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CD4+ Lymphocyte-Based Immunologic Outcomes of Perinatally HIV-Infected Children During Antiretroviral Therapy Interruption

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Abstract

Objective—To assess the characteristics and outcomes of antiretroviral therapy (ART) interruption (TI) in perinatally HIV-infected (PHIV) children.

Design—The Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study is a prospective cohort study that enrolled 7-16 year old PHIV children between 2007 and 2009 from 15 sites in the US and Puerto Rico.

Methods—TI was defined as ART discontinuation for ≥3 months after ≥6 months of continuous ART. Subjects with and without TI were compared. Rates of change (slopes) in CD4+ T-lymphocyte (CD4) count and percentage (%) per month during TI were calculated. Factors related to CD4 slope in univariable analyses were included in multivariable linear regression.

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Results—Of 444 eligible AMP subjects, 101 (23%) had at least one TI. Subjects with TI were born in earlier years but were otherwise similar to those without TI. For 81 TI subjects with complete data, the median (range) CD4% and CD4 count slopes were -0.66%/month (-3.54% to +1.34%) and -12.7 cells/mm^3 per month (-148 to +31 cells/mm^3 per month), respectively. On multivariable linear regression, there was a trend for lower CD4% slope to be associated ($p<0.1$) with female sex, higher CD4% at TI, and higher peak viral load before TI. Advanced HIV disease stage and numerous ART regimens were more common in TI subjects in the lowest (fastest-declining) CD4% slope quartile.

Conclusion—TIs in PHIV youth are common. During TIs, CD4 values decline on average but with high intersubject variability. Factors predicting CD4 slope during TI need further study.

Keywords

HIV-1; Children; Adolescents; Perinatal HIV infection; Treatment interruption; CD4+ T cell percentage

Background

Antiretroviral therapy (ART) is recommended for all infants diagnosed with perinatally acquired HIV infection because of the high risk of rapid disease progression, the superior outcomes when therapy is initiated early, and the inability to readily identify those who would not have clinical progression in the absence of ART [1,2,3]. However, most untreated children do not experience significant clinical or immunologic progression in the short-term, and up to 10% of untreated children may not exhibit such progression for many years [4-8]. Universal ART for infants and children commits this subset of children to lifetime ART from infancy without as much potential for benefit and with the potential for increased toxicity and resistance. One of the aims of the ongoing Children with HIV Early Antiretroviral Therapy (CHER) study is to determine the relative risks and benefits of limiting ART duration by randomizing children whose ART was initiated in infancy to discontinue ART at 40 or 96 weeks [1]. Beyond early childhood, treatment interruptions (TIs) may also be helpful in some clinical circumstances for the management of selected older children failing ART in the context of ongoing poor adherence and more generally, for reducing cost, toxicity, and development of drug resistance with continuous therapy. Therefore, therapeutic TI may be an important part of the armamentarium of long term treatment in children. However, additional information is necessary to assess the risks and benefits of the process.

Studies in HIV-infected adults have demonstrated that TI (among those who have already met clinical or immunologic criteria for ART in the past) results in higher mortality and morbidity than continuing ART without interruption [9,10]. The only published study in which children were randomized to CD4-guided TI compared to continuous ART for 48 weeks reported no short-term serious clinical events in either arm [11]. Observational studies [12,13,14] indicate that unplanned TIs are common in perinatally infected children and adolescents and are often associated with CD4+ lymphocyte (CD4) declines that result in ART reinitiation. However, some of these children do not experience substantial CD4 declines or HIV disease progression despite TI and factors associated with such low-risk ART discontinuation have not been well characterized. We assessed the characteristics and immunologic outcomes of children who discontinued ART in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), a prospective cohort study designed to determine outcomes of children with perinatally-acquired HIV.

Methods

Adolescent Master Protocol of the Pediatrics HIV/AIDS Cohort Study

The source population for this study was the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), which is a prospective cohort study designed to evaluate the impact of HIV-infection and ART on pre-adolescents and adolescents with perinatal HIV infection. Between March 2007 and December 2009, infected and uninfected children from 15 study sites in the US and Puerto Rico were eligible for enrollment into AMP if they were born to HIV-infected mothers, were between 7-16 years of age, and previously enrolled in another protocol team-approved longitudinal cohort study such as: the Pediatric AIDS Clinical Trials Group (PACTG) protocols 219 and 219C, which were earlier prospective observational studies designed to evaluate the long-term effects of HIV infection and *in utero* and postnatal exposure to antiretroviral drugs; and the Women and Infants Transmission Study (WITS), a longitudinal study of HIV-infected pregnant women and their infants. Children with a complete medical history since birth, including details of HAART use, HIV RNA concentrations, and lymphocyte subsets, were also eligible for enrollment. The AMP protocol was approved by the institutional review boards at each participating site and the Data and Operations Center (Harvard School of Public Health), and written informed consent was obtained from each child's parent or legal guardian, as well as each child's assent, when appropriate.

Definition of ART TI

TI was defined as discontinuation of all ART for at least three consecutive months after a period of at least six months of continuous ART. Discontinuation of ART for up to 2 weeks was not considered a break in continuous ART. Only the most recent TI with available CD4 data was included in analyses.

Predictor and Outcome Definitions

Change in CD4% per month (CD4% slope) during TI was used as the primary outcome of interest due to the greater stability of CD4% compared to CD4 count across the pediatric age range. CD4% slope for each child was calculated as the difference between the CD4% at time of ART reinitiation or last visit (whichever came first) and the CD4% at the time of TI, divided by the total duration (in months) of the TI. A similar calculation of CD4 count slope was used as a secondary outcome. Antiretroviral regimen changes were defined as any single drug change in a regimen. Highly active ART (HAART) was defined as the concomitant use of at least three drugs from at least two classes of HIV drugs. HIV drugs were classified into six categories: nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), integrase inhibitors (IIs), and entry inhibitors (EIs).

Statistical Analysis

Differences between children with TI and those without TI were assessed using Fisher's exact test for categorical variables and the Kruskall-Wallis test for continuous characteristics.

Covariates considered as potential predictors of CD4% and CD4 count slope included socio-demographic and clinical characteristics at the time of or prior to the TI. Clinical history of antiretroviral drug use, CD4 percentages and counts, HIV viral loads (VL), and HIV disease progression as measured by the CDC clinical classification, were abstracted from medical charts and obtained from available databases of prior studies. HIV VL measurements at the time of TI were missing for 22% of the study population because these measurements were not routinely collected or available before 2000.

To identify independent predictors of CD4% and CD4 count slope during ART interruption, univariable linear regression models were fit with the following covariates: sex, race, ethnicity; age, calendar year, CD4%, CD4 count, log HIV VL, CDC clinical category, and HAART use at TI; and nadir CD4%, nadir CD4 count, peak log HIV VL, duration of most recent antiretroviral regimen, and number of antiretroviral regimens prior to TI. The difference between the nadir CD4% and the CD4% at time of TI was also considered as a potential predictor of CD4% slope; the same approach was taken using CD4 counts. Covariates associated with CD4% or CD4 count slope during TI with a p-value of 0.20 or less in univariable models were included in a final multivariable linear regression model.

To identify characteristics that differed between children with faster declines in CD4% or CD4 count during TI and children whose CD4% or CD4 count remained relatively stable during TI, the extreme quartiles of CD4% and CD4 count slope were compared. Fishers exact and Kruskall-Wallis tests were used to identify the socio-demographic and clinical characteristics that differed between the extreme quartiles of CD4% and CD4 count slope. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Of 451 HIV-infected children enrolled in AMP, 444 completed the baseline visit and had received ART continuously for at least six months as of May 1, 2010. Of these 444 children, 101 (23%) had at least one ≥3 month TI. There were 12 (2.7%) children who had two TIs. First TIs occurred prior to enrollment in AMP for 90 (89%) of the 101 children with a documented TI. Children with TI were born significantly earlier than those who never interrupted therapy (Table 1, $p<0.0001$). Children with TI were similar to those without TI in terms of sex (40% vs. 48% males, $p=0.14$), race (71% vs. 72% Black, $p=0.14$), ethnicity (26% vs. 24% Latino, $p=0.24$), age at ART initiation (1.0 vs. 0.8 years, $p=0.6$), CDC class at entry to AMP (26% vs. 23% class C, $p=0.92$). Of the 101 interrupters, the 81 who had CD4 results available at the time of TI and at least one additional time point during the interruption were included in subsequent analyses.

The majority of the 81 children who interrupted ART were female and Black (Table 2). At the time of TI, 55% were at least 10 years old, 62% had been on a HAART regimen, and the median duration of their most recent ART regimen was 36.6 months. ART was initiated at a median age of 1.0 year (interquartile range 0.4-2.3 years). At TI, the median CD4% (32%) and CD4 count (709 cells/mm^3) reflected generally good immunologic status; 3.7% (3/81) had a CD4% <15% at TI. The median log HIV VL at TI was 3.1, but only 24% had VL ≤400 copies/mL. CDC clinical category C conditions occurred in 28% of children at some time before TI. The nadir CD4% of 21.0% occurred at a median age of 3.8 years (Q1-Q3, 1.7, 7.3), while the nadir CD4 count of 470 cells/mm^3 occurred at a median age of 6.8 years (Q1-Q3, 3.8-10.1). Most children had experienced a rise in CD4% (median increase of 10%) and in CD4 count (median increase of 194 cells/mm^3) between their historical CD4 nadir and the time of TI.

During TI, the CD4 percent dropped a mean of -0.66% and median (IQR) of -0.51% (-0.92% to -0.13%) per month, and the CD4 count dropped a mean of -20 and median (IQR) of -12.7 (-29.7 to -4.8) cells/mm^3 per month. However, there was a wide range of CD4 slopes among the interrupters, ranging from children with extreme rates of decline in CD4% (-3.54% per month) and CD4 count (-148 cells/mm^3 per month) to those who had actual increases (positive slope) in CD4 values after interruption, as high as +1.34% and +31.3 cells/mm^3 per month. The median (Q1, Q3) duration of TI was 16.2 (6.5, 24.4) months. Most (79%) subjects reinitiated ART; the reasons for re-initiating ART were not available,

but there were no AIDS-defining illnesses or deaths during TI. The median (range) duration of follow-up from the time of TI was 4.5 years (0.3, 14.2).

Of all of the demographic and clinical characteristics evaluated (Table 2), the only factors potentially associated ($p<0.2$) with more rapid rate of decline in CD4% were female sex (-0.76% vs. -0.51% per month, p=0.09), higher CD4% at interruption (-0.02% per month for each 1% higher CD4% at TI, p=0.05), CDC clinical category C (-0.89% vs. -0.58%, p=0.16), and higher peak VL before interruption (-0.15% per one log increase in VL, p=0.06) (Table 3). The strength of these associations was unchanged in multivariable analysis.

When children were divided into the quartile with the fastest rate of CD4% decline (lowest quartile, $\Delta CD4\% \leq -0.92\%$ per month) and the quartile with the most stable CD4% (highest quartile, $\Delta CD4\% \geq -0.13\%$ per month), the children in the lowest quartile were significantly more likely than those in the highest quartile to have a history of CDC category C disease (45% vs. 10%, p=0.03) (Table 4). There was a non-significant trend for those in the lowest quartile to have had a greater increase in CD4% from nadir until interruption, to have a higher peak VL before interruption, and to have been on a greater number of ART regimens prior to interruption.

Discussion

Among this large number of ART-experienced, perinatally HIV-infected school-aged children in the United States, over one-fifth have interrupted ART for three months or more at least once in their lifetime. This rate is similar to the 17.8% rate reported in another recent US pediatric cohort [14]. Reasons for TI were not available in the present study but are most likely related to medication fatigue, as previously reported [14]. Unlike other reports of unplanned TIs in children [12,13,14], the current study involved an observational cohort that permitted comparison of characteristics of children who have and have not interrupted ART. Most children (70%) with an interruption were born before 1996, while most (57%) without an interruption were born in 1996 or later; this finding may mean that interruptions are becoming less common over time (perhaps related to availability of more potent, better tolerated HAART regimens) or that more recently born children have not yet reached the adolescent ages when increased adherence difficulties may lead to a greater likelihood of TI. Otherwise, there were no other obvious differences in demographics, ART initiation age, or HIV disease progression that distinguished the two groups, suggesting that higher rates of female and Black race patients with TIs simply reflect the composition of the overall pediatric HIV population.

As expected and as reported in other TI studies in children, CD4 percentage and CD4 counts, on average, decline during TIs. There are important differences in TI definition, treatment history and cohort composition between the current study and prior reports of TI in children (Table 5). The average declines in CD4% and CD4 count in the current study were similar to those observed in a younger, pediatric cohort in the UK [12], but less than the declines reported by a more contemporary US cohort using a similar TI definition [14]. In addition, the median (range) CD4% slope of -0.29% (-0.89% to -0.09%) per month in a group of 7 perinatally infected children with a planned TI at 2- 6 years old suggests that CD4 decline patterns in younger children may be similar [15]. However, as also observed by Gibb *et al.* [12], there was tremendous variability in CD4 slopes during TI in the current study, suggesting that some children on ART may not experience immunologic deterioration if ART is discontinued. Similarly, only about one third of children in the TI of the PENTA trial reached CD4-decline outcomes within initial 48-week period [11]. Such differences in CD4 changes during TI could be used to classify children into slower and faster

immunologic progressors as a means to identify additional host genetic and immunologic determinants of HIV-related immunologic progression [18, 19].

As infants and young children are increasingly routinely prescribed HAART as soon as HIV is diagnosed, it becomes important to determine whether some of these children can safely interrupt therapy later in childhood. The potential adverse effects of HAART must be balanced against the potential detrimental effects of untreated HIV in the growing and developing child, but the balance is not likely to be the same for all children. The current study offers some clues to factors that identify those children who are less likely to experience rapid immunologic decline, including male sex, less advanced HIV disease, less robust CD4 response while receiving ART, lower HIV VL before ART initiation, and lower CD4 values at time of interruption. Many of these factors represent potential indicators of children who are less in need of therapy or who have not benefited from the therapy that has been prescribed. The association of low CD4 at TI with more stable CD4 slope during TI, for instance, likely represents children with low CD4 values because of ineffective HAART (due to non-adherence and/or resistance) whose immunologic status is no worse off with TI. Saitoh *et al* found that better CD4 response to pre-interruption ART was a significant predictor of faster CD4 decline [14]. While CD4 nadir predicts faster CD4 loss in adult TI studies [16,17] and in the PENTA trial [11], CD4 nadir was not a predictor of faster CD4 decline in this or other pediatric TI studies. The immunologic outcomes of TIs in the small group of young children who initiated ART in early infancy and the finding of older age as a risk factor for faster CD4 decline in the PENTA trial suggest a better outcome when TIs occur at younger ages [11,15]. These findings may assist clinicians managing children and adolescents for whom a short-term TI is desired while working out psychosocial and other barriers to reliably taking a suppressive HAART regimen. Future studies of TI in children in the era of routine initiation of HAART in infancy will likely rely on a combination of such clinical predictors along with genetic determinants to identify the lowest-risk children for TI.

Data from the SMART (Strategies for Management of Antiretroviral Therapy) study in adults raise important concerns about increased risk of cardiac and other-noninfectious complications, in addition to traditional HIV-associated infections, in patients undergoing TI [9,10]. The current observational study in children demonstrates no evidence of serious HIV-related illness during TI, while other pediatric cohorts reported AIDS-defining illness at rates of 0-7% during TIs. The PENTA trial, which was limited to children with baseline virologic suppression and lack of CD4-defined immunosuppression, reported no AIDS events during or following CD4-guided, planned treatment interruptions. However, the relatively low rates of serious illness during TI in these pediatric studies should be interpreted with caution for several reasons: the current study includes only children who survived to at least age seven years in order to enroll in AMP; ART regimens have changed over time; all of these pediatric studies are small and, with exception of PENTA 11, non-randomized; and, even with HIV infection, children would be expected to have much lower rates of cardiac and other non-infectious complications. TIs may result in inflammatory responses that may cause multifaceted, deleterious effects; inflammatory marker levels during TI were not available in this study. In addition, subtle but potentially permanent deleterious neurocognitive effects of TI in children are a major concern; these outcomes were not evaluable in the current study but will be the subject of future PHACS investigations and will be evaluated in the subjects scheduled for TI in the ongoing CHER study.

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Table 1

Comparison of population with antiretroviral treatment interruption (TI) (N=101) to population that initiated but never interrupted antiretroviral treatment (N=343)

Characteristic	TI N=101	No TI N=343	P-value
Sex			
Male	40 (40)	166 (48)	0.14
Female	61 (60)	177 (52)	
Birth Cohort			
1991-1993	41 (40)	62 (18)	
1994-1995	30 (30)	87 (25)	<0.0001
1996-1997	17 (17)	74 (22)	
1998-2002	13 (13)	120 (35)	
Race			
Black	72 (71)	248 (72)	0.14
Not Black	20 (20)	81 (24)	
Unknown	9 (9)	14 (4)	
Ethnicity			
Hispanic	26 (26)	81 (24)	0.24
Not Hispanic	74 (73)	262 (76)	
Unknown	1 (1)	0 (0)	
Age at ART initiation (years), Median (Q1, Q3)	1.0 (0.4, 2.3)	0.8 (0.3, 2.6)	0.60
CDC Class at AMP Entry	46 (45)	167 (49)	0.92
N/A	28 (28)	93 (27)	
B	26 (26)	80 (23)	
C	1 (1)	3 (1)	
Missing			

Table 2

Demographic and clinical characteristics of the 81 perinatally HIV-infected children with antiretroviral therapy interruption (TI) and available CD4 information.

Characteristic	Total (N=81)
Sex, N (%)	
Male	31 (38)
Female	50 (62)
Birth Cohort, N (%)	
1991-1993	33 (41)
1994-1995	25 (31)
1996-1997	13 (16)
1998-2002	10 (12)
Race, N (%)	
Black	59 (73)
Not Black	15 (18)
Unknown	7 (9)
Ethnicity, N (%)	
Hispanic	19 (24)
Not Hispanic	61 (75)
Unknown	1 (1)
Age at ART initiation (years), Median (Q1, Q3)	1.0 (0.4, 2.3)
Age at TI (years), Median (Q1, Q3)	10.3 (6.8, 12.9)
CD4% at TI, Median (Q1, Q3)	32.0 (25.3, 37.0)
Log HIV viral load at TI,[1] Median (Q1, Q3)	3.1 (2.6, 4.1)
CDC clinical category at TI, N (%)	
N/A/B	58 (72)
C	23 (28)
Nadir CD4% before TI,[3] Median (Q1, Q3)	21.0 (14.0, 27.0)
Difference between CD4% at TI and Lowest CD4% before TI, Median (Q1, Q3)	10.0 (3.8, 15.0)
Peak Log HIV viral load before TI,[4] Median (Q1, Q3)	5.3 (4.5, 5.8)
Most recent regimen prior to TI, N (%)	
HAART	50 (62)
PI-based HAART	43 (53)
Non-PI-based HAART	7 (9)
Non-HAART	31 (38)

Characteristic	Total (N=81)
NRTI only – 3 drugs	4 (5)
NRTI only – 1 or 2 drugs	27 (33)
Ever use of HAART prior to TI?, N (%)	
Yes	57 (70)
No	24 (30)
Duration of most recent regimen prior to TI (months), Median (Q1, Q3)	36.6 (12.7, 70.6)
# of regimens prior to TI, Median (Q1, Q3)	3 (2, 6)
Calendar year of TI, N (%)	
1996-2000	10 (12)
2001-2005	39 (48)
2006-2008	32 (40)

[1] N=63 with viral load information

[2] N=14 with Nadir CD4=CD4 at TI

[3] N=8 with Nadir CD4%=CD4% at TI

[4] N=4 with Peak viral load=viral load at time of TI.

Table 3

Univariable and multivariable predictors of CD4% slope (change in CD4% per month) during antiretroviral therapy interruption (TI).*

Characteristic	Mean Slope	Univariable Mean Difference in Slope (95% CI)	Multivariable Mean Difference in Slope (95% CI)	Adjusted P-value
Sex				
Male	-0.51	0.26 (-0.12, 0.63)	0.31 (-0.05, 0.67)	0.09
Female	-0.76	Referent	Referent	
CD4% at TI, (1 unit increase)	--	-0.02 (-0.04, 0.005)	-0.02 (-0.04, 0.00)	0.05
CDC clinical category at TI				
N/A/B	-0.58	Referent	Referent	0.16
C	-0.89	-0.31 (-0.71, 0.09)	-0.28 (-0.67, 0.11)	
Peak HIV viral load before TI, (1 log increase)	--	-0.15 (-0.33, 0.03)	-0.18 (-0.38, 0.01)	0.06

*All demographic and clinical characteristics in Table 1 were evaluated as predictors of CD4% slope. Only those characteristics associated with CD4% slope with a p-value<0.2 in univariable analyses are included in this table and entered into the multivariable model, including sex, CD4% at TI, CDC clinical category at TI, and peak viral load before TI.

Table 4

Characteristics associated with extreme quartiles of CD4% slope during treatment interruption (TI).

Characteristic	Lowest Quartile: ≤-0.92 (Fastest CD4 Decline) N=20	Highest Quartile: ≥-0.13 (Most Stable CD4) N=20	P-value*
% with CDC C disease	45%	10%	0.03
Age at ART initiation (years)	0.6 (0.3, 1.6)	1.5 (0.4, 2.5)	0.12
Difference between CD4% at TI and Lowest CD4% before TI: Median (Q1,Q3)	11.5 (8.2, 15.7)	10.5 (0, 15.2)	0.19
Highest Log HIV viral load before TI: Median (Q1, Q3)	5.9 (5.0, 5.9)	5.5 (5.0, 5.6)	0.18
# of regimens prior to TI: Median (Q1, Q3)	5 (3, 9)	3 (2, 4)	0.07

*Fisher's exact p-value for categorical variables, Kruskall-Wallis p-value for continuous variables

TABLE 5

Comparison of Studies of Antiretroviral Therapy Interruption (TI) in HIV-infected Children

Study	TI definition	N	Age (yr)	% Female	% Black	% CDC C	CD4% [#, cells/ mm^3] at TI	VL at TI	HAART at TI	TI Duration	% ART Restart	CD4 during TI	Clinical Outcome: AIDS events
Gibb 2004	≥ 4 wk TI after ≥3mo HAART	71	7.0 (med)	NR	58%	48%	24% [NR] (med)	VL<400: 15%	100%	4.1mo (med)	72%	%: -0.52%/mo By CD4#at TI (cells/mm^{3}per mo): 200: -10.4 250: -13.8 500: -16.4	7%
Montpoux 2004	Not defined	24	10.5 (med)	79%	NR	21%	26% [686]	VL<40: 25%	NR (<100%)	40 wk (med)	NR	-11.25 cells/mm^3 /wk	0
Saitoh 2008	≥ 3mo TI after ≥6mo ART	72	12.8 (mn)	60%	42%	NR	27% [679] (mn)	VL<400: 24%	80%	14 mo (mn)[1]	67%	-10.8 cells/mm^3/wk	3%
Current	≥ 3mo TI after ≥6mo ART	101 / 81[2]	10.3[2] (med)	60%[2]	71%[2]	26%[2]	32% [709] (med)	VL<400: 24%	62%	16.2mo (med)	79%	%: -0.66%/mo (mn) #: -20 cells/mm^3/mo (mn) %: -0.51%/mo (med) #: -12.7 cells/mm^3/mo (med)	0
PENTA 11 trial 2010[3]	≥6mo of ≥3 ARV drugs. Randomized to TI or no TI[3]	56	9.0 (med)	52%	30%	18%	37% [967]	VL<50: 86%	100%	48 wk (med)	<48wk: 41% ≥48wk: 98%	N/A	0

Abbreviations: TI= treatment interruption. N= number of subjects. Yr = year(s). #= absolute CD4 count, in cells/mm^3. VL = viral load. Wk = week(s). Mo= month(s). HAART = highly active antiretroviral therapy. Med = median. Mn = mean. NR = not reported.

[1]Discrepancy in article between duration of 14mo and 15.9mo mean duration.

[2]Total 101 children with TIs, including demographic and CDC C data; 81 with complete laboratory data for remainder of results.

[3]PENTA 11 (2010) was a randomized (1:1) trial of TI vs. no TI for up to 48wk; table values for this trial refer only to the study subjects randomized to TI.