



# CD4+ and CD8+ T cell Responses in Acutely Infected Infants receiving Early HAART and STI



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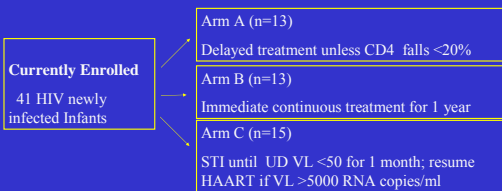
## ABSTRACT

The ultimate goal of HAART and STI interventions in adults has been to induce immune responses that can control viral replication following complete withdrawal of HAART. To investigate this approach in children, we have enrolled 41 HIV-infected infants who have been divided into one of three arms: delayed treatment, immediate treatment and structured treatment interruption. Subjects on the delayed treatment arm had higher CD8+ T cell responses than those who received immediate treatment following diagnosis as measured by interferon-gamma ELISPOT and intracellular cytokine staining. Subjects on the treatment interruption arm had low CD8+ T cell responses during therapy but these increased following exposure to the virus by interruption of treatment. Interruption of treatment after 1 year of HAART resulted in augmented responses in two subjects. It is still to be determined if the high CD8+ T cell responses will have a negative effect on viral load and this will be compared with the outcome of subjects undergoing treatment interruption and those on the delayed treatment arm. CD4+ T cell responses were low in all subjects irrespective of the study arm. Identification of epitopes targeted by children during acute infection will aid in the paediatric vaccine design.

## INTRODUCTION

Although the effect of HAART and STI during acute HIV infection in adults has previously shown to control viral replication for longer following withdrawal of HAART, recent reports questioned the duration of the initially perceived benefit of this intervention. Implementing these studies in children could prevent life-long dependence on HAART and also reduce side effects and drug resistance associated with continuous drug intake. This study will also provide insight on the presently undefined role of T cell responses in children. Children are likely to have a better prognosis than adults as they have the ability to reconstitute immune responses more rapidly and more completely than adults. The aim of this study is to use early HAART and STI to protect pediatric immune system against devastating high viral loads while allowing time for generation of HIV-specific immune responses to control viral replication.

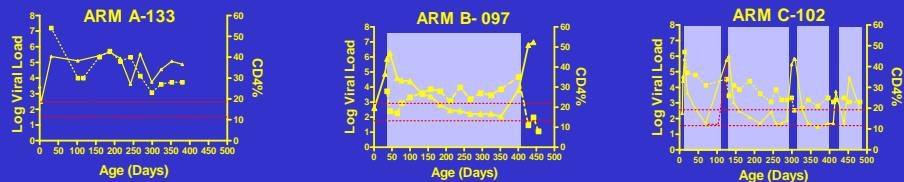
## METHODS



- Monitor Viral Loads and CD4 counts
- Evaluate T cell responses:
- IFN-gamma ELISPOT (used 410 overlapping peptides spanning HIV C-clade consensus sequence)
  - Intracellular cytokine staining for IFN-gamma, IL-2 and TNF-alpha; used pooled peptides comprising Gag, Nef, Acc, Reg, Pol and Env HIV-1 proteins

## RESULTS

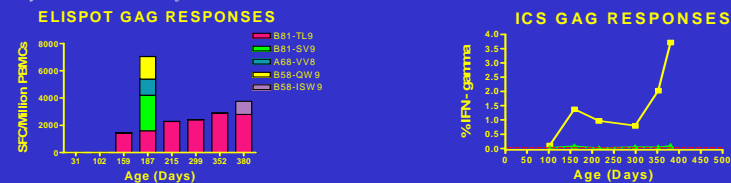
Of the 41 enrolled subjects thus far, 28 were infected intra-uterine and 13 subjects were infected intra-partum. Arm A subjects showed an increase in viral load and a rapid decrease in CD4% except for subject A-133 (Fig.1) who still had good CD4 T cell counts and controlled viral load after 1 year off therapy. Arm B and C subjects had undetectable VL and high CD4 T cell counts during therapy but had viral rebound and a fall in CD4 percentage following interruption of HAART.



**Figure 1.** Representative of Viral load (▲) and CD4% (■) for subjects on Arm A (A-133), Arm B (B-097) and Arm C (C-102). The shaded area indicates treatment period; dotted lines indicate undetectable viral load of <400 and <50 RNA copies/ml.

## RESULTS CONT...

Subjects on the three arms targeted the entire HIV genome but the most targeted regions were NEF>GAG>ENV>POL> ACC>REG. CD8+ T cell responses were detected as early as week 1 in 10 subjects. Of the three groups, Arm A (untreated) subjects (Fig.2.) had the highest magnitude of responses (3725 SFC/Million PBMCs) due to exposure to high viral loads. These responses were detected both on ELISPOT and ICS. CD4+ T cell responses were very low in all studied subjects.



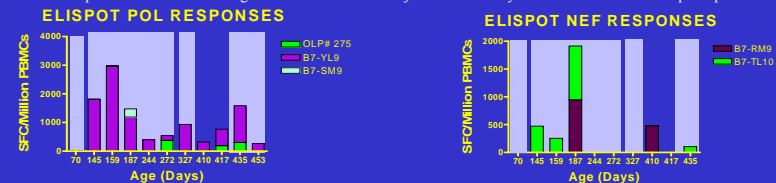
**Figure 2.** CD8+ and CD4+ T-cell responses in subject A-133 as measured by IFN-gamma ELISPOT and ICS.

Arm B subjects (Fig.3.) had no detectable responses for 1 year while on therapy, but these subjects had a high turn-over of responses following interruption of HAART.



**Figure 3.** T cell responses in GAG and NEF in Arm B subject B-097 as measured by IFN-gamma ELISPOT

Viral rebound in Arm C (Fig.4.) subjects was followed by detection of T cell responses. These responses however, decreased when treatment was resumed. Treatment interruption has lasted an average of 2 weeks in the 4 subjects who already reached treatment interruption phase.



**Figure 4.** T cell responses in POL and NEF as measured by IFN-gamma ELISPOT in Arm C subject C-102

## CONCLUSIONS

Children have detectable CD8+ T cell responses soon after birth, however CD4+ T cell responses are undetectable. HAART reduced viremia and T cell responses in treated children and CD8+ T cell responses were augmented following interruption of treatment. Although CD8+ T cell responses in children targeted mainly GAG and NEF, the entire HIV genome was recognized, a similar pattern has been noted in the same settings. The short duration of interruption periods in children undergoing STI could indicate the slow development of effective immune responses in first few months of life. The ongoing research will help establish the role played by CD8+ T cell responses and the epitopes targeted during early infection in infants.

## ACKNOWLEDGEMENTS

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