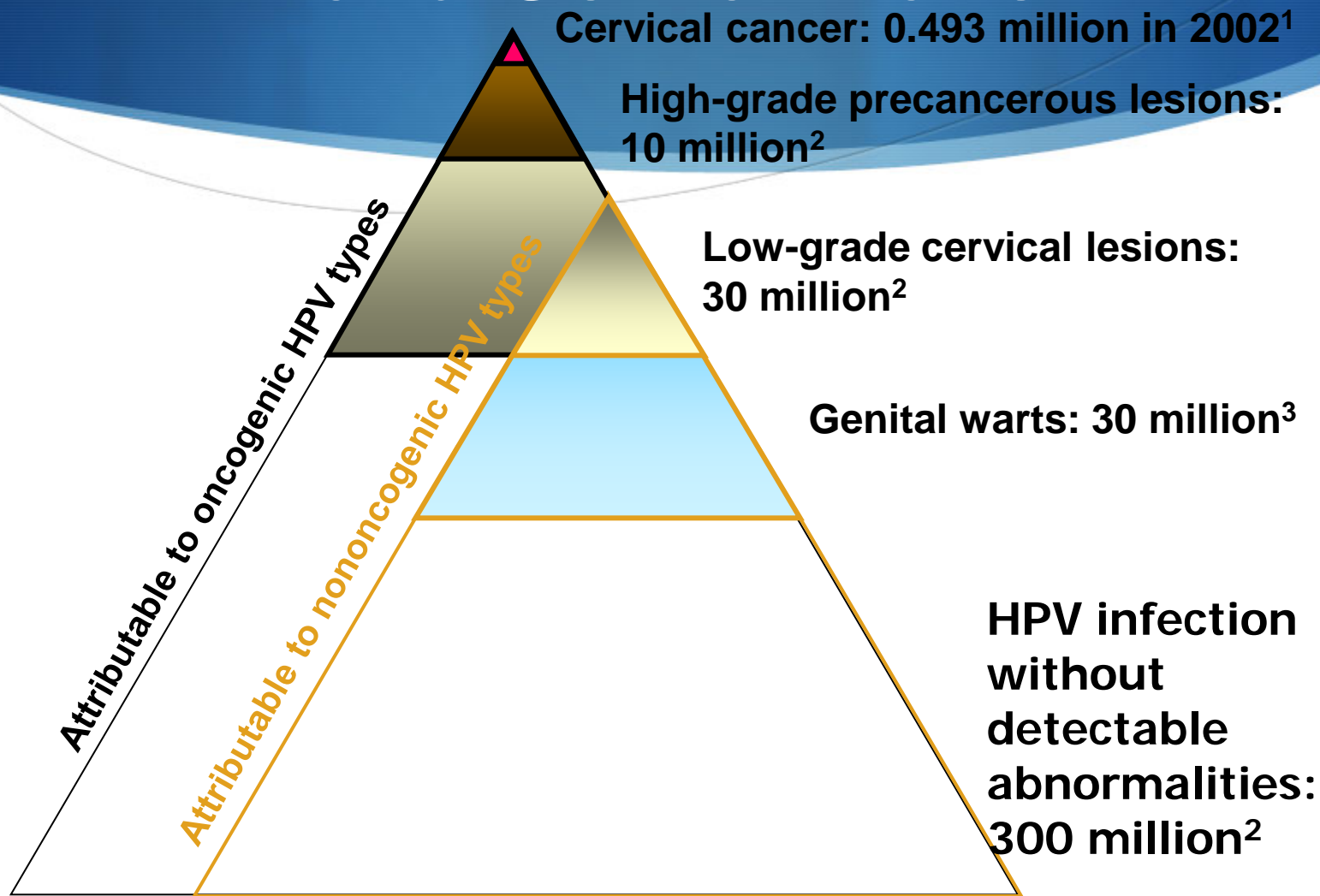
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Walmsley and the CTN 236 study team\*

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# Conflicts of interest

- ◆ Merck provided vaccine and funding in kind for serology

# World Burden of Cervical Disease and Genital Warts



1. Parkin DM, Bray F, Ferlay J, Pisani P. *CA Cancer J Clin.* 2005;55:74–108. 2. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22. 3. World Health Organization. WHO Office of Information. *WHO Features.* 1990;152:1–6.



# Burden of disease -HPV

- ◆ Cervical cancer
  - ◆ HPV infection of 16, 18 responsible for over 70% of cervical<sup>1</sup>
  - ◆ Most prevalent in countries with highest prevalence of HIV<sup>1</sup>
- ◆ Genital warts – HPV 6 & 11 causes > 90%<sup>2</sup>
- ◆ Other less common diseases can be caused by HPV<sup>2</sup>
- ◆ Head and neck cancers – 22-50%
- ◆ Respiratory papillomatosis – 76%

<sup>1</sup>Ferlay, J., Bray, F., Pisani, P., Parkin, DM. GLOBOCAN, 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase 5(2)

<sup>2</sup> Center for Disease Control. (2012). Epidemiology and prevention of vaccine preventable diseases. 12(2)



# HPV in HIV positive women

- ◆ HIV positive women have high rates of HPV infection
  - ◆ More multiple infections (J Acquir Immune Defic Syndr, 2013)
  - ◆ HIV positive women have higher rates of HPV infection than HIV negative women (48.6 vs 28.7%) (*Blitz et al. JID 2013*)
- ◆ Types found in HIV positive are different than HIV negative (J Med Virol 2008)
  - ◆ N. York cohort – 56,53,16,58,MM7,MM8, and 33 (JID 2006)
- ◆ However in some studies the most prevalent types in HIV positive women are 16 and 18 assoc. with HSIL (Lancet Oncology, 2009)
- ◆ HAART is associated with increased regression of pre-cancerous lesions and clearance of oncogenic HPV (*Blitz et al. JID 2013*)

# HPV Vaccines

- ◆ Preventative HPV vaccines first introduced in 2008 have significantly reduced rates of cervical cancer and HPV infection rates.
- ◆ There are 2 widely available vaccines approved for use in women and girls age 9-55 and men and boys age 9-26
  - ◆ qHPV – 6,11,16,18
  - ◆ bHPV – 16, 18
- ◆ 9 Valent (6,11,16,18, 31,33,45,52 and 58) vaccine now FDA and Health Canada approved for use in HIV- women and girls age 9-26
  - ◆ Study shows a 96.7% efficacy rates against cervical, vaginal and vulvar cancers



# HPV vaccine in HIV pos women

- ◆ **Kahn et al. CID 2013;55(5):735:**
- ◆ 99 women aged 16-23 years, safe and high rate of seroconversion
- ◆ Lower peak GMT's in those not taking ART vs those on ART for HPV-16 (2393 vs 3892 mMu/ml) and HPV-18 (463 vs 801 mMU/ml)
- ◆ **Kojic et al. CID, 2014 (ACTG 5240):**
- ◆ Per protocol analysis of 319 HIV pos women (age 13-45 yrs) receiving qHPV
- ◆ Safe, and highly immunogenic, 1 month post series, 100% to 6, 11, & 16, 91% to 18
- ◆ Lower responses in women with VL > 10,000 c/ml and CD4 < 200.

# A Study of an HPV VLP Vaccine in a Cohort of HIV+ Girls and Women – CTN 236

Primary objective - to evaluate the sero-responsiveness of HIV positive women to an HPV VLP quadrivalent vaccine.

- ◆ Study population: HIV positive women and girls, at 14 Canadian sites
- ◆ Study launched in November 2008
- ◆ Enrollment closed in December 2012: 407
- ◆ CIHR, Merck and CTN supported



# Methods

- Inclusion criteria:
  - HIV positive, > age 9, able to consent, not pregnant, cervix present
- Exclusion:
  - Allergy to vaccine, prior HPV vaccine, another study of investigational agent, likely to become pregnant, site investigator deems health to be exclusionary
- Duration of study for each subject = 27 months
- Demographic, clinical and HIV labs, genital HPV sampling, liquid based cervical cytology and HPV serology conducted at -3, 0, 2, 6, 7, 12, 18 and 24 months.
- Data entry and stewardship completed by CTN

# HPV Antibody analysis

- ◆ Anti- HPV serology testing for HPV types 6,11,16 and 18 using Competitive Luminex-based immunoassays (cLIA) developed by Merck
- ◆ Seropositivity cutoffs vary by HPV type, any value  $\geq$  cutoff is considered AB positive

# Analysis

- ◆ **306 women aged 15 or older received at least 1 dose of qHPV**
- ◆ **190 women** who received 3 doses of the vaccine within 1 year and had 1 month post 3<sup>rd</sup> vaccine AB data were included in this analysis
- ◆ HPV type-specific analysis were limited to those who were AB negative at baseline and HPV DNA negative up to 1 month post 3<sup>rd</sup> vaccine for at least 1 HPV type
- ◆ Generalized linear models were used to estimate the ratio of geometric mean titers (GMT) between those with a suppressed (<50 copies/mL) and unsuppressed HIV viral load (VL)

# Characteristics of study population

Demographic	Per Protocol Population (n=190)
Age	39 (34-46)
Race	
White	71 (37%)
Black	83 (44%)
Aboriginal	21 (11%)
Other	15 (8%)
Country of Origin	
Canada	95 (50%)
Endemic Country	66 (35%)
Other	29 (15%)
HIV Risk Factor	
Sexual Contact	141 (74%)
Injection Drug Use	18 (9%)
MTCT	14 (7%)
Other	18 (9%)
Years since HIV diagnosis	9 (4-13)
Suppressed Viral Load at time of 1st Vaccine	142 (75%)
CD4 Count at time of 1 <sup>st</sup> Vaccine (/mm <sup>3</sup> )	520 (390-710)
CD4 Nadir (/mm <sup>3</sup> )	230 (110-320)

# Baseline Eligibility by HPV Type

HPV Type	AB Negative	DNA Negative	AB & DNA Negative
6	112	168	<b>108</b>
11	159	173	<b>159</b>
16	124	153	<b>115</b>
18	161	159	<b>150</b>

# AB Serostatus at 7 months by HPV Type

HPV Type	N Seroconverted/ N Eligible	% Seroconverted
6	98/99	99.0%
11	144/148	97.3%
16	103/105	98.1%
18	130/142	91.5%



# Comparison of serologic response to age comparable HIV-ve

## HIV Negative vs HIV Positive Age 15-26

Month	HPV Type	HIV Negative GMT *	N	HIV + GMT	95% CL	p value
7	6	543	14	322.7	(180.8-576.1)	0.07
	11	762	18	251.1	(147.9-426.6)	<b>&lt;0.001</b>
	16	2294	15	1761.2	(1016.7-3051)	0.32
	18	462	17	128.7	(61.2-270.7)	<b>&lt;0.01</b>
24	6	113	8	55.6	(23.9-129.2)	0.09
	11	145	8	49	(21.1-113.8)	<b>0.02</b>
	16	460	9	135.7	(66.7-276.2)	<b>&lt;0.01</b>
	18	52	9	10.3	(5.9-18.1)	<b>&lt;0.001</b>

\*Joura et al. Vaccine (2008); 26: 6844-6851

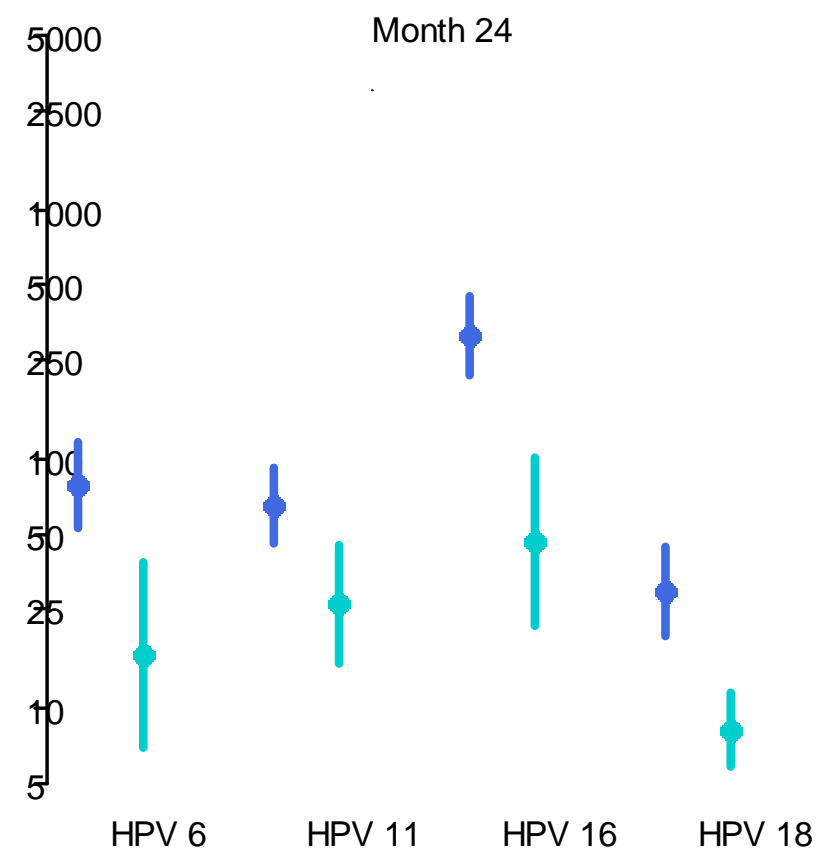
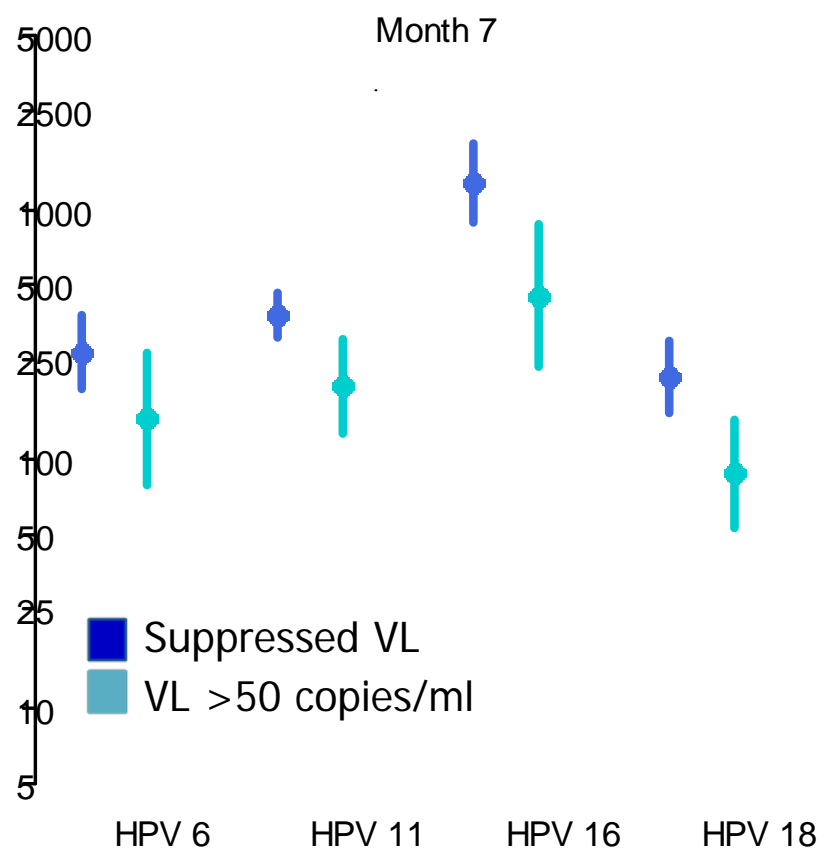
# Comparison of serologic response to age comparable HIV-ve

## HIV Negative vs HIV Positive Age 24-45

Month	HPV Type	HIV Negative GMT *	N	HIV + GMT	95% CL	p value
7	6	416	57	209.8	(162.7-270.5)	<0.0001
	11	551	92	238.5	(187.2-303.8)	<0.0001
	16	2226	61	733.4	(512.3-1049.9)	<0.0001
	18	357	90	140.4	(106.0-185.9)	<0.0001
24	6	70	37	65	(42.4- 99.4)	0.72
	11	78	53	58.3	(43.7 – 77.8)	0.05
	16	278	36	207.2	(138.7- 309.4)	0.15
	18	28	53	27.1	(19.1- 38.1)	0.84

\*Castellsague et al. British Journal of Cancer (2011) 105, 28-37.

# Seroresponse by VL Status at Baseline



Ratio of GMTs	1.82	2.19	2.19	2.76
95% CI	1.2-2.8	1.5-3.3	1.3-3.8	1.6-4.6
P-value	<.01	<.001	<.01	<.001

Ratio of GMTs	3.80	2.83	2.88	3.11
95% CI	2.0-7.3	1.6-4.9	1.4-5.8	1.7-5.8
P-value	<.001	<.001	<.01	<.001

# Conclusions

- ◆ Although seroconversion rates were higher than anticipated in HIV+ women, peak AB levels were significantly lower than in HIV- women
- ◆ Women with a suppressed viral load had a 2-3 fold higher antibody response that was sustained through to 24 month follow up
- ◆ Longer follow up is needed to fully understand the rate of decline in AB titers in this population
- ◆ Need to consider dosing of HPV in high HIV endemic countries and populations

# Thank you:

To the women and girls who participated in our study  
and the study team:

◆ Sharon Walmsley

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◆ Gavin Stuart

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