

An Open-Label Randomized Trial to Determine the Virologic and Immunologic Effects of 4-Weeks of Cyclosporine A (CsA) Given in Combination with Antiretroviral Therapy (ART) during Acute and Early Infection (AEI).



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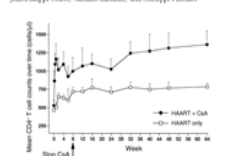
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INTRODUCTION

- Acute HIV-1 infection is characterized by unchecked rounds of viral replication with resultant massive CD4+ T cell depletion and immune activation.
- CsA suppresses the cellular immune response via inhibition of IL-2 transcription after TCR-mediated signal transduction (see figure)
- In patients given ART and CsA for 8 weeks during AEI, levels of CD4+ T cells were higher when compared to historical controls (see figure)
- We hypothesized that immune modulation during AEI in conjunction with ART would have virologic and immunologic benefit.

Treatment of primary HIV-1 infection with cyclosporin A coupled with highly active antiretroviral therapy

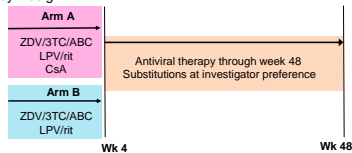
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METHODS AND RESULTS

Study Design



Cyclosporine A Dosing

- Liquid formulation dosed at 0.3mg/kg twice daily
- Dosing based on ideal body weight
- Target concentration 250 to 450 ng/mL
- Levels measured on day 3, weeks 1, 2, 3
- Dose adjustments for levels out of the target range were made using the following formula-

$$300(\text{measured level} \times \text{current dose} = \text{adj. dose})$$

Results- Study Participants

	Arm A (N=28)	Arm B (N=13)
Age (median, IQR)	36 (30, 40)	35 (30, 43)
Sex (M, F)	27M, 1F	13M, 0F
Race/Ethnicity	20C, 0AA, 8H	10C, 1AA, 1H, 1other
Baseline CD4+T cells (median, IQR)	407 cells/mm ³ (340, 587)	490 cells/mm ³ (399, 623)
Baseline log HIV RNA (median, IQR)	5.0 log copies/ml (4.9, 5.8)	4.9 log copies/ml (4.5, 5.8)
EIA negative at entry	7	3
EIA + W.B. 3 bands or less at entry	16	7
EIA + W.B. 4 to 5 bands at entry	5	3

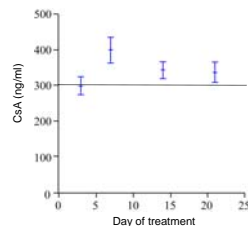
Treatment Regimens

	Arm A (N=28)	Arm B (N=13)
Remained on regimen	10	5
Switched to 3TC/ABC	7	3
Switched to 3TC/ABC/EFV	2	3
Switched to TDF/FTC/EFV	4	2
Switched to 3TC/ABC/ATZ/r	1	0
Total changed to TDF/FTC	7	2
Total changed to ABC/3TC	9	6
Total changed to EFV	6	5
Total changed RX	18	8

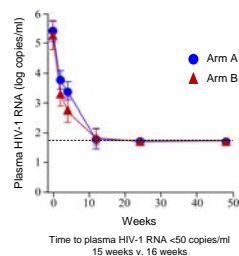
Statistical Considerations

- Analyses were randomized with completers only included in the analysis
- The Wilcoxon rank test or the Gehan-Wilcoxon rank test (adjusted for censoring) was used for comparisons between Arm A and B with a p value of 0.05 or less being statistically significant
- Primary endpoint
 - Levels of proviral DNA between arms at 48 weeks
- Secondary endpoints
 - Virologic
 - Immunologic

Median CsA Levels



Levels of HIV-1 RNA



Patient Disposition

- 54 randomized, 41 completed, 13 withdrew
- Reasons for patient withdrawal as reported on CRF completed at clinical site
 - Primary Drug resistance N=1
 - Adverse events N=1
 - Non-compliance with medications/visits N=4
 - Lost to follow up N=3
 - Death due to suicide N=1
 - Virologic failure N=2 (non-adherence)
 - Investigator/clinician decision N=1

CONCLUSIONS

When compared to combination antiviral therapy used alone over 48-weeks the addition of 4-weeks of Cyclosporine A dosed at 0.3mg/kg twice daily and targeted to 250 to 450 ng/ml to combination antiviral therapy did not add apparent immunological or virological benefit.

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Protocol team

- M. Markowitz- Protocol Chair
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- F. Vaida- Statistician
- Celsa Spina, Peter Lopez- Protocol Immunologists
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