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SLOW CD4/CD8 RATIO RECOVERY RATES OF CHILDREN AND ADOLESCENTS DESPITE VIROLOGICAL SUPPRESSION

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BACKGROUND

- There are limited data on the long-term prognosis of young adults living with HIV who are successfully treated with combination antiretroviral therapy (cART).
- We investigated the recovery rates of CD4/CD8 ratio, a suggested marker for chronic immune activation, among Thai children and adolescents after they initiated cART.

METHODS

- This study was carried out in an ongoing HIV Thai cohort that includes children and adolescents (both perinatally [PaHIV] and behaviorally [BaHIV] acquired HIV infections) who had started cART at ≥5 years of age.
- CD4/CD8 normalization was defined as two consecutive values of the ratios ≥ 1 on two consecutive visits.
- Participants were eligible for inclusion in this analysis if they achieved and maintained viral suppression at <50 copies/mL after starting cART, and if CD4/CD8 ratio at first viral suppression was < 0.8.
- Follow-up was censored once participants had viral rebound (HIV-RNA ≥ 50 copies/mL) after achieving suppression.
- This cohort study was reviewed and approved by the Institutional Review Boards of the Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from the participating adolescents and their caregivers.

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RESULTS

TABLE 1. Participants characteristics of both perinatally infected (PaHIV) and behaviorally infected children and adolescents

Median (IQR) or number (%)	N	Perinatal transmission (N=101)	Sexual transmission (N=37)	P
Gender	138			<0.001
Male		50 (49.50)	34 (91.89)	
Female		51 (50.50)	3 (8.11)	
Age at start ARV	138	8.8 (7.5-11.3)	19.1 (17.3-20.5)	<0.001
HIV mode of transmission		N/A	27 (73)	
MSM				
Heterosexual				
Baseline HIV-RNA level (log_{10} copies/mL)	109	5.00 (4.61-5.16)	4.78 (4.50-5.27)	0.82
Baseline CD4 count (cells /mm^3)	110	115 (18-308)	263 (176-439)	0.004
Baseline CD8 count (cells /mm^3)	107	969 (636-1364)	937 (616-1257)	0.76
Baseline CD4/CD8 ratio	107	0.13 (0.03-0.24)	0.30 (0.18-0.38)	0.0001
CDC grading	90			0.008
N		12 (18.75)	0 (0.00)	
A		21 (32.81)	17 (65.38)	
B		15 (23.44)	6 (23.08)	
C		16 (25.00)	3 (11.54)	
Months since ART start to first viral suppression	138	28 (6-71)	5 (3-6)	<0.001
Duration of ART (years)	138	10.6 (7.9-13.7)	2.4 (1.4-3.3)	<0.001
Duration of viral suppression (years)	138	4.71 (2.39-8.59)	1.80 (0.86-2.69)	<0.001
CD4/CD8 ratio at first viral suppression	138	0.45 (0.25-0.60)	0.49 (0.35-0.66)	0.33
Positive HBsAg	127	0/94 (0.0)	3/33 (9.09)	0.016
Positive HCV Ab	65	0/36 (0.00)	1/29 (3.45)	0.45
Baseline ARV regimen	138			<0.001
PI based exposure		9 (8.91)	3 (8.11)	
NNRTI based exposure		91 (90.10)	26 (70.27)	
INSTI based exposure		1 (0.99)	8 (21.62)	

IQR, interquartile range, ART, antiretroviral therapy; MSM, men who have sex with men; antiretroviral drugs; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitors; ART, antiretroviral therapy

TABLE 2. Incidence of CD4/CD8 ratio normalization (ratio ≥1) among both PaHIV and BaHIV

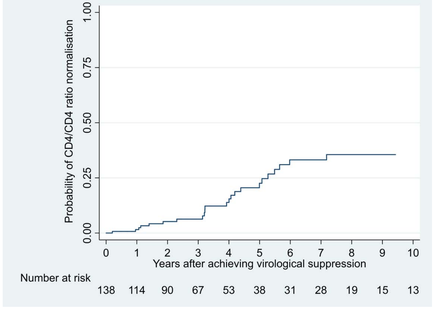
	Number of events	Person years of follow-up	Rate per 100 PYS (95%CI)
CD4/CD8 ratio ≥1	23	559	4.11 (2.73-6.19)
			Probability
Year 2	6		5.21 (2.36-11.27)
Year 5	11		22.57 (14.31-34.54)
Year 10	6		35.55 (24.51-49.66)

TABLE 3. Characteristics of children and adolescents with and without CD4/CD8 ratio normalization

Median (IQR) or number (%)	All children (n=138)	CD4/CD8 ratio <1 (N=115)	CD4/CD8 ratio ≥1 (N=23)	P
Gender				0.16
Male	84 (60.87)	73 (63.48)	11 (47.83)	
Female	54 (39.13)	42 (36.52)	12 (52.17)	
Age at start ARV	10.6 (8.1-16.3)	11.1 (8.3-17.0)	8.3 (7.4-11.5)	**0.036**
Baseline HIV-RNA level (log_{10} copies/mL)	5.00 (4.56-5.22)	5.00 (4.57-5.23)	4.88 (4.10-5.00)	0.48
Baseline CD4 count (cells /mm^3)	178 (37-320)	178 (39-318)	165 (14-408)	0.87
Baseline CD8 count (cells /mm^3)	964 (616-1332)	959 (662-1286)	1060 (476-1830)	0.52
Baseline CD4/CD8 ratio	0.17 (0.05-0.33)	0.18 (0.06-0.32)	0.15 (0.03-0.35)	0.58
Route of transmission				**0.04**
Perinatal	101 (73.19)	80 (69.57)	21 (91.30)	
Sexual *(73% MSM)*	37 (26.81)	35 (30.43)	2 (8.70)	
Months since ART to first viral suppression	9 (5-57)	9 (5-60)	11 (6-45)	0.99
Duration of viral suppression (years)	3.10 (1.78-7.63)	2.84 (1.4-6.88)	8.05 (5.13-11.82)	**<0.001**
CD4/CD8 ratio at first viral suppression	0.47 (0.29-0.62)	0.45 (0.28-0.59)	0.53 (0.33-0.68)	0.074
<0.3	35 (25.36)	30 (26.09)	5 (21.74)	
0.30-0.45	31 (22.46)	28 (24.35)	3 (13.04)	
>0.45	72 (52.17)	57 (49.57)	15 (65.22)	
Positive HBsAg	3/127 (2.36)	3/105 (2.86)	0/22 (0.0)	1.00
Positive HCV Ab	1/65 (1.54)	1/53 (1.89)	0/12 (0.0)	1.00
Baseline ART regimen				0.63
PI-based	12 (8.70)	9 (7.83)	3 (13.04)	
NNRTI-based	117 (84.78)	98 (85.22)	19 (82.61)	
INSTI-based	9 (6.52)	8 (6.96)	1 (4.35)	

IQR, interquartile range, ART, antiretroviral therapy; MSM, men who have sex with men; antiretroviral drugs; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitors; ART, antiretroviral therapy

FIGURE.
Kaplan-Meier Curve showing CD4/CD8 normalization rates of children and adolescents (both PaHIV and BaHIV) who had achieved virological suppression after ART initiation



- A total of 138 children and adolescents (101 PaHIV and 37 BaHIV) aged <25 years old met inclusion criteria.
- Among 37 BaHIV adolescents, 27 (73%) of them reported homosexual risks. Median (interquartile range, IQR) age of ARV initiation was 10.6 (8.1-16.3) years old with median (IQR) baseline CD4 and CD8 cell counts as 178 (37-320) cells/mm^3 and 964 (616-1332) cells/mm^3, respectively. Median duration of cART was 9.3 years (10.6 for PaHIV and 2.4 for BaHIV) and median duration of virological suppression was 3.1 years (4.7 for PaHIV and 1.8 for BaHIV).
- Overall CD4/CD8 ratio of children and adolescents at first virological suppression was 0.47 (0.29-0.62). Of 559 person years of follow-up (PYFU), the overall incidence rate of CD4/CD8 ratio normalization among children and adolescents <25 years old was 4.1 per 100 PYFU (95% confidence interval [CI]: 2.7-6.2).
- With Kaplan-Meier estimation methods, the probabilities of normalization at 2, 5 and 10 years after virological suppression were 5.2%, 22.6% and 35.6%, respectively. At year 2 of virological suppression, the normalization probability of PaHIV children and adolescents was higher than that of BaHIV (6% vs. 11.1%).

CONCLUSION

- CD4/CD8 ratio recovery rates were slow among children and adolescents after initiated cART despite virologically suppressed.
- Long-term prognoses such as ongoing immune activation and clinical outcomes among children and adolescents on suppressive cART without CD4/CD8 normalization needs to be further investigated.

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