

# Divergent Immune Responses in HIV-1 Vertically Infected Monozygotic Twins

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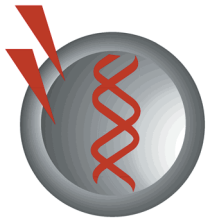
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## Abstract

Mother-to-infant transmission of HIV remains one of the fastest growing facets of the worldwide AIDS pandemic. In pediatric HIV infection, the pattern of disease progression is bimodal, with AIDS developing in a subgroup of infants very early in life and progressing much more slowly in others. These distinct patterns in disease progression are determined by a complex interplay between host genetic factors, the developing immune system, and viral pathogenesis. Strong T-cell immune responses elicited against HIV viral antigens have been shown to play a central role in controlling disease progression. Here we present a unique study of a set of vertically infected monozygotic twins that differ greatly in their disease progression where one twin is thriving while the other is not. Such a study provided us with the opportunity to analyze immune responses in individuals with identical genetic backgrounds that have been infected by closely related, if not identical, viral quaspecies. We hypothesized that the strength of cell-mediated immune responses may account for the divergent rates of disease progression in the twins. HIV-1-specific T-cell responses were assessed with overlapping peptides using ELISPOT analysis and intracellular cytokine staining. We observed that the thriving twin with drastically higher CD4<sup>+</sup> T-cell counts (median, 1294 vs 362 cells/mL), lower viral loads (median, 3.03 vs. 5.59 log<sub>10</sub> RNA copies/mL), and lower activation levels had strong and broad immune responses as well as robust CD4<sup>+</sup> and CD8<sup>+</sup> T-cell proliferative responses to HIV Gag and Tat antigens. High levels of HIV-specific cytotoxic CD8<sup>+</sup> T-cells as measured by the production of both IFN- $\gamma$  and TNF- $\alpha$  as well as CD107a and CD107b were also evident in the thriving twin. Viral sequencing and additional functional analyses are currently underway.

## Background

### Pediatric HIV Disease Progression

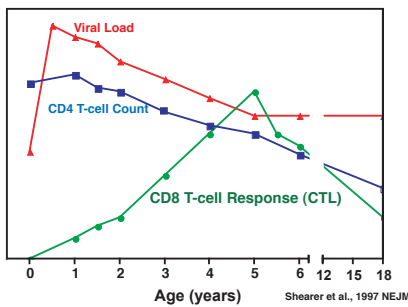
- Children have a greater viral burst and viral load decreases slowly with time
- Children have a high number of CD4<sup>+</sup> T-cells at young age that decrease with time
- Age of patient, type and number of circulating CD4<sup>+</sup> T-cells, as well as characteristic and availability of antigen are important in influencing anti-HIV CD8<sup>+</sup> T-cell responses.

≤3 yo

- Decreased CD4 help
- increased limiting age factor X
- Decreased CD8 response
- increased viral load

>3 yo

- Increased CD4 help
- Decreased limiting age factor X
- Increased CD8 response
- Decreased viral load



## Study Design

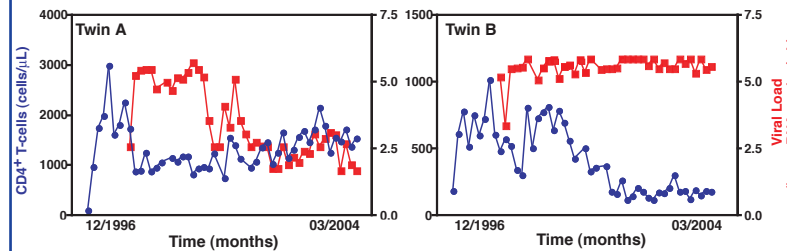
- A unique study of a set of monozygotic twins infected at birth from their mother
- The twins differ greatly in their disease progression where one twin is thriving while the other is not
- An opportunity to study immune responses in individuals with an identical genetic background that have received the same viral inoculum at the same time

## Results

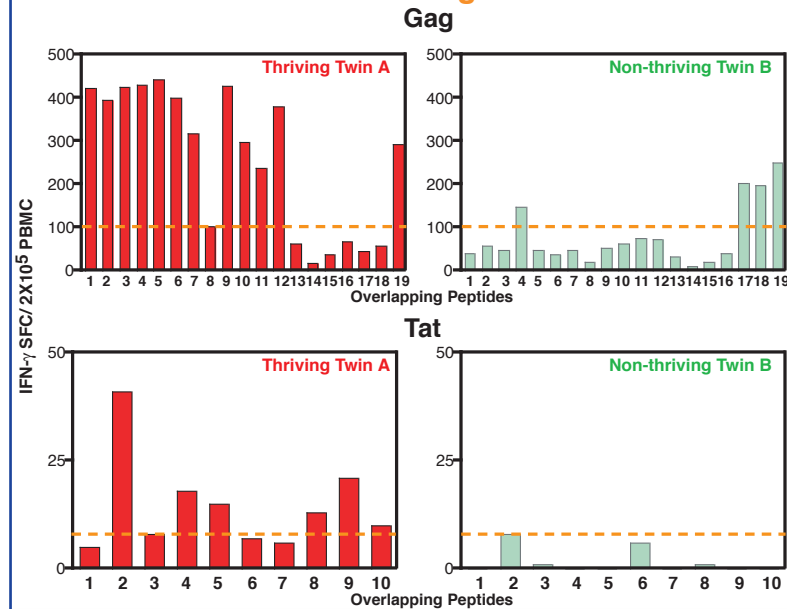
### Clinical Observations for Monozygotic Twins

- Date of birth 03/31/1990
- Twin B was born 15 minutes before her Twin A
- Twin B is doing much worse overall than Twin A who is thriving
- Non-thriving Twin B is the smaller of the two, but has never had any opportunistic infections.
- Thriving Twin A had active TB at 17 months
- Thriving Twin B was PPD positive, but had no active disease
- Both Twins started Protease Inhibitor therapy (ritonavir) in 09/1996

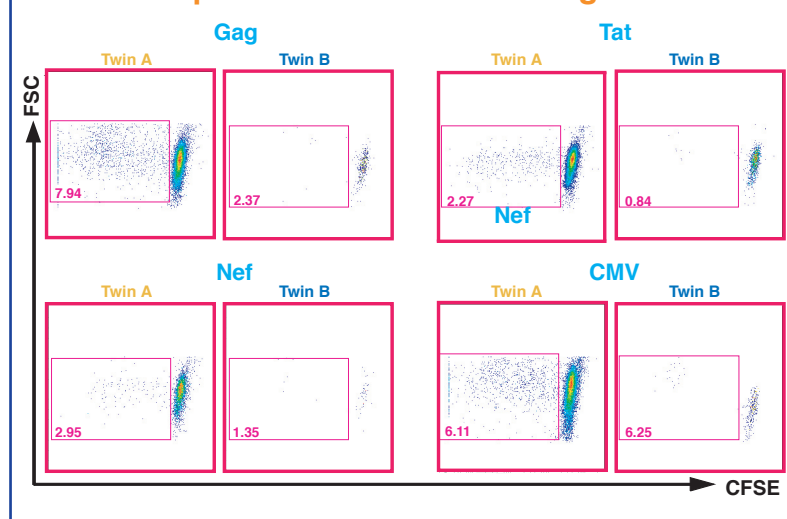
### Longitudinal Immunological and Virologic Assessment of Perinatally Infected Twins



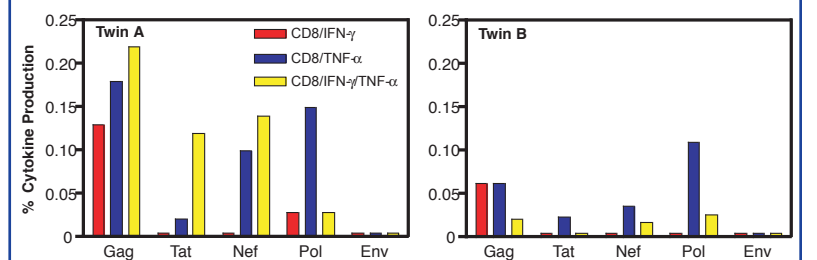
### Increased Breadth and Magnitude of HIV Gag and Tat Specific Immune Responses in the Thriving Twin



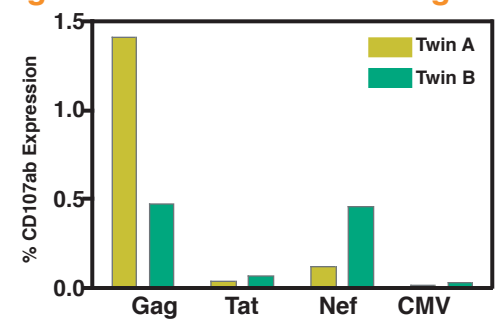
### Diminished HIV-Specific CD4+ T-cell Proliferative Responses in the Non-thriving Twin



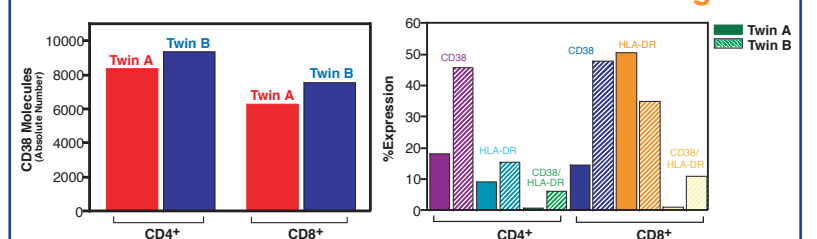
### Prevalence of HIV-Specific CD8+ T-cells Producing both IFN- $\gamma$ and TNF- $\alpha$ in the Thriving Twin



### Evidence of Significant Degranulation to HIV Gag in CD8+ T-cells of Thriving Twin



### Increased T-cell Activation in the Non-thriving Twin



## Summary

	Thriving (Twin A)	Non-thriving (Twin B)
Strong & Broad Immune Responses	++++	+
T-cell Proliferation	++++	+
T-cell Activation	+	++++
Cytotoxic CD8+ T-cells	++++	+

## Future Directions

- Test whether thriving Twin A's PBMCs can inhibit non-thriving Twin B's viral replication
- Test role of apoptosis:
  - FLIP, Bcl-2, TNF and TRAIL
- Sequence HIV gene products to measure immune evasion
- Measure T-cell maturation status
- Test role of opportunistic infections in immune-protection