

Clinical and Laboratory Consequences of Unplanned Treatment Interruptions in Perinatally HIV Infected Children and Adolescents

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Background

- With the realization that current therapeutic strategies are incapable of eradicating HIV and that medication toxicity and lifelong pill burden are significant, there is greater interest in investigating methods that would minimize drug exposure while maintaining immunological status.
- Several recent reports in adult patients have indicated that nadir CD4 count is the most important variable related to duration of successful treatment interruption (TI).
- Although two pediatric studies have been published recently, they did not evaluate nadir CD4 as a predictor of TI duration.

To examine the consequences of unplanned treatment interruptions in a cohort of heavily pretreated, perinatally, HIV infected, pediatric patients, we examined the relationship between nadir CD4 count and duration of treatment interruption.

Women and Children Care Center (WCCC)

- The WCCC is a hospital based clinic that provides a wide array of services to HIV infected women, children, and their affected family members.
- The clinic is located in Northern Manhattan and serves the populations of the Southern Bronx, Washington Heights/Inwood, and the Upper West Side.

Definitions

- Treatment Interruption:** patient who stopped therapy on their own or with a providers advice and remained off antiretrovirals for at least 3 months. Sixteen of 76 (21%) perinatally HIV infected patients qualified.
- Age:** age in years at the time of the treatment interruption.
- CD4 count:** Patients were grouped into 2 categories for purposes of Kaplan-Meier analysis; < 350 and > 350.
- Nadir CD4 count:** Lowest CD4 count recorded at any time prior to the TI (either on or off of therapy).

Study Population and Evaluations

- Perinatally HIV infected children/adolescents were eligible for the study if they had an unplanned treatment interruption which started any time within the years 2000-2004.
- Immunologic/Virologic parameters evaluated:**
 - Nadir CD4 count;
 - CD4 count and plasma RNA just prior to interruption;
 - CD4 count and plasma RNA just prior to therapy re-initiation;
 - CD4 count and plasma RNA 4-8 weeks, 3-4 months, and 6 months after therapy re-initiation.
- Clinical Parameters evaluated:**
 - Age;
 - Gender;
 - Race/Ethnicity;
 - Use of PCP prophylaxis and incidence of opportunistic infections (OI's);
 - Evidence of immune reconstitution;
 - Reasons for treatment interruption.

Analyses

- Paired t tests were used to analyze differences in mean CD4 counts.
- Kaplan-Meier analysis was used to model CD4 count category versus duration of treatment interruption.
- Multivariate regression modeling predicting duration of TI adjusted for age, race/ethnicity, gender, nadir CD4 count, CD4 count just prior to interruption, and plasma RNA just prior to interruption

Patient Characteristics

Number of Patients:	16
Number of TI's:	19 (range 1-2)
Duration of TI:	12.4 mo. (range 3-42 mo.)
Age:	14.8 yrs. (range 4-23 yrs.)
Gender/Race/Ethnicity:	53% female, 53% Hispanic, 47% African American

Results

Reasons For TI (Provider Interpretation)*

- Medication fatigue – 11/16 (69%)
- Patient reported side effects – 3/16 (19%)
- Medication toxicity – 4/16 (25%)
- Psychiatric diagnosis – 4/16 (25%)
- Social situation – 3/16 (19%)
- Behavioral issues – 3/16 (19%)

*some patients had more than one reason for interrupting therapy

Clinical Parameters

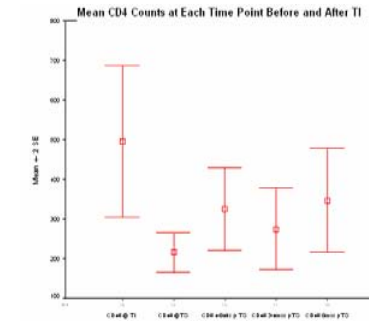
% on Pneumocystis prophylaxis:	63
Incidence of OI's:	0
Incidence of immune reconstitution:	0
3 patients (19%) currently remain off therapy	

Laboratory Results Pre TI

Mean Nadir CD4:	1428	293 (range 26-
Mean CD4 at TI:	459 (range 23-1428)	27-707)
Mean log plasma RNA at TI:	1.7-5.39)	4.79 (range
Mean CD4 at re-initiation:	193 (range 24-308)	1.7-5)
Mean log plasma RNA at re-initiation:	5.16 (range 2.6-5.86)	3.97 (range

Laboratory Results Post TS

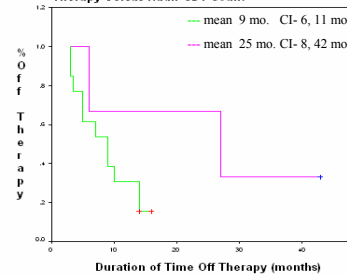
Mean CD4 count 4-8 weeks:	302 (range
Mean log plasma RNA 4-8 weeks:	3.97 (range
Mean CD4 count at 6 months:	332 (range 174-
Mean log plasma RNA at 6 months:	3.73 (range 1.7-



CD4 decline during TI: 21 cells/mo.
CD4 rise after re-initiation: 257 cells/yr.

CD4 Comparison	Mean	95% CI Lower	95% CI Upper	t	P(2 tailed)
CD4 at TI - CD4 at TS	253.85	43.17	464.52	2.625	.022
CD4 at TS - CD4 4-8 wks pTS	-110.00	-190.62	-29.38	-2.973	.012
CD4 at TS - CD4 3-4 mo. pTS	-75.45	-167.23	16.32	-1.832	.097
CD4 at TS - CD4 6 mo. pTS	-131.00	-280.92	18.92	-1.977	.079

Kaplan-Meier Analysis of Duration of Time Off Therapy Versus Nadir CD4 Count



Multivariate Model Predicting Time Off Therapy

Variable	Beta	t	p value
Constant		-.266	.796
Age (yrs)	.235	.934	.375
Gender	.147	.895	.394
Race	-.278	-1.688	.126
VL@TI	.296	1.705	.122
Nadir CD4	.953	3.061	.014
CD4@TI	.081	.233	.821

Summary and Conclusions

- The majority of patients halted therapy due to medication fatigue, but there were multiple reasons in some cases.
- There was a significant drop in CD4 count during treatment interruptions and a significant rise in CD4 count 4-8 weeks after re-initiating therapy.
- The rate of CD4 decline during TI is similar to previously published studies (21 cells/mo. and 257 cells/yr.).
- The majority of patients (63%) were taking OI prophylaxis and there were no opportunistic infections or episodes of immune reconstitution.
- Kaplan-Meier analysis indicated that patients with a CD4 nadir > 350 could remain off therapy almost 3 times as long as patients with a CD4 nadir < 350; however, this result was not significant, probably due to small numbers.
- Similar to previously published data in adults, CD4 nadir was the only variable in a multivariate model that could predict duration of time off therapy.
- This is the first pediatric study to show the significance of CD4 nadir in predicting duration of treatment interruption. Perinatally HIV infected pediatric patients with a CD4 nadir > 350 may be able to come off therapy safely with close monitoring. Further large scale analyses are warranted.