



Lower Immune Response in HIV-Positive Girls to the Quadrivalent Human Papillomavirus Vaccine

July 17-18, 2015

7th International Workshop on HIV Pediatrics
Vancouver, Canada

J. Brophy, A. Bitnun, J. Raboud, E. Moses, S. Blitz, L. Samson, N. Lapointe and D. Money for the HPV/HIV study group, CTN 236



Conflicts of interest

- Merck provided vaccine and funding in kind for serology



Burden of HPV Disease

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

- Ferlay, J et al. GLOBOCAN (2002). Cancer incidence, mortality and prevalence worldwide. IARC CancerBase 5 (2)

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



HPV in HIV+ Women

- HIV+ women have higher rates of HPV infection than HIV-negative women (48.6 vs 28.7%)
- HIV+ women have higher rates of HPV persistence, and 10x greater risk of abnormal cervical cytology
- Successful cART is associated with increased regression of pre-cancerous lesions and clearance of oncogenic HPV

- Blitz, S et al. (2013) JID
- IDSA HIV Primary Care Guidelines (2013)



HPV Vaccine in HIV-Negative Populations

- Quadrivalent HPV vaccine (qHPV) was approved for use in HIV-negative adolescents in 2006
 - Adolescents 9-13 years of age had the highest level of antibody response
 - More than 99% of males and females receiving 3 doses of the qHPV vaccine seroconvert
- High rates of protection from HPV infection and CIN2+

- Markowitz, L et al. (2007) Quadrivalent Human papillomavirus vaccine: recommendations of the Advisory Committee on immunization practices, 56:1-24

- Villa L. et al. (2006) *British Journal of Cancer*. 95;1459-66



qHPV Vaccine in HIV+ Children & Adolescents

Lower response rates to qHPV in previous studies in HIV+ children

- Levin 2010:
 - 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+
 - 30 to 50% weaker immune response to HPV 6 and 18 compared to HIV negative controls
- Weinberg 2012
 - >90% seroconversion rates to HPV types 6,11,16, >76% to HPV18 in 7-12 year old children

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

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



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

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

- Study launched at 11 Canadian sites in November 2008
- Enrollment completed in December 2012
 - N = 407
- CIHR, Merck and CTN funding



Methods

- Inclusion criteria:
 - HIV+ females, age >9 years, cervix present
- Exclusion:
 - Allergy to vaccine, prior HPV vaccine, another study of investigational agent, site investigator deems health to be exclusionary



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				

* Primary outcome

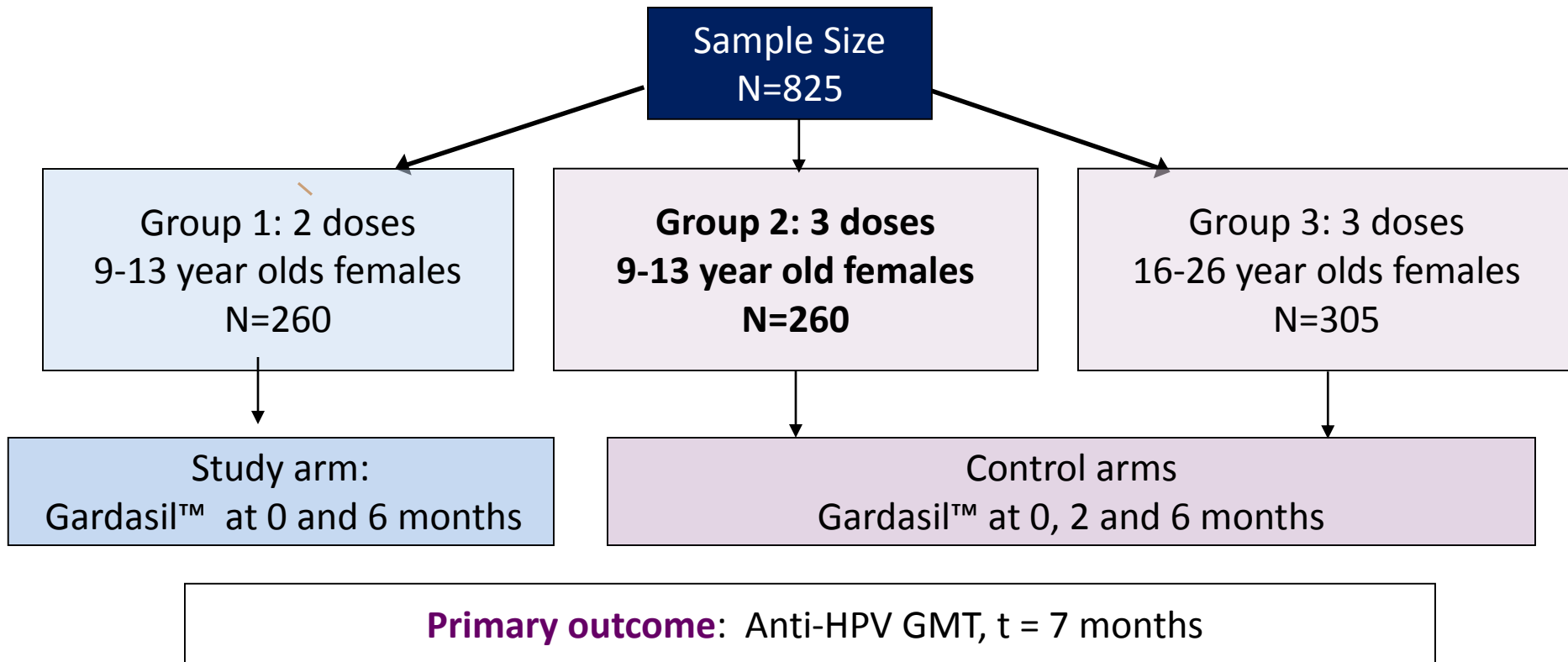
At each visit:

Demographic, clinical status, HIV laboratory data
HPV serology to measure antibody response

Genital HPV DNA sampling & liquid based cervical cytology
(not performed in girls who were not sexually active)



HIV-Negative Comparator Group: 2-dose / 3-dose Study (Dobson, 2013)



*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.



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

- 37 girls aged 9-13 years received at least 1 dose of vaccine
 - 2 girls did not complete the series
 - 32 girls had 7-month post-vaccination serology samples



Demographics

Variables	HIV + Age 9-13 n=32	HIV – Age 9-13 n=261	p-value
Age (years)	11 (10-13)	13 (11-13)	<0.01
BMI (kg/m ²)	18.7 (17.2-22.0)	19.0 (17.2-21.5)	0.74
Premenarchal	22 (69%)	137 (54%)	0.12
Country of Origin			
Canada	19 (59%)	Not collected	
Endemic Country	12 (38%)		
Race			
White	1 (3%)	239 (92%)	
Africa Canadian	26 (81%)	-	
Other	5 (16%)	22 (8%)	

Clinical Characteristics of HIV+ Girls

Variables	HIV + Age 9-13 n=32
HIV Risk Factor	
Sexual Contact	1 (3%)
MTCT	31 (97%)
Suppressed Viral Load at Baseline	19 (59%)
CD4 Count at Baseline (/mm ³)	692 (547-929)
CD4 Nadir (/mm ³)	442 (246-594)



Results: 9-13 year old HIV+ Girls

- 31/32 were seronegative to all 4 qHPV types at baseline
 - 1 girl was seropositive to HPV18 at baseline
- All girls seroconverted to all vaccine containing serotypes post series (ie. month 7) – **100% response**
- By month 24, the proportion of HIV+ girls with titres above the seropositive cutoff were:
 - 84.2%, 78.9%, 100% & 66.7% for serotypes 6, 11, 16 & 18
- In HIV- girls, all but one subject maintained titres above the seropositive cutoff at month 24.



Results: Month 7

HPV Type	HIV + Age 9-13		HIV- Age 9-13*		Age-adjusted GMT Ratio	p-value
	N	GMT (95% CI)	N	GMT (95%CI)		
16	32	4382 (3045-6305)	251	7640 (6558-8900)	0.52 (0.33-0.82)	0.01
18	31	640 (376-1092)	252	1703 (1479-1960)	0.31 (0.20-0.49)	<.0001
6	32	830 (567-1214)	248	1856 (1582-2178)	0.41 (0.25-0.65)	<.001
11	32	977 (680-1405)	251	2096 (1870-2349)	0.42 (0.30-0.60)	<.0001

* Adjusted for age

- 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.



Results: Month 24

HPV Type	HIV + Age 9-13		HIV- Age 9-13*		Age-adjusted GMT Ratio	p-value
	N	GMT (95% CI)	N	GMT (95%CI)		
16	21	688 (374-1264)	186	1739 (1519-1992)	0.39 (0.25-0.63)	<.0001
18	20	71 (31-164)	187	267 (219-324)	0.23 (0.12-0.46)	<.001
6	21	122 (60-249)	186	359 (315-410)	0.32 (0.20-0.52)	<.001
11	21	114 (57-229)	186	422 (369-483)	0.24 (0.15-0.39)	<.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.



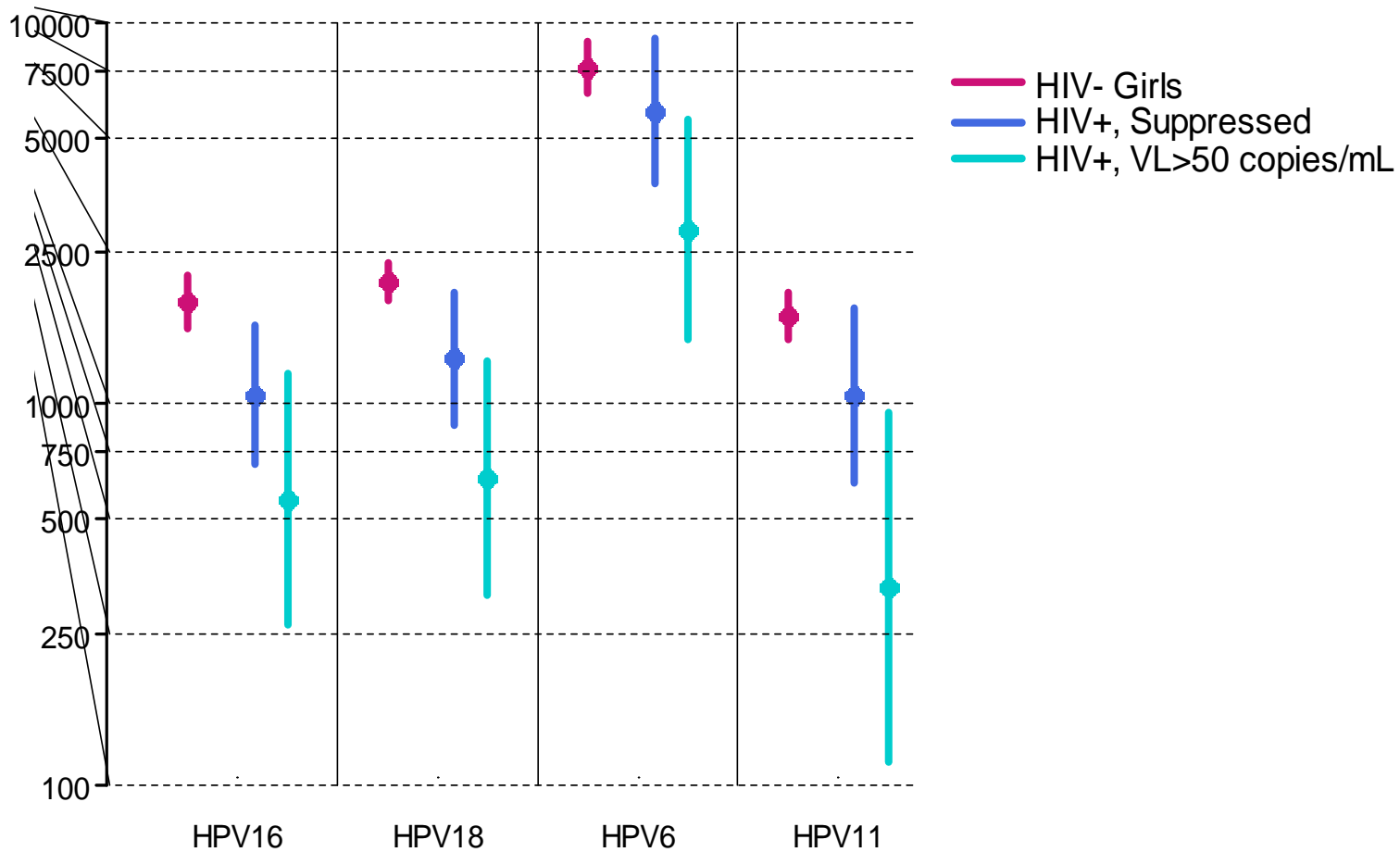
Month 7 AB Response by Viral Load Among HIV + Girls

HPV Type	Suppressed		Not Suppressed		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	2.04 (1.01-4.13)
18	18	1032 (626-1702)	13	330 (115-948)	0.03	3.12 (1.01-9.70)
6	19	1083 (726-1616)	13	562 (264-1198)	0.08	1.93 (0.91-4.08)
11	19	1307 (896-1907)	13	639 (315-1297)	0.05	2.05 (1.01-4.13)



GMT AB Titers at Month 7

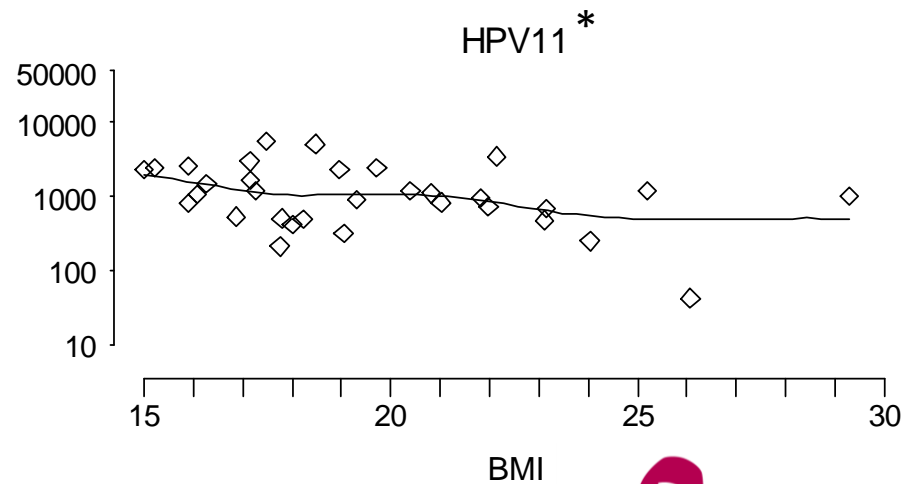
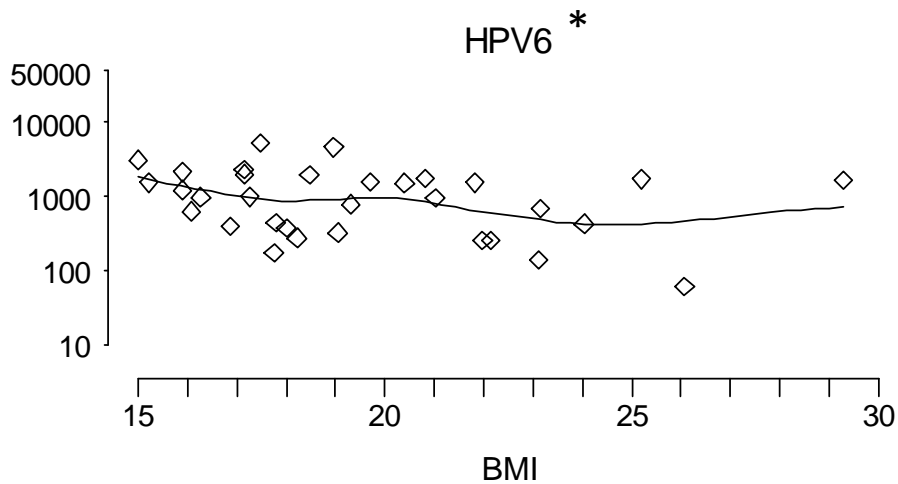
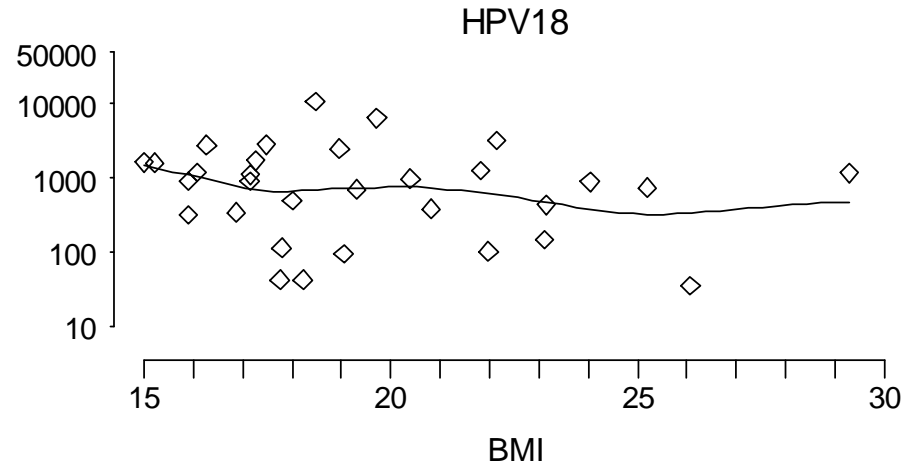
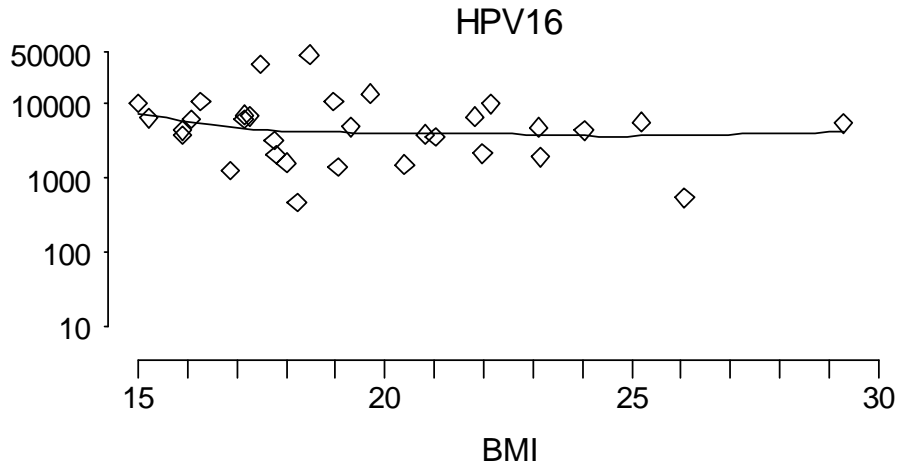
HIV+ Girls: Suppressed and Unsuppressed Viral Load



Exploratory analysis of factors affecting month 7 AB levels

	HPV16		HPV18		HPV6		HPV11	
Univariate	B (SE)	p-value	B (SE)	p-value	B (SE)	p-value	B (SE)	p-value
Age	-0.10 (0.12)	0.42	-0.18 (0.17)	0.31	-0.17 (0.12)	0.16	-0.18 (0.11)	0.13
BMI	-0.06 (0.05)	0.27	-0.07 (0.08)	0.35	-0.09 (0.05)	0.10	-0.11 (0.05)	0.03
CD4	0.06 (0.06)	0.33	-0.01 (0.08)	0.87	-0.02 (0.06)	0.69	0.01 (0.06)	0.81
CD4 Nadir	-0.06 (0.06)	0.32	-0.10 (0.08)	0.22	-0.03 (0.06)	0.63	-0.05 (0.06)	0.35
Suppressed Viral Load	0.71 (0.35)	0.05	1.14 (0.50)	0.03	0.66 (0.37)	0.08	0.72 (0.34)	0.05
Multivariate								
BMI	-0.07 (0.05)	0.16	-0.09 (0.07)	0.21	-0.10 (0.05)	0.05	-0.12 (0.05)	0.01
Suppressed Viral Load	0.77 (0.34)	0.03	1.21 (0.49)	0.02	0.74 (0.35)	0.04	0.81 (0.31)	0.01

Month 7 AB Response by BMI in HIV + Girls



Adverse Events Reported by HIV+ Girls

		Ever	Dose 1	Dose 2	Dose 3
		N=35	N=35	N=34	N=33
Any AE		17 (48.6%)	15 (42.9%)	13 (38.2%)	12 (36.4%)
Injection Site	Any	16 (45.7%)	13 (37.1%)	13 (38.2%)	11 (33.3%)
	Pain	16 (45.7%)	12 (34.3%)	13 (38.2%)	11 (33.3%)
	Swelling	1 (2.9%)	1 (2.9%)	1 (2.9%)	0
	Redness	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (3.0%)
Systemic	Any	5 (14.3%)	3 (8.6%)	3 (8.8%)	2 (6.1%)
	Fatigue	4 (11.4%)	0	3 (8.8%)	2 (6.1%)
	Headache	4 (11.4%)	1 (2.9%)	3 (8.8%)	1 (3.0%)
	Elevated CK	1 (2.9%)	0	0	1 (3.0%)
	Fever	1 (2.9%)	1 (2.9%)	0	0
	Gastrointestinal	1 (2.9%)	1 (2.9%)	1 (2.9%)	0
	Hives	1 (2.9%)	1 (2.9%)	0	0

- AEs not collected in comparator study by Dobson et al.
- In another study of HIV-negative girls & boys aged 9-15 (Reisinger et al, PIDJ 2007), similar but slightly higher rates of AEs were reported
 - any = 67%
 - pain = 54%



Discussion

- High rate of seroconversion seen in HIV+ girls given the qHPV vaccine by standard dosing
- However, significantly lower peak GMT was observed in HIV+ girls compared to HIV-negative girls, at both 7 and 24 months
- As an immune correlate of protection is not yet known, the real impact of such differences in response remain to be seen



Discussion

- Lower titres in girls with unsuppressed viral load at the time of first vaccination
 - This has been seen in other vaccines given to HIV+ children (eg. influenza)
- BMI likewise appeared to have negative impact (HPV 6/11)
 - Leptin-mediated effect (adipocyte-derived cytokine & hormone); documented in other vaccines (influenza, HAV/HBV, and HPV)

- Harper, et al. (2014) PLOS One

- Reisinger, et al. (2007) PIDJ



Discussion

- Booster dosing may be needed to ensure adequacy of protection during HIV+ adolescent's period of highest HPV acquisition risk (late teens/early adulthood)
- Long-term evaluation of this cohort to understand efficacy, correlates of protection and need for booster dosing is underway



Limitations

- Small numbers of HIV+ girls
- HIV-negative control population, while in the same setting, was predominantly Caucasian, while HIV+ were predominantly Black
- Study conducted in Canadian setting – applicability may not extend to other settings (eg. high-prevalence countries)



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



