

# Serological responses to recall and initiation of HAART in severely immunosuppressed HIV-infected children initiating HAART enrolled in PACTG P1006



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**ABSTRACT**

**BACKGROUND:** To establish if severely immunocompromised HIV-infected children initiating HAART can mount serological responses to vaccines, data from PACTG1006 were reviewed. **METHODS:** Severely immunocompromised children (CD4% <15%) who demonstrate a reduction of >0.75 log in plasma HIV RNA within 4 weeks of initiating HAART are randomized in two groups. Group I (GRPI) is vaccinated with a recall antigen tetanus toxoid (TT) at weeks (wks) 8,16, 24 and receives Hepatitis (HepA) vaccine, a neoantigen, at wks 32, 40, 48. Group2 (GRPII) is vaccinated initially with Hep A followed by immunization with TT at same time points. Serological responses measured by ELISA are evaluated. Children that demonstrate a titer of >0.1 IU/ml and >20 IU/ml are considered serologic responders for TT and HepA, respectively. **RESULTS:** The median titers (in IU/ml) and number of evaluated serologic responders (SR) after immunizations are reported in tables I and II for TT and HepA, respectively.

**TABLE 1**

WKS	GRP I		GRP II	
	Median Titer	SR (N)	Median Titer	SR (N)
0	0.11	10(18)	0.11	9(16)
12	0.51	13(18)	0.07	9(19)
28	2.98	14(14)	0.10	8(16)
36	1.37	15(15)	0.37	10(14)
52	0.69	11(12)	1.79	11(13)
76	0.43	12(12)	2.22	11(14)
100	0.21	6(8)	0.80	10(12)

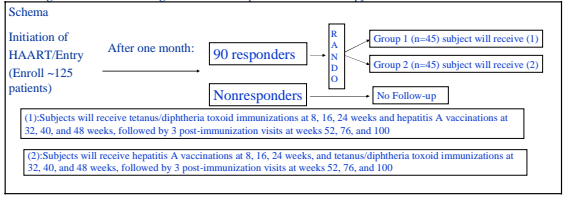
**TABLE 2**

WK	GRP I		GRP II	
	Median Titer	SR(N)	Median Titer	SR(N)
0	7.71	2(18)	5.61	0(16)
12	7.74	0(18)	9.00	3(19)
28	6.44	1(14)	26.30	9(16)
36	8.15	1(15)	22.41	8(15)
52	146.48	10(12)	14.39	6(14)
76	102.96	11(13)	13.88	6(14)
100	31.98	6(8)	20.39	6(12)

TT titers and SR rates after 3 TT vaccines (wk 28 in Grp I) are higher, but not statistically different when compared to wk 52 in GrpII (p>0.2), and wk 76 in GrpI compared to wk 100 in GrpII (p>0.4). Titers after Hep A vaccines were significantly higher at wk 28 (p<0.01) in children vaccinated in Grp I when compared to unvaccinated children as well as when compared to children that received vaccines in GrpI (wk 52) (p=0.02). Titers and SR were not statistically significant in GrpI at wk 100 compared to GrpII at wk 76. **CONCLUSIONS:** 1) Serological response to a recall antigen is boosted after 3 doses of vaccine independent of timing of immunization (early or late). 2) Serological response to a neo-antigen, Hep A, seems to develop if immunization is delayed after initiation of HAART.

**STUDY DESIGN AND METHODS:**

**Patient Population:** HIV-infected, severely immunosuppressed (CD4% < 15%) children age 2-24 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.



- PRIMARY OBJECTIVES**
- 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
  - To assess the ability to develop protective antibody responses to a T-cell-dependent "neo" antigen using a primary series of hepatitis A vaccinations
  - 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**

**ENROLLMENT DATA**

86 subjects have enrolled in the protocol so far. 37 of these were virologic responders at week 4 and have sufficient data to be included in these analyses. Baseline Characteristics and Demographics of the groups:

	AGE	MALE/FEMALE	CD4%	CD4 COUNT	RNA (median)
GRP I (n=18)	12	9/9	8	115	82,812
GRP II (n=19)	11	10/9	6	122	55,062

NOTE: Not all subjects had evaluable values in all the categories

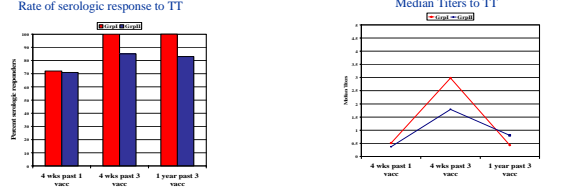
**IMMUNOLOGIC AND VIROLOGIC RESPONSES**

Groups (N)	WEEK	Median CD4 COUNT (N)	Median CD4 percent (N)	Median log 10 RNA (N)
All (37)	0	84 (35)	7 (36)	4.9 (37)
	24	279 (30)	14 (36)	2.6 (36)
	48	441 (34)	18 (36)	2.6 (36)
	52	589 (16)	12 (26)	2.6 (33)
	76	544 (28)	25 (29)	2.6 (29)
	100	462 (25)	21 (26)	2.9 (26)
GrpI (18)	0	84 (17)	7 (17)	4.9 (18)
	24	395 (14)	15 (18)	2.6 (17)
	48	524 (15)	24 (17)	2.6 (17)
	52	632 (7)	11(14)	2.6 (16)
	76	599 (12)	28 (13)	2.6 (13)
	100	697 (11)	24 (11)	2.6 (11)
GrpII (19)	0	30 (18)	6 (19)	4.7 (19)
	24	253 (16)	13 (18)	2.6 (19)
	48	381 (19)	17 (19)	2.6 (19)
	52	513 (9)	12 (12)	2.6 (17)
	76	428 (16)	18 (16)	2.6 (16)
	100	397 (14)	17 (15)	3.5 (15)

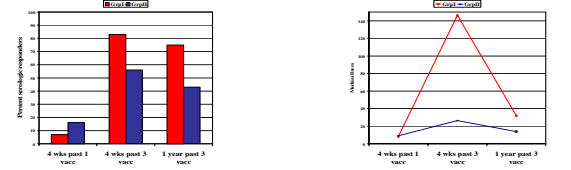
**BACKGROUND**

With the advent of HAART, it is not clear at which point severely perinatally-infected children and adolescents are capable of recognizing antigens experienced (i.e. recall antigens) in the past or antigens seen anew (i.e. neoantigens). We chose to study the former by measuring cellular and humoral immune responses to tetanus toxoid after initiating HAART and after 1 or 3 boosters vaccination. We chose to study the response to a neoantigen by selecting individuals without previous hepatitis A experience or anti-hepatitis A IgG. Cellular and humoral immune responses were measured after initiating HAART and after receiving 1 and 3 vaccinations with hepatitis A vaccine. In order to determine the appropriate timing of antigen exposure to elicit immunity, patients were randomized to receive vaccinations with either tetanus or hepatitis A vaccines during the first 6 months of HAART and these groups would receive the alternative vaccine during the next 6 months of HAART. It was assumed that CD4 T cells would continue to increase over time while HIV viremia might reach a nadir during the first 6 months and possibly climb thereafter due to the development of viral resistance or due to decreasing adherence. We previously reported on the lymphoproliferative response to these antigens (Rigaud et al. The 11<sup>th</sup> Annual Conference on Retroviruses 2004). We now report on the serologic responses.

**SEROLOGIC RESPONSES**

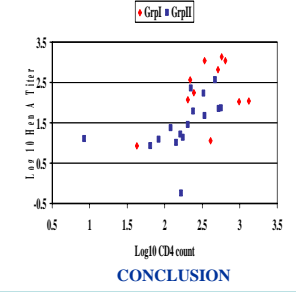


**Rate of serologic response to Hep A**



**CORRELATION OF CD4 COUNT AND LYMPHOPROLIFERATIVE RESPONSE (LPR) TO TETANUS TOXOID AND HEPATITIS A WITH SEROLOGIC RESPONSE**

- There was no correlation between LPR response to vaccines and the measured serologic response
- There was no significant correlation between the CD4 count and the serologic response to tetanus toxoid
- There was an overall (group 1 and 2) statistically significant correlation (Spearman Coefficient of 0.70; p<0.0001) between the CD4 count and the serologic response to Hepatitis A vaccine despite the fact that this correlation was not significant for Group 1.



- 1) There is no significant difference in the baseline, week 24 and week 48 CD4 and HIV RNA levels between the 2 groups.
- 2) Serological response to a recall antigen is boosted after 3 doses of vaccine independent of timing of immunization (early or late).
- 3) Serological response to a neo-antigen, Hep A, seems to develop if immunization is delayed after initiation of HAART.
- 4) Serological response to Hepatitis A appears to correlate with the CD4 count at the time of vaccination.
- 5) There is no correlation between lymphoproliferative response to tetanus toxoid or hepatitis A and the serologic response to these antigens.