

Lymphoproliferative (LP) and Serologic Responses (SR) to Recall and Neoantigens in Severely Immunocompromised HIV-infected Children and Adolescents Initiating HAART (48 week follow-up)

Abstract #S-58; Poster 916

Authors: Rigaud M¹, Borkowsky W¹, Weinberg A², LaRussa P³, Muresan P⁴, Fenton T⁴, Jankelevich S⁵, Read J⁶, Ferguson E⁷, Smith D⁸ and Zimmer B⁹, representing the PACTG P1006 team.



NYU School of Medicine
Pediatric Infectious Diseases
550 First Ave NY NY 10016
Tel:212-263-7891
Fax:212-263-7806
e-mail:mona.rigaud@med.nyu.edu

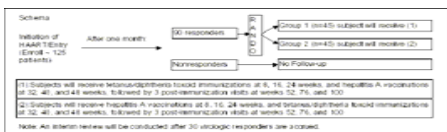
¹NYU School of Medicine, New York, NY;²Univ. Colorado Health Sci. Ctr. Denver Co;³Columbia Pres. Medical Ctr. New York NY;⁴FSTRF-Harvard School of Public Health, Boston MA;⁵NIAID/NIF, Bethesda MD;⁶NICHD/NIH, Bethesda MD;⁷NIAD/PAB, Bethesda MD;⁸U MASS Memorial Health Care, Worcester MA; ⁹FrontierSci and Tech Res Fndn, Amherst, NY

ABSTRACT

BACKGROUND: HIV-infected children with advanced disease tend to have high viral loads and low CD4 counts. It has been shown that treatment with HAART suppresses HIV viremia and significantly increases CD4%. The breadth of immune restoration, however, continues to be an area of active research. P1006 is assessing the LP and SR responses after vaccination with recall and neoantigens. **METHODS:** In this ongoing, prospective study of severely immunosuppressed (CD4% <15), children who initiate HAART and who demonstrate a decrease of >0.75 log in plasma HIV RNA copy number within 4 weeks ("virologic responders") are randomized to receive tetanus toxoid (TT) (GrpI), representative of a recall antigen, or hepatitis A vaccine (GrpII), representative of a neoantigen, at 8, 16, and 24 weeks after starting therapy. Subjects then are vaccinated with the other vaccine at weeks 32, 40, and 48. Antigen-specific responses to tetanus and hepatitis A are measured by LP assays performed after vaccinations. A positive LP response is defined as a stimulation index of >=3. SR responses to tetanus and to hepatitis A are measured by ELISA. A serological value of >0.1 IU/ml corresponds to a positive response for tetanus and a level of >20 IU/ml for hepatitis A. CD4% and HIV plasma RNA at times of immunization are correlated with immune responses. **RESULTS:** 32/53 virologic responders received vaccines. The two groups were similar at baseline: age (median 11 yrs), CD4% [(median 8 (GrpI) and 7 (Grp II)] and log RNA [(5.10 (GrpI) and 4.7 (GrpII)]. Overall, CD4% increased from 7 (baseline) to 15 (24 weeks) and 17 (48 weeks). LP responses to tetanus were seen in 50% and 27% in GrpI and GrpII, respectively. LP responses to hepatitis A were seen in 25% and 21% in GrpI and GrpII, respectively. Serologic responses to tetanus were seen in both groups after 3 immunizations with TT. Antibody responses to hepatitis A were seen more often than LP responses but were of very low titer. **CONCLUSIONS:** Severely immunosuppressed children and adolescents on HAART with some suppression of HIV viremia and increased CD4% have limited LP to recall and neoantigens. SR response to neoantigens also appears attenuated. Although limited by the relatively small number of subjects in each group, there is no evidence of difference in LP and SR responses between the two groups.

STUDY DESIGN AND METHODS:

Patient Population: HIV-infected, severely immunosuppressed (CD4% < 15%) children age 2-17 years who are initiating open-label HAART (at least 2 new drugs) and have shown a >0.75 log decrease or becoming undetectable in plasma HIV RNA copy number.



ENROLLMENT DATA

58 subjects enrolled in the protocol. 32 of these, the group of virologic responders at week 4, are included in the study population. Baseline Characteristics and Demographics of the groups:

	AGE	MALE	FEMALE	CD4%	CD4 COUNT	RNA(median)
Gp 1 (n=15)	11	9	6	8	103	102,900
Gp2 (n=17)	11	7	10	7	144	55,062

*Not all subjects had evaluable values in all the categories

PRIMARY OBJECTIVES

- 1) To assess the ability of newly derived CD4 T cells to **spontaneously** develop responses to a recall antigen (tetanus toxoid) or to develop responses after 1 or several booster vaccinations with tetanus vaccine
- 2) To assess the ability to develop protective antibody responses to a T-cell-dependent "neo"antigen using a primary series of hepatitis A vaccinations
- 3) To measure the durability of any response beyond the last vaccination

SECONDARY OBJECTIVES

- To correlate CD4 percentages at the time of vaccination with the establishment of immune responses
- To assess the ability to develop lymphoproliferative responses to a T-cell-dependent "neo"antigen using a primary series of hepatitis A vaccinations
- To assess whether the recovery of functional immunity is seen early or late after HAART
- To correlate the HIV plasma copy number at the time of vaccination(s) with the establishment of immune responses

RESULTS

IMMUNOLOGIC AND VIROLOGIC RESPONSES

Groups (N)	WEEK	Median CD4 COUNT (N)	Median CD4 percent (N)	Median log 10 RNA (N)
All (32)	0	84 (27)	7 (29)	4.98 (32)
	24	390 (21)	15 (20)	2.6 (28)
	48	469 (32)	17.5 (22)	2.6 (25)
GrpI (15)	0	84 (13)	7 (13)	5 (15)
	24	422 (9)	20 (12)	2.6 (13)
	48	691.5 (8)	29 (8)	2.6 (11)
GrpII (17)	0	29.5 (14)	6 (16)	4.7 (17)
	24	384.5 (12)	13 (14)	2.6 (15)
	48	441 (14)	17 (14)	2.7 (14)

CELL-MEDIATED IMMUNE RESPONSES

Group	Spontaneous TT SRs-3 before vaccination	TT SRs-3 After 1 vaccination	TT SRs-3 two or more times	Hep A SRs-1 or more times
GrpI		3/11 (27%)	5/10 (50%)	2/8 (25%)
GrpII	3/13 (23%)	7/13 (54%)	3/11 (27%)	3/14 (21%)

SEROLOGIC RESPONSES

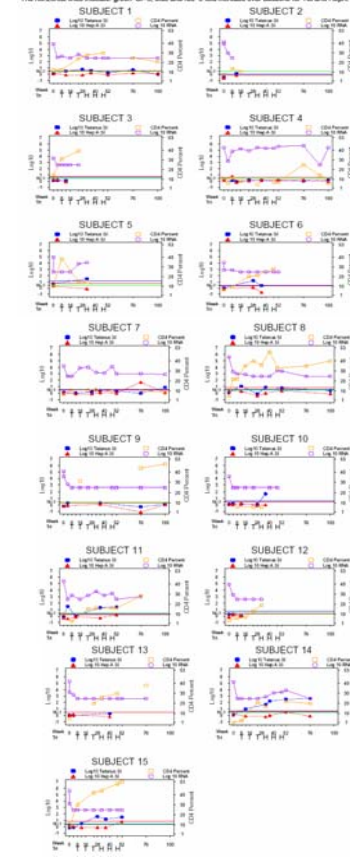
Group	Week of Study	TT serology based to >0.1 IU/ml or 4x	HepA inter->20MIU	Median HepA inter (mIU)
GrpI	0	3/9 (33%)	0/9	4.8
	12	6/11 (55%)	0/9	7.3
	28	9/9 (100%)	1/8 (13%)	5.3
	36	10/10 (100%)	1/9 (11%)	6.3
	52	6/6 (100%)	6/7 (86%)	126.8
GrpII	0	5/12 (42%)	0/7	13.7
	12	5/13 (38%)	2/12 (17%)	7.3
	28	3/11 (27%)	8/11 (73%)	68.5
	36	6/9 (67%)	3/7 (43%)	18.3
	52	9/10 (90%)	5/8 (63%)	47.9

CONCLUSION

- 1) SPONTANEOUS RESPONSE TO A RECALL ANTIGEN NOT PRESENT IN ENVIRONMENT OCCURS INFREQUENTLY WITH HAART THERAPY.
- 2) AFTER 3 VACCINATIONS WITH A RECALL ANTIGEN SUCH AS TETANUS TOXOID FOLLOWING INITIATION OF HAART, A BOOST OF CELL-MEDIATED (CMI) OCCURRED IN < 50% OF SUBJECTS WHILE HUMORAL IMMUNE RESPONSE OCCURRED IN MOST INDIVIDUALS.
- 3) CMI RESPONSE TO A "NEO"ANTIGEN SUCH AS HEPATITIS A OCCURS INFREQUENTLY IN HIGHLY IMMUNOCOMPROMISED INDIVIDUALS WHO ARE TREATED WITH HAART, EVEN WITH VIROLOGIC OR IMMUNOLOGIC IMPROVEMENT
- 4) HUMORAL RESPONSE TO HEPATITIS A OCCURS MORE OFTEN THAN THE CMI RESPONSE BUT THE TITERS ARE LOW (TYPICALLY <10% OF EXPECTED IN NORMAL INDIVIDUALS).

P1006 - LPA, RNA and CD4 Data

The horizontal lines indicate: green: 0-3, blue and red: 3 fold increase over baseline for Tat and HepA.



P1006 - LPA, RNA and CD4 Data

The horizontal lines indicate: green: 0-3, blue and red: 3 fold increase over baseline for Tat and HepA.

