Geographic Analysis of Cellular Immunity to Human Cytomegalovirus in Clinical Trial Volunteers

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BACKGROUND

- Human cytomegalovirus (HCMV) has emerged as a promising vaccine vector given its ability to elicit robust, sustained immune responses and persistent antigen expression.
- Pre-existing HCMV cellular immunity is not well characterized across demographic populations.
- Intracellular cytokine staining (ICS) is an assay designed to assess T-cell responses for which CMV pp65 peptide pool has been used as a control stimulation in multisite HIV vaccine trials.
- This study leveraged ICS data in which CMV was used as assay control to define epidemiology of pre-existing CMV cellular immunity among trial participants

METHODS

- We used data from eligible phase I/II HIV Vaccine Trials Network (HVTN) protocols that were conducted in different geographic locations and in which a CMV peptide stimulation was used as an assay control for ICS and multi-parameter flow cytometry.
- Baseline CMV pp65-specific ICS response, determined by statistical comparison (Fisher's exact test) of the percent of T-cells expressing IFN-ɣ and/or IL-2 as compared to negative control, was assessed overall, by region, sex, and age group.
- Magnitudes of positive responders were assessed by the same categories.
- Response rates were compared using Barnard's Exact test, and magnitudes of response among responders were compared using Wilcoxon rank sum test.

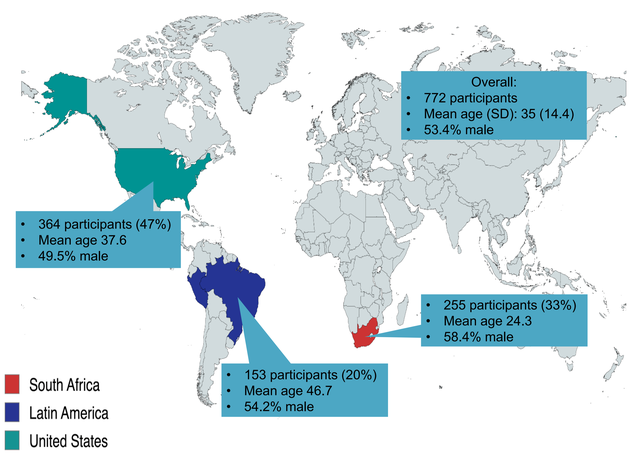


Figure 1. Baseline demographics of study population

Prevalence and magnitude of pre-existing HCMV cellular immunity varies, with lower response rates noted in the United States and among those of female sex.

Magnitudes for CD8+ T-cells were significantly higher in Latin America than in South Africa and in the United States.

RESULTS

- Seven protocols (HVTN 100, 137, 204, 300, 302, 305, 405) were identified yielding 772 unique participants with mean age 35 (SD 14.4) and 53.4% male. [Figure 1]
- Response rates to IFN-ɣ and/or IL-2 in the overall population for CD4+ and CD8+ cells were 68% and 71%, respectively. CD4+ response rate was significantly higher in South Africa (SA) compared to Latin America (LA) (p=0.025) and to the United States (US) (p<0.001). CD8+ response was significantly lower in the US compared to SA and LA (p<0.001). Response rate in males was significantly higher than in females for both CD4+ (p=0.005) and CD8+ (p<0.001) cells.
- Among responders, magnitudes of response for CD8+ T-cells were significantly higher in LA compared to those in the US (p=0.003) and SA (p<0.001). Magnitude of response among those who did respond was significantly lower in the 18-25 age group for both CD4+ (p=0.007) and CD8+ (p=0.004) cells and significantly higher in the >55 age group for both CD4+ and CD8+ cells (p<0.001). [Figure 2]
- Among sites in the US, aggregated response rates for CD4+ and CD8+ cells were 58 and 56% in the South, 43 and 48% in the West, 45 and 44% in the Northeast, and 60% for both in the Midwest. Substantial site to site variation existed [Table 1]

Figure 2. Magnitude of T-cell response to CMV (A) by region, (B) by sex, (C) by age (boxplots on positive responders only)

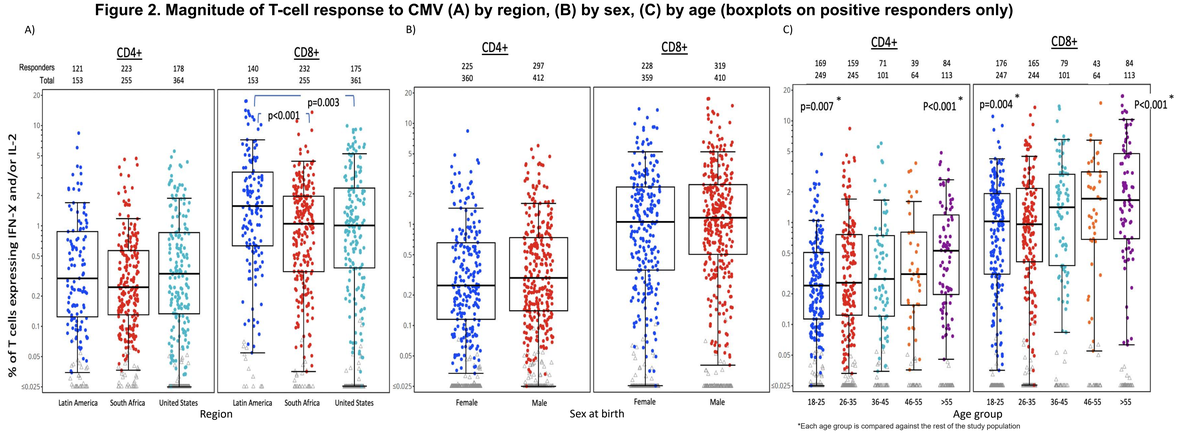


Table 1. CD4 and CD8 Responses to CMV pp65 by site, grouped by region

SITE	CD4 N	CD4 Response rate	CD8 N	CD8 Response rate
SOUTH				
Atlanta - Hope Clinic	21	71.4%	21	57.1%
Birmingham RAVE	25	56%	25	56%
Birmingham - Univ of Alabama	8	62.5%	8	50%
Chapel Hill CRS	10	70%	10	70%
George Washington University CRS	7	71.4%	7	57.1%
Nashville	31	54.8%	31	54.8%
New Orleans Adolescent Trials Unit (NO/ATU) CRS	1	0%	1	0%
Ponce de Leon Center CRS	3	100%	3	100%
Vanderbilt University	7	0%	7	42.9%
WEST				
Bridge HIV CRS	8	37.5%	8	50%
Seattle CRS	24	50%	24	50%
UCLA Vine Street Clinic CRS	8	25%	8	37.5%
NORTHEAST				
Baltimore - Univ of Maryland	1	100%	1	0%
Boston - Beth Israel Deaconess Medical Center	5	40%	5	40%
Boston - Brigham	19	42.1%	19	47.4%
Boston - Brigham and Women's Hospital Vaccine CRS	28	32.1%	26	26.9%
Bronx Prevention Research Center CRS	13	100%	13	92.3%
Fenway Health CRS	15	53.3%	15	53.3%
Harlem Prevention Center CRS	3	66.7%	3	66.7%
Harvard	11	9.1%	11	9.1%
Johns Hopkins University CRS	1	0%	1	0%
New Jersey Medical School Clinical Research Center CRS	3	66.7%	3	66.7%
New York - Physicians & Surgeons CRS	23	52.2%	22	40.9%
New York Blood Center CRS	11	81.8%	11	81.8%
Penn Prevention CRS	38	39.5%	38	44.7%
Pittsburgh CRS	7	14.3%	7	14.3%
Rochester CRS	17	29.4%	17	29.4%
University of Rochester	11	36.4%	11	45.5%
MIDWEST				
Adolescent and Young Adult Research at the CORE Center	5	60%	5	60%

CONCLUSIONS

- Prevalence of pre-existing HCMV cellular immunity varies, with lower response rates noted in the United States and among those of female sex
- We found regional differences in magnitudes of response among positive responders, with Latin America having significantly higher magnitude of responses than South Africa or the United States.
- We found increasing magnitudes of response with age
- These findings set the stage for future work to determine how pre-existing HCMV cellular immunity impacts immunogenicity of HCMV-vectored HIV and other vaccines.

LIMITATIONS

Our study is limited by only looking at responses to CMV pp65 protein, unavailable seropositivity / CMV antibody data for participants, unknown demographics of interest that may impact CMV acquisition and reactivation, and a unique population exclusively of clinical trial participants limiting generalization of findings.

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PLAIN LANGUAGE SUMMARY

Human cytomegalovirus is being tested as a vaccine vector to develop an HIV vaccine, but we don't know if previous exposure to CMV will impact how well the vaccines will work. To start to answer this, we studied the distribution of people previously exposed to CMV.