Baseline Data of a Phase 3 Trial of the Quadrivalent HPV Vaccine in HIV+ males and females: ACTG 5298

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Background:
Human papillomavirus (HPV) is the main cause of anogenital and oropharyngeal squamous cell cancer, with individual HPV types broadly divided into low-risk (e.g. 6 and 11) and high-risk (e.g. 16 and 18) based on their historical association with cervical cancer. Following infection, HPV can cause cellular abnormalities ranging from low-grade squamous intraepithelial lesions (LSIL) to high-grade SIL (HSIL). HSIL is considered the precursor lesion to anal cancer. The prophylactic quadrivalent HPV vaccine (qHPV 6, 11, 16, 18) is indicated for males and females aged 9-26 years to prevent HPV infection, anogenital dysplasias and cancer. ACTG 5298 is an ongoing randomized placebo controlled phase 3 study of qHPV to prevent anal HPV infection in HIV-positive males and females >26 years.

Methods:
ACTG sites with certified high resolution anoscopy (HRA) practitioners and access to minimally invasive treatment for HSIL were eligible to take part in A5298. Entry criteria for participants (ppts) included; HIV-positive females, and males who have sex with males; ≥ 27 years old; and no history of anogenital or oral cancer. Two baseline anal and oral specimens for HPV genotyping by polymerase chain reaction were collected. Anal cytology and HRA with or without biopsies were performed. Half of the females were required to have anal HSIL on biopsy at screening. The chi-square test was used to assess the association between HPV infection and HSIL status at baseline with no adjustment for co-infections. All statistical tests were performed at the 0.05 level without adjustment for multiple comparisons.

Results:
575 ppts were enrolled (82% male and 18% female). Median age was 47 years. Race/ethnicity was 45% White, 31% Black and 21% Hispanic. Plasma HIV RNA was <50 copies/mL in 83% and median CD4 count was 602 CD4 T cells/μL. (Table 1) Abnormal anal cytology was detected in 61%, and 15% of ppts with HSIL had normal cytology. (Table 3) HSIL was detected on biopsy in 33%. Anal HPV 6, 11, 16 and 18 was detected in 25%, 13%, 32%, and 18% of ppts respectively (data not shown). The simultaneous prevalence of 0, 1, 2, 3, and 4 qHPV vaccine types was 40%, 39%, 17%, 4%, and 1 %, respectively (Table 2). The prevalence of high-risk HPV types 31, 33, 45, 52 and 58 ranged from 13% to 25% (data not shown). Types 16, 18, 31, 33, 45, 52, and 58 were significantly associated with detection of HSIL (p-values <.05). (Figure 1) In 448 ppts, oral infection with HPV 6, 11, 16 and 18 was present in 2%, 1%, 4%, and 2% of ppts respectively, (Table 4) with > 1 quadrivalent HPV type detected in 5 (1%) ppts (data not shown).

Conclusions:
In this trial population with well controlled HIV infection, there was a high proportion of abnormal anal cytology, HSIL on anal biopsy, and anal HPV infection. However, less than one-quarter of ppts had more than one anal qHPV type detected, and could theoretically derive protection from the qHPV vaccine. The proportion of oral HPV in this population was low. A5298 is investigating whether qHPV vaccination will reduce the incidence of anal infection with vaccine types and whether it will lead to a lower burden of anal HSIL. The five additional high risk types contained in the investigational nine-valent vaccine (31, 33, 45, 52, 58) appear to be associated with anal HSIL, and this vaccine should provide broader protection against anal HSIL and cancer in HIV-infected adults.

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Table 1: Demographics of Study Population by Presence of HSIL on Biopsy

Characteristic		Presence of HSIL on biopsy at study entry HSIL (N=187)	No HSIL (N=388)	Total (N=575)
Age at study entry	N	187	388	575
	Median	47	47	47
	Q1, Q3	41, 53	41, 53	41, 53
Sex	M	134 (72%)	338 (87%)	472 (82%)
	F	53 (28%)	50 (13%)	103 (18%)
Race/ethnicity	White Non-Hispanic	73 (39%)	188 (48%)	261 (45%)
	Black Non-Hispanic	60 (32%)	118 (30%)	178 (31%)
	Hispanic (Regardless of Race)	50 (27%)	69 (18%)	119 (21%)
	Asian, Pacific Islander	3 (2%)	9 (2%)	12 (2%)
	American Indian, Alaskan Native	0 (0%)	2 (1%)	2 (0%)
	More than one race	1 (1%)	2 (1%)	3 (1%)
IV drug history	Never	169 (90%)	360 (93%)	529 (92%)
	Previously	18 (10%)	28 (7%)	46 (8%)
HIV RNA results (copies/mL)	<50	141 (79%)	321 (85%)	462 (83%)
	50-<200	15 (8%)	22 (6%)	37 (7%)
	200-<500	8 (4%)	9 (2%)	17 (3%)
	500-<1000	1 (1%)	6 (2%)	7 (1%)
	1000-<10000	3 (2%)	13 (3%)	16 (3%)
	>= 10000	10 (6%)	5 (1%)	15 (3%)
	Missing	9	12	21
Lowest documented CD4 count	N	169	346	515
	Median	203	273	255
	Q1, Q3	66, 356	135, 419	110, 403
Absolute CD4 count	N	183	386	569
	Median	542	629	602
	Q1, Q3	389, 727	458, 801	436, 767

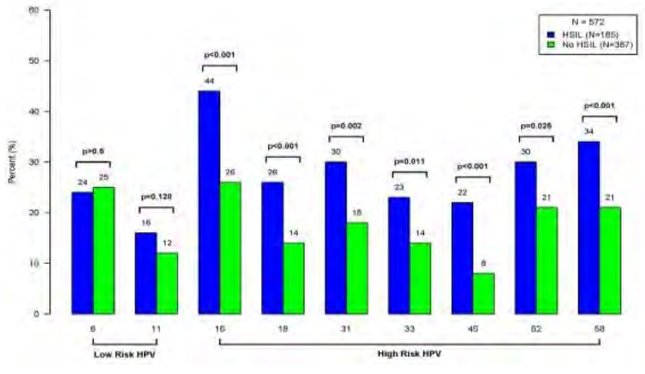
Table 2: Anal HPV Type by Presence of HSIL on Biopsy

Characteristic		Presence of HSIL on biopsy at study entry HSIL (N=185)	No HSIL (N=387)	Total (N=572)
HPV infection status (of vaccine type)	Negative	50 (27%)	177 (46%)	227 (40%)
	6	20 (11%)	46 (12%)	66 (12%)
	11	10 (5%)	20 (5%)	30 (5%)
	16	37 (20%)	53 (14%)	90 (16%)
	18	13 (7%)	22 (6%)	35 (6%)
	6 11	0 (0%)	7 (2%)	7 (1%)
	16 18	13 (7%)	9 (2%)	22 (4%)
	6 11 16 18	3 (2%)	2 (1%)	5 (1%)
Number of HPV infections (of vaccine type)	0	50 (27%)	177 (46%)	227 (40%)
	1	80 (43%)	141 (36%)	221 (39%)
	2	44 (24%)	52 (13%)	96 (17%)
	3	8 (4%)	15 (4%)	23 (4%)
	4	3 (2%)	2 (1%)	5 (1%)
HPV infection risk (of vaccine type)	None	50 (27%)	177 (46%)	227 (40%)
	Only low grade	30 (16%)	73 (19%)	103 (18%)
	Any high grade	105 (57%)	137 (35%)	242 (42%)
Any HPV (6/11/16/18)	No	50 (27%)	177 (46%)	227 (40%)
	Yes	135 (73%)	210 (54%)	345 (60%)
Any HPV (31/33/45/52/58)	No	38 (21%)	175 (45%)	213 (37%)
	Yes	147 (79%)	212 (55%)	359 (63%)
Any HPV (6/11/16/18/31/33/45/52/58)	No	10 (5%)	88 (23%)	98 (17%)
	Yes	175 (95%)	299 (77%)	474 (83%)

Table 4: Oral HPV Type by Presence of HSIL

Characteristic		Presence of HSIL on biopsy at study entry HSIL (N=127)	No HSIL (N=321)	Total (N=448)
HPV 6	No	126 (99%)	315 (98%)	441 (98%)
	Yes	1 (1%)	6 (2%)	7 (2%)
HPV 11	No	125 (98%)	317 (99%)	442 (99%)
	Yes	2 (2%)	4 (1%)	6 (1%)
HPV 16	No	123 (97%)	309 (96%)	432 (96%)
	Yes	4 (3%)	12 (4%)	16 (4%)
HPV 18	No	125 (98%)	315 (98%)	440 (98%)
	Yes	2 (2%)	6 (2%)	8 (2%)

Figure 1: Association of Anal HPV types with HSIL on Biopsy



A5298 Study Sites:
Pittsburgh CRS, New York University HIV/AIDS CRS, Cornell CRS, University of California San Diego Medical Center, Evandro Chagas Clinical Research Institute, University of North Carolina, Beth Israel Deaconess, Rochester, AIDS Care CRS, Harvard Massachusetts General, New Jersey Medical School, Rush Presbyterian/St. Luke's, University of Colorado Health Sciences, Washington University, HIV Prevention and Treatment CRS, Northwestern University, Houston AIDS Research Team, Denver Public Health CRS, San Francisco General Hospital, Stanford University, University of Cincinnati College of Medicine, University of Puerto Rico, University of California Los Angeles Medical Center, Miriam Hospital Rhode Island, Boston Medical Center

Table 3: Baseline Anal Cytology Results

Characteristic		Presence of HSIL at study entry HSIL (N=187)	No HSIL (N=388)	Total (N=575)
Baseline Cytology Results	Normal	28 (15%)	170 (44%)	198 (34%)
	Abnormal	153 (82%)	200 (52%)	353 (61%)
	Other, specify	5 (3%)	14 (4%)	19 (3%)
	Not specified	1 (1%)	1 (0%)	2 (0%)
	No results	0 (0%)	3 (1%)	3 (1%)