



Immune response in HIV positive girls to the qHPV vaccine

January 14, 2014
4th International HIV in Women Workshop,
Washington, DC

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Conflicts of interest

- Merck provided vaccine in kind and performed serology
- Merck and GSK have provided honoraria and travel funding to D. Money in the past
- Merck and GSK have provided grants in aid to students of D. Money



Burden of disease -HPV

- Cervical cancer
 - 2nd most common cancer in women worldwide
 - HPV infection of 16, 18 responsible for over 70% of cervical cancer ¹
 - Most prevalent in countries with highest prevalence of HIV ¹
- Genital warts – HPV 6 & 11 causes > 90% ²
- Other less common diseases can be caused by HPV²
 - Head and neck cancers – 22-50%
 - Respiratory papillomatosis – 76%
 - Other genital and anal cancers – 70%

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

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



HPV in HIV positive women

- 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 – N. York cohort – 56,53,16,58, MM7 in HPV83, MM8 in HPV84, and 33 (JID 2006)
- HAART is associated with increased regression of pre-cancerous lesions and clearance of oncogenic HPV *Blitz et al. JID 2013*



HPV Vaccine in HIV Negative persons

- qHPV vaccine was approved for use in HIV negative adolescence in 2006.³
- Adolescents 9-13 years of age had the highest level of antibody response.³
- More than 99% of males and females receiving 3 doses of the qHPV vaccine seroconvert.⁴
- High rates of protection from HPV infection and CIN2+

³ Markowitz, L., Dunne, E., Saraiya, M., Lawson, H., Chesson, H., Unger, ER., (2007) Quadrivalent Human papillomavirus vaccine: recommendations of the Advisory Committee on immunization practices, 56:1-24

⁴ Villa L., Costa, R., Petta, C et al. (2006). High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus like particle vaccine through 5 year follow up. *British Journal of Cancer*. 95;1459-66

qHPV Vaccine in HIV Positive Adolescents

- seroconversion >96% to all 4 qHPV types 6, 11, 16, 18 month 7 following a 3 dose schedule in age 7-12 year old HIV+ ⁵
- Booster dose demonstrated enhanced immune response
- qHPV in 99 16-23 yr old – high seroconversion rates but noted that lower GMT's in ART vs non-ART treated⁷
- >90% serconversion rates to HPV types 6,11,16, >76% to HPV18 in 7-12 year old children⁶

⁵Levin, M., et al. *Journal of Acquired Immune Defic Syndrome*. 2010;55:197-204

⁶Weinberg, A. et al. *Journal of Infectious Diseases*. 2012;206:1309-1318

⁷Kahn J et al, *Clin Infect Dis* 2013;57(5):734



A Study of an HPV VLP Vaccine in a Cohort of HIV+ Girls and Women

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

- Study population: HIV positive women and girls, at 11 Canadian sites, planned target N=500
- Study launched in November 2008
- Enrollment completed in December 2012: N = 407
- CIHR, Merck and CTN funding



Methods

- Inclusion criteria:
 - HIV positive, age >9 females, able to consent, cervix present
- Exclusion:
 - Allergy to vaccine, prior HPV vaccine, another study of investigational agent, site investigator deems health to be exclusionary
- Duration of study for each subject = 27 months



Study Design of HPV/HIV study

Visit	S	1	2	3	4	5	6	7
Months on Study	(-3)	0	2	6	7	12	18	24
Vaccine		X	X	X				

At each visit: Demographic, clinical status, HIV laboratory data,

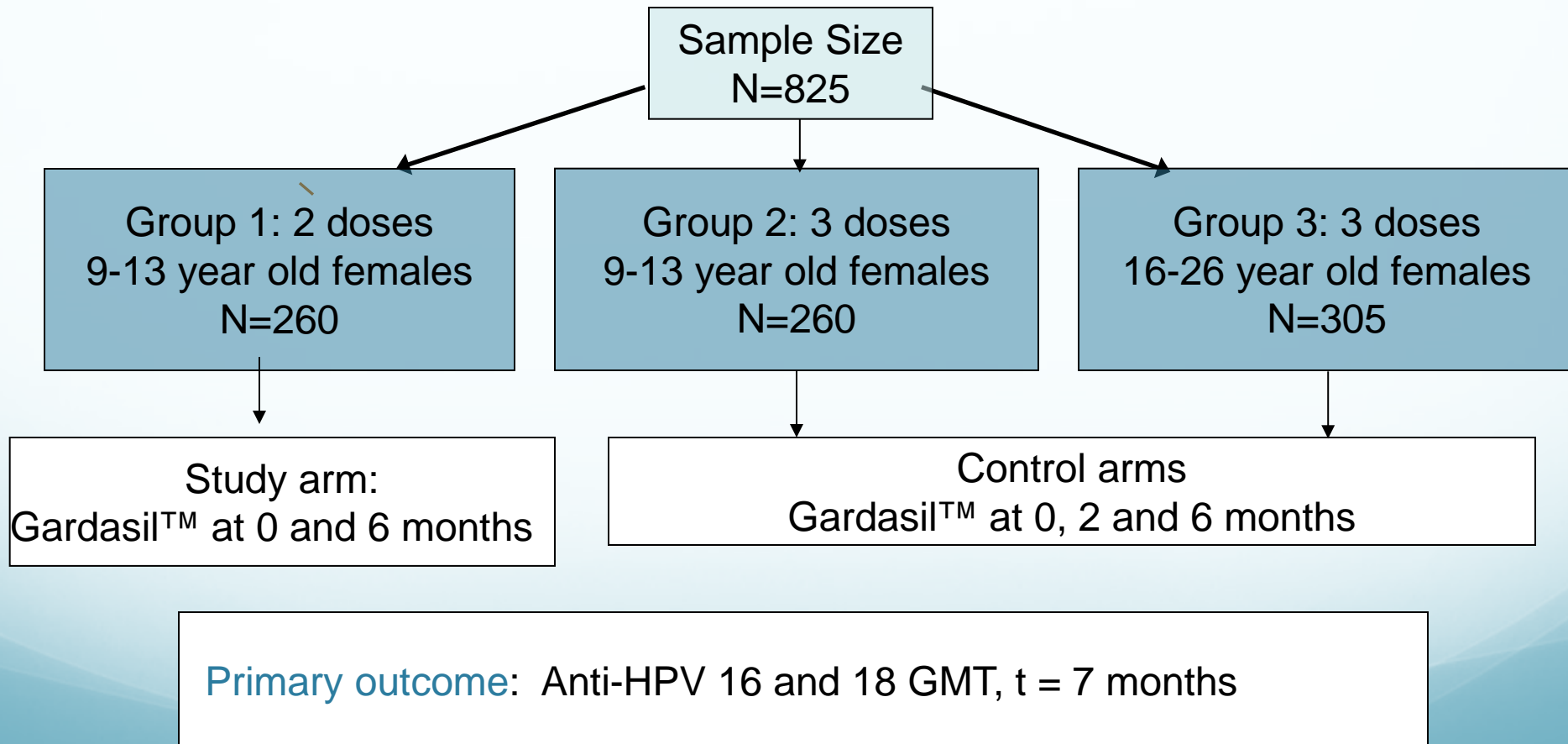
Genital HPV DNA sampling*

Liquid based cervical cytology*

HPV serology to measure antibody response

*not performed in girls who were not sexually active

HIV negative comparison from 2-dose 3-dose study





Methods

- HPV testing done by the Linear array assay (Roche Diagnostics) – CRCHUM virology laboratory, Montreal, Canada
- Cervical cytology – BC Cancer Agency
- Serology – Merck cLIA assay to 6, 11, 16, 18
- Statistical analysis
 - Wilcoxon rank sum tests for comparisons between groups and Spearman's correlations for within HIV analyses
 - Generalized linear model to compare GMT between groups to account for age differences



HPV Antibody Data

- Uses Competitive Luminex-based immunoassays (cLIA) developed by Merck
- Seropositivity cutoffs vary by HPV type
- Any value \geq cutoff is considered AB positive

HPV Type	Seropositive Cutoff (mMU/mL)
6	20
11	16
16	20
18	24

Results:

9-13 year old HIV+ girls

- 32 girls under age 9-13 were enrolled of a total of 407 subjects
- 1 girl was sero-positive to HPV18 at baseline all others seronegative to all types in the quadrivalent vaccine (6,11,16,18)
- All subjects completed vaccine schedule per protocol
- All girls seroconverted to all vaccine containing serotypes post series (100% response) – 99% response seen in entire cohort
- No vaccine related serious adverse events

Demographics



Variables	HIV + Age 9-13 n=32	HIV – Age 9-13 n=252	p-value
Age (years)	11 (10-13)	13 (11-14)	<0.01
BMI (kg/m ²)	19 (17-22)	19.0 (17-21)	0.74
Premenarchal	22 (69%)	137 (54%)	0.12
Country of Origin		Not collected	
Canada	18 (67%)		
Endemic Country	9 (33%)		
Race			
White	1 (4%)	80%	
African Canadian	19 (70%)	0	
Asian	7 (26%)	18%	
Other		2%	
Number of Lifetime Sexual Partners	0 (0%)	0	



Clinical characteristics in HIV cohort

Variables	HIV + Age 9-13 n=32
HIV Risk Factor Sexual Contact MTCT	1 (3%) 31 (97%)
Years since HIV diagnosis	9 (5-11)
Suppressed Viral Load at Baseline	19 (59%)
CD4 Count at Baseline (/mm ³)	692 (547-960)
CD4 Nadir (/mm ³)	442 (246-594)

Results: Month 7



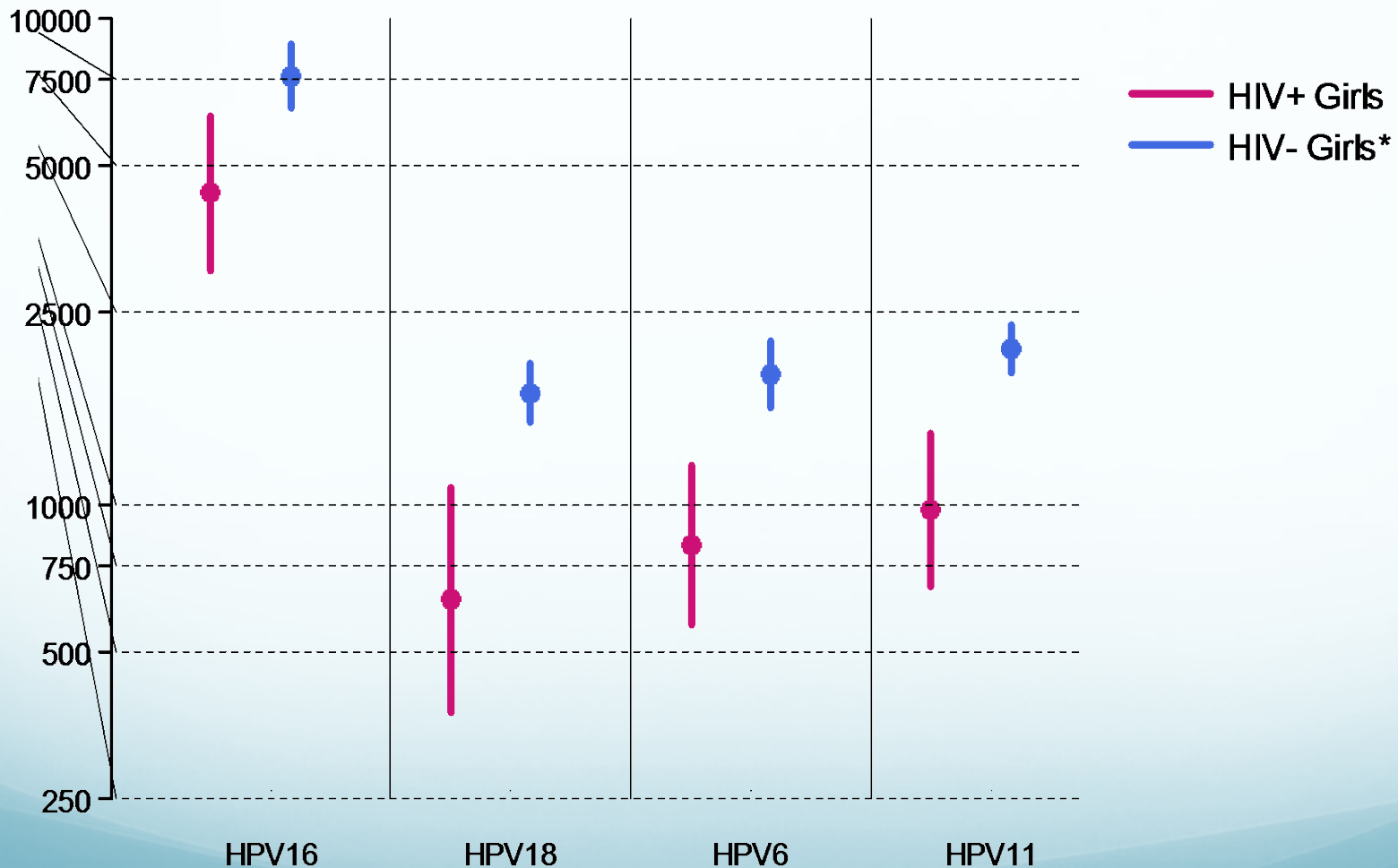
HPV Type	HIV + Age 9-13		HIV- Age 9-13*		P Value**
	N	GMT (95% CI)	N	GMT (95%CI)	
16	32	4382 (3045-6305)	251	7650 (6558-890)	<.01
18	31	640 (376-1092)	252	1703 (1479-1960)	<.0001
6	32	830 (567-1214)	248	1856 (1582-2178)	<.001
11	32	977 (680-1405)	251	2096 (1870-2349)	<.0001

*Dobson SM, McNeil S, Dionne M, et al. Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women: A Randomized Clinical Trial. *JAMA*. 2013;309(17):1793-1802.

** adjusted for age

GMT AB Titers at Month 7

HIV positive girls compared to HIV negative girls



Results: Month 24



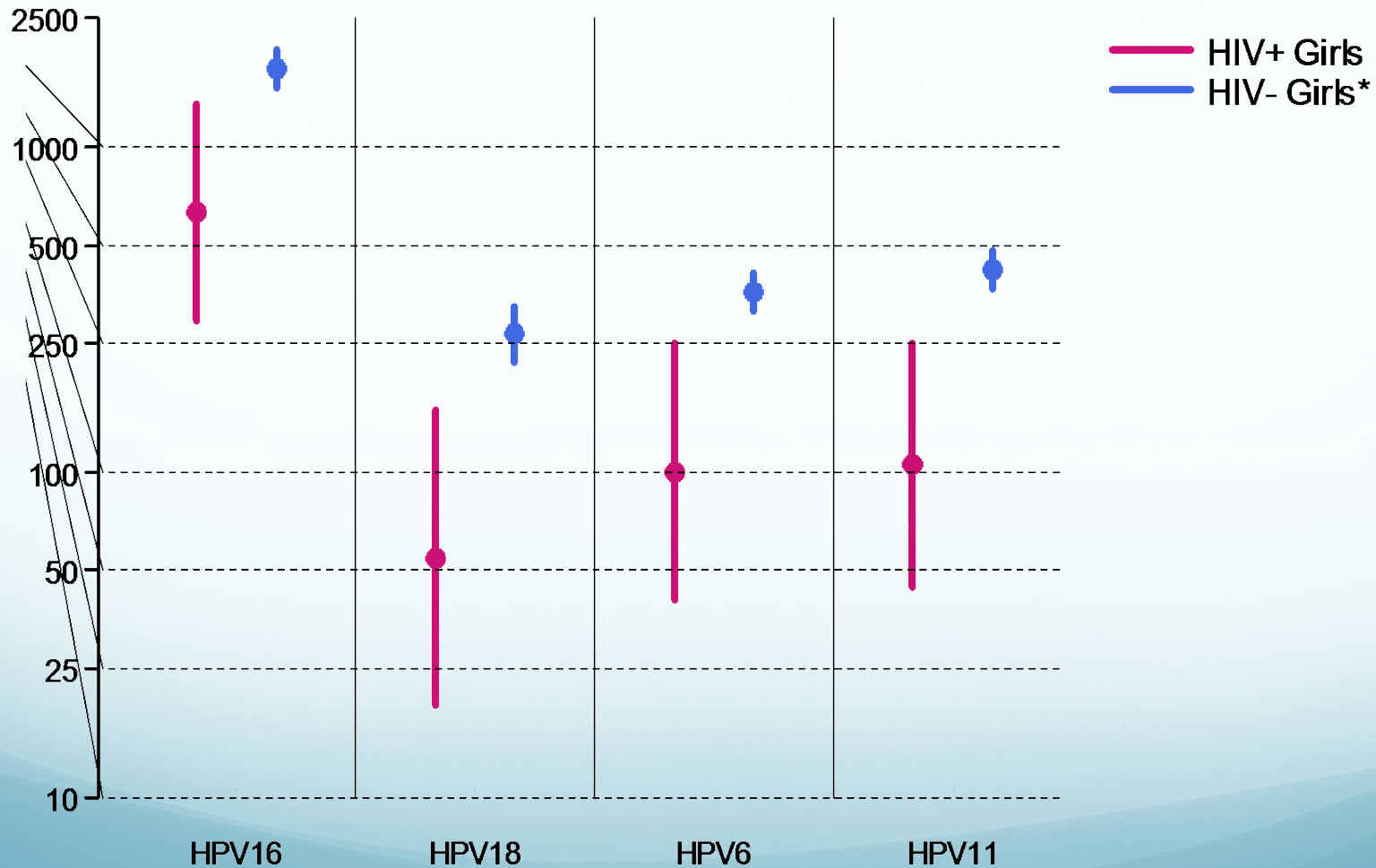
HPV Type	HIV + Age 9-13		HIV- Age 9-13*		P Value**
	N	GMT (95% CI)	N	GMT (95%CI)	
16	16	628 (291-1357)	186	1739 (1519-1992)	<.001
18	15	55 (19-155)	187	267 (219-324)	<.0001
6	16	101 (41-249)	186	359 (315-410)	<.0001
11	16	105 (44-250)	186	422 (369-483)	<.0001

*Dobson SM, McNeil S, Dionne M, et al. Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women: A Randomized Clinical Trial. *JAMA*. 2013;309(17):1793-1802.

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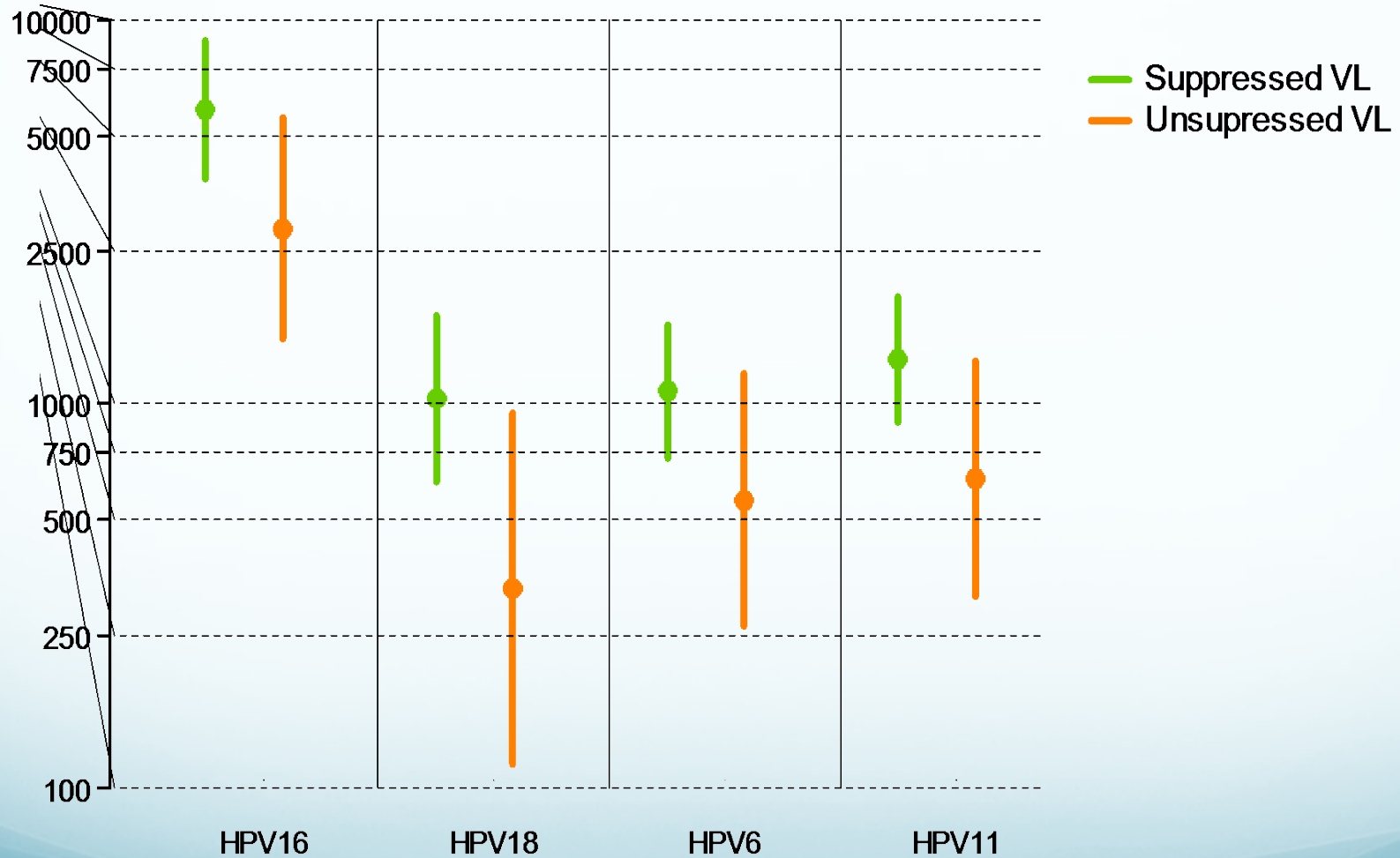


AB Response by HIV Viral Load Among HIV + Girls

HPV Type	Suppressed (<50c/ml)		Not Suppressed (>50c/ml)		p-value	Ratio of GMTs (95% CI)
	N	GMT (95% CI)	N	GMT (95% CI)		
16	19	5851 (3865-8857)	13	2872 (1483-5559)	0.05	2.02 (0.99-4.12)
18	18	1032 (626-1702)	13	330 (115-948)	0.03	3.11 (1.13-8.55)
6	19	1083 (726-1618)	13	562 (264-1198)	0.09	1.90 (0.91-3.97)
11	19	1307 (898-1907)	13	639 (315-1297)	0.05	2.01 (1.01-4.01)

GMT AB Titers at Month 7

HIV+ Girls: Suppressed and Unsuppressed Viral Load





Conclusions

- High rate of seroconversion seen in HIV positive girls given the qHPV vaccine by standard dosing
- Lower peak GMT was observed in these HIV positive girls compared to HIV negative girls
- However, levels of response were comparable to levels seen in 'older' women for whom data is available that these levels confer efficacy against HPV infection and disease
- Until an immune correlate of protection is defined in HIV negative and HIV positive persons, understanding of the meaning of antibody levels remains limited
- The role of booster dosing remains to be evaluated

Thank you

- To the girls and women that participated in our studies
- To our sponsors, CIHR, CTN, Merck, MSFHR
- To our staff
- To the co-investigator group:

Ari Bitnun

Jason Brophy

Jan Christilaw

Chris Karatzios

Mel Krajden

Mona Loufty

Gina Ogilvie

Lindy Samson

Fiona Smail

Sharon Walmsley

Mark Yudin

Sandra Blitz

Francois Coutlee

Simon Dobson

Marina Klein

Normand Lapointe

Jessica McAlpine

Janet Raboud

Joel Singer

Sylvie Trottier

Wendy Wobeser

