Dyslipidemia and Lipodystrophy in HIV-Infected Thai Children on Highly Active Antiretroviral Therapy (HAART)

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Background: *Previous cross sectional studies revealed that dyslipidemia occurs in 50-70% of children receiving highly active antiretroviral therapy (HAART). However, there is no information in children in developing countries where children may have a different nutritional status.*

Objective: *To evaluate the incidence and associated risk factors of dyslipidemia following HAART in HIV-infected Thai children. The occurrence of clinical lipodystrophy among these children was also evaluated.*

Material and Method: *Twenty-three HIV-infected children who initiated HAART from "Access to Care Program" sponsored by MOPH around October 2001. Non-fasting blood tests for lipid profile were performed at enrollment and every 6 months. Triglyceride level was not analysed due to a non-fasting condition. The assessment of clinical lipodystrophy was done every 1-2 months.*

Results. *As of October 2003, 19 (83%) children experienced dyslipidemia. There were 10, 13, 5, and 8 children who had dyslipidemia at 6, 12, 18, and 24 months of HAART. The mean total cholesterol, low density lipoprotein (LDL), and high density lipoprotein (HDL) tended to increase over time while the children were on HAART. There was a correlation of elevated total cholesterol and CD4 percentage gain particularly at 18-24 months of treatment (r = 0.596, p = 0.007). Two children developed peripheral lipoatrophy. There were no dyslipidemia-associated risk factors identified. Most of the children had transient abnormal lipid profile. There were only 3 children that had persistent abnormality throughout the 24 months of HAART.*

Conclusion: *Dyslipidemia was found from 6-12 months of HAART, and were mostly transient over time. Peripheral lipoatrophy were found in 2 children. Further follow-up will elucidate the long-term incidence, the association factors, and clinical consequences.*

Keywords: *HIV, Children, Dyslipidemia, HAART*

HIV-infected adults treated with highly active antiretroviral therapy (HAART) are at risk of dyslipidemia, insulin resistance, and abnormal fat distribution[1-5]; i.e.peripheral lipoatrophy[6] and visceral fat gain[7]. Increased risk of cardiovascular disease has been recognized in HIV infected patients with hyperlipidemia and fat redistribution syndrome[5,11,12]. In adults who received protease inhibitor (PIs) containing regimens, approximately 50% had hyperlipidemia and 18%-83% had fat redistribution[1,4,6,8,9]. Hyperlipidemia was also reported in patients receiving non nucleoside reverse transcriptase inhibitor (NNRTI) containing regimens[10]. More recent studies have suggested that the regimens of NNRTI plus PIs markedly increased the incidence of elevated total cholesterol level[12] and were associated with lipodystrophy syndrome[13-17]. Limited studies in children also found hyperlipidemia in 50-70% of children on HAART, with the 20-30% incidence of lipodystrophy[18-21]. There was great concern of long term impact to the development of cardiovascular complications[19] and diabetes mellitus type 2 later in life. Moreover, psychosocial impact of lipodystrophy might affect adherence to antiretroviral therapy (ART). Children are generally more vulnerable than adults to metabolic

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side effects of therapy due to the potential impacts on growth after cumulative exposure[22].

So far, there has been no report of antiretroviral associated dyslipidemia reported in children in developing countries where children may have a different nutritional status. The aim of this study was to evaluate the incidence and associated risk factors of dyslipidemia, and to evaluate the incidence of clinical lipodystrophy, in HIV-infected Thai children receiving HAART.

Material and Method

A longitudinal prospective cohort study was carried out at the Pediatric HIV clinic, Siriraj hospital, Bangkok, from October 2001. The study population included twenty-three HIV infected children who initiated triple combination ART (HAART) and had a history of good adherence. These children were enrolled into the "Access to Care Program" for ART sponsored by the Thai Ministry of Public Health (MOPH) around October 2001. All children were perinatally HIV infected. Thirteen children were seen in the Pediatric HIV clinic from the neonatal period. Ten children came from Bangkok, 11 from the central provinces, and 2 from northern provinces. The patients were followed up every 1-2 months. The physical examination including assessment of fat wasting in the extremities, buttock and face, and fat accumulation in the abdomen and dorsocervical spine were performed at every visit. Nursing staff obtained measurements of height and weight at every visit. During the study period, the determination of ARV regimens depended on the consensus of the care team and caretakers. The records of the patients' demographic and clinical data including gender, age, weight, height, body mass index (BMI), stage of HIV infection, the type and duration of previous and current ART, CD4 cell count, and CD4 cell percentage (CD4%), were collected. The weight for age z-scores (z-W/A), the height for age z-scores (z-H/A), and body mass index z-scores (z-BMI) were calculated by Epi-Info program using anthropometric data (CDC/WHO 1978 Reference). Laboratory monitoring including non-fasting morning lipid profile; cholesterol, low density lipoprotein (LDL direct measurement), trigly-ceride, high density lipoprotein (HDL), CD4 cell count and CD4%, were performed at the initiation of HAART and at 6 monthly intervals. All of the blood samples were obtained between 7.00 AM and 8.00 AM and processed using an automated analyser. The variables considered in assessing the associated risks of dyslipidemia were z-W/A, z-H/A, z-BMI, CD4%, and the development of fat redistribution syndrome during the follow-up period.

Data analysis

The present report was the result of analysis as of October 2003. All the children who remained in the study had received HAART for more than 24 months. The data was analyzed by using SPSS version 10.0. Descriptive statistics were used to describe lipid profiles, dyslipidemia and lipodystrophy at baseline, 6 months, 12 months, 18 months, and 24 months of treatment. Due to the nature of the non-fasting blood sample, hyperTG were not counted although the data was shown as abnormal. The changes of mean cholesterol level in patients who had had hypercholesterolemia (hyperCH) and the change of mean LDL level in patients who had had hyperLDL from baseline to 24 months of treatment were analyzed by using the student paired t-test. The comparative analysis of the continuous variable in the different groups was tested by using the Mann-Whitney for non-parametric tests, and the student t-test for parametric tests. P value < 0.05 was considered statistically significant.

Definitions of dyslipidemia

The authors defined dyslipidemia according to the National Cholesterol Education Program (NCEP) guidelines as follows[23].

Hypercholesterolemia (hyperCH)	> 200 mg%
Hypertriglyceridemia (hyperTG)	> 200 mg%
Hyper-low density lipoprotein (hyperLDL)	> 130 mg%
Hypo-high density lipoprotein (hypoHDL)	< 40 mg%

With the absence of standard definition for lipodystrophy, children were assessed based on visible change of individual features associated with lipohypertrophy and/or lipoatrophy (fat loss) of the limbs, cheeks and trunk.

Results

Of the twenty- three HIV-infected children enrolled into the present study at the initiation of HAART, the median age was 4.2 years (range 1.9 to 9.1 years); 14 were boys and 9 were girls. Stages of HIV disease defined by CDC classifications[24] were: clinical category N, 3; clinical category A, 6; clinical category B, 7; and clinical category C, 7. One child had immunological stage 1, 3 had immunological stage 2,

and 19 had immunological stage 3. The baseline median CD4 count was 143 cells/mm³ (range 2-1556 cells/mm³), and median CD4% was 9.33% (range 0.18-29.63%). The baseline median W/A z- scores was -2.00 (range -4.64 to -0.1), median H/A z- scores was -2.00 (range -4.01 to -0.83), and median BMI was 14.92 kg/m² (range 10.68-18.14 kg/m²).

Before enrollment, 3 children were ART naïve and 20 children had experienced dual nucleoside reverse transcriptase inhibitors (NRTIs); 11 were receiving AZT + ddI, 9 were receiving AZT+3TC, and 8 were receiving ddI + d4T for a mean duration of 29 months. Nine children experienced more than one regimen of dual NRTIs.

The HAART regimens initiated were: EFV-based in 18 children, IDV-based in 3 children, and RTV-based in 2 children. After 12 months of treatment 2 children (1 received EFV and 1 received RTV) were lost to follow up. Another child who received EFV died from pneumothorax after 15 months of treatment. Three children had to change from NNRTI or PI that they were receiving after 12- 24 months of treatment; 1 due to clinical and/ or immunological failure and 2 due to drug intolerance. The children who failed changed from efavirenz (EFV) in the regimen to boosted indinavir (IDV) with ritonavir (RTV). Those who had drug intolerance changed from IDV and RTV to EFV.

At baseline before initiation of HAART, one child who had received dual NRTI for 56 months had hypercholesterolemia, and 9 children; 2 were ARV naïve, 7 received dual NRTI with the mean duration of 25 months, had hypoHDL. There was no parental history of dyslipidemia in any of the children.

The change in lipid profile after HAART is shown in Table 1. The mean total cholesterol, LDL, and HDL increased over time on HAART. However, the difference from baseline was not statistically significant (all $p > 0.05$ by student paired t-test). The cholesterol and LDL levels of the 7 children with hyperCH and 5 children with hyperLDL are shown in Fig. 1 and 2. The mean cholesterol level among the children with hyperCH at 24 months of treatment was higher than baseline level, but not significantly different (208.6 ± 13.29 mg/dl. vs 155.8 ± 22.91 mg/dl, $p = 0.145$). Likewise, the mean LDL level among the children with hyperLDL at 24 months of treatment was higher than baseline level; but not significantly different (139.28 ± 17.23 mg/dl. vs 88.42 ± 29.91 mg/dl, $p = 0.817$). Total LDL level in the children with hypercholesterolemia significantly higher than in those without hypercholesterolemia at 6 months ($p = 0.001$), at 12 months ($p = 0.003$), and at 24 months ($p = 0.005$).

The number of children who developed dyslipidemia excluding these with isolated hyperTG at 6, 12, 18, and 24 months of treatment were 10 (43%), 13 (56%), 5 (22%), and 8 (35%) cases (Table 2). The child who had hyperCH at baseline became normal after 6 months of HAART. Of the nine children with

Table 1. Lipid profile change after HAART

	Baseline (n = 20)	6 months (n = 20)	12 months (n = 20)	18 months (n = 20)	24 months (n = 20)	p value
Mean CH (mg%)	153	167	164	164	187	0.42
range	(114-205)	(111-244)	(94-215)	(100-222)	(128-226)	
No. of patients with hyperCH	1	3 (2)	4 (1)	1	4	
Mean TG (mg%)	118	129	123	103	139	0.385
range	(39-200)	(72-307)	(49-272)	(60-183)	(43-361)	
No. of patients with hyperTG	-	3 (2)	4 (1)	-	2	
Mean LDL(mg%)	86	102	105	103	117	0.218
range	(37-126)	(62-153)	(38-163)	(59-144)	(74-178)	
No. of patients with hyperLDL	-	4 (2)	6 (2)	2	6	
Mean HDL(mg%)	39	45	46	52	54	0.92
range	(22-61)	(27-71)	(8-67)	(24-77)	(41-76)	
No. of patients with hypoHDL	9	7 (5)	5 (1)	3 (1)	0	
Total cases* (new cases)		10 (6)*	13 (2)*	5 (1)*	8 (0)*	

* Number in bracket was new cases diagnosed
Isolated hyperTG was not count because the blood samples were non-fasting but the number of patients with hyperTG were shown

Table 2. Lipid profile after HAART in each child

	Baseline	6 mo. (n = 10)*	12 mo. (n = 13)*	18 mo. (n = 5)*	24 mo. (n = 8)*
1.	N	N	hypoHDL (28)	N	N
2.	hypoHDL (22)	hypoHDL (32)	hyperLDL (133)	N	hyperLDL (136)
3.	hypoHDL (28)	N	N	N	N
4.	-NA-	N	hyperCH (208) +hyperLDL (144)	hyperLDL (144)	hyperCH (204) +hyperLDL (140)
5.	hypoHDL (22)	hypoHDL (33)	hyperCH (202) *+hyperTG (307)*	N *+hyperTG (215)*	*hyperTG (361)*
6.	-NA-	hypoHDL (34) *+hyperTG (218)*	hypoHDL (8) *+hyperTG (255)*	..........................Dead..........................	
7.	N	N	N	hypoHDL (25)	N
8.	N	hypoHDL (32)	N	N	hyperCH (217) +hyperLDL (165)
9.	N	N	N	N	N
10.	N	hyperCH (235) +hyperLDL (150)	hyperCH (215) +hyperLDL (151)	hyperCH (222) +hyperLDL (138)	hyperCH (216)
11.	N	hypoHDL (33)	hypoHDL (33)	........................loss F/U........................	
12.	hypoHDL (34)	hyperCH (244)	N +hyperLDL (153)	N	N
13.	hypoHDL (28)	N	N	N	hyperLDL (135)
14.	N	*hyperTG (214)*	hypoHDL (38)	........................loss F/U........................	
15.	N	N	*hyperTG (201)*	N	N
16.	hyperCH (205)	N	N	N	*hyperTG (211)*
17.	N	hyperCH (213) +hyperLDL (133)	hyperCH (208) +hyperLDL (133) *+hyperTG (272)*	N	hyperLDL (132) *+hyperTG (225)*
18.	hypoHDL (38)	N	hyperLDL (148)	N	hyperLDL (134)
19.	N	N	N	N	N
20.	hypoHDL (35)	hyperLDL (132) +hypoHDL (38)	hyperLDL (163) +hypoHDL (37)	hypoHDL (38)	hyperCH (226)
21.	hypoHDL (24)	-NA-	hypoHDL (25)	hypoHDL (24)	N
22.	N	hypoHDL (27)	hypoHDL (33)	N	*hyperTG (245)*
23.	hypoHDL (33)	N	N	N	*hyperTG (258)*

* n = number of children with dyslipidemia detect; N = normal value of lipid profile; -NA- = no blood sample available
The numbers in bracket were values of the abnormal profile
HyperTG (in iItalics) were not count because the blood samples were non-fasting but the abnormal TG levels were shown

hypoHDL at baseline; 5 children became normal at 6 months of HAART, while 4 developed other types of dyslipidemia along the course of treatment. Of these latter 4 children, 3 became normalized at 12-18 months of treatment. There were 6 additional children who developed dyslipidemia at 6 months of HAART; i.e. 3 hypoHDL, 2 hyperCH + hyperLDL, and 1 hyperTG + hypoHDL. Of these, 2 became normal after 12-18 months of treatment. There were 2 additional cases who developed dyslipidemia at 12 months of HAART; i.e. 1 hyperCH + hyperLDL, and 1 hypoHDL. One of these became normal at 18-24 months. There was 1 additional case of hypoHDL which developed at 18

months of HAART. Because the specimens were non-fasting, isolated hyperTG were not counted. The number of children who had had dyslipidemia after HAART was 19 (83%). Of these, 9 had normal lipid profiles at baseline. However, only 3 children had persistent dyslipidemia beyond 24 months of treatment. The rest had transient abnormality.

Types of dyslipidemia

There were 14 occasions of isolated types of dyslipidemia found in 11 (48%) children; i.e, hyperCH in 2, hyperLDL in 4, and hypoHDL in 8. The other occasions in 8 children were mixed types of dyslipi-
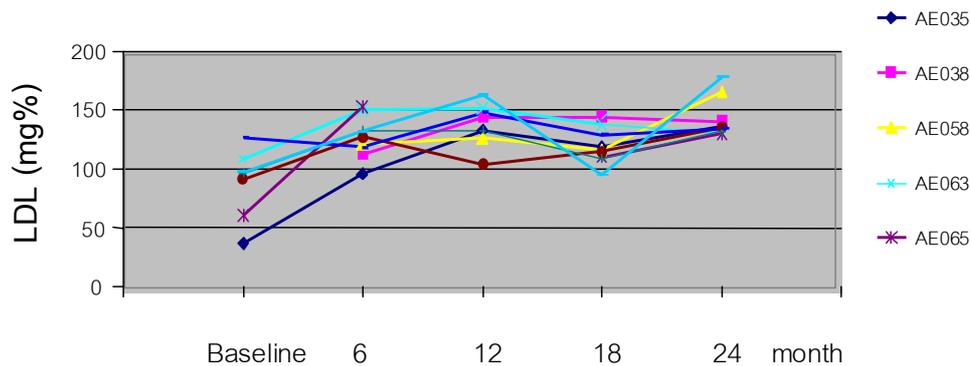
Patients who ever have hyperCH following HAART
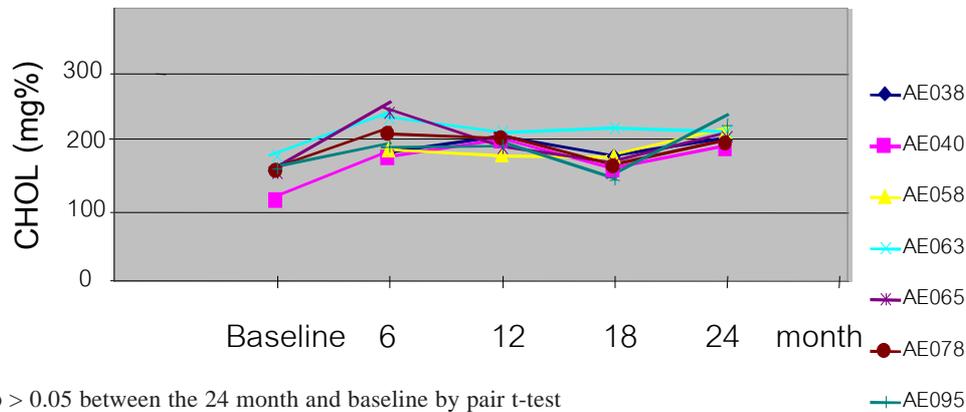
p > 0.05 between the 24 month and baseline by pair t-test

Fig. 1   The cholesterol levels of children who ever have hyperCH

Patients who ever have hyperLDL following HAART

p > 0.05 between the 24 month and baseline by pair t-test

Fig. 2   The LDL levels of children who ever have hyperLDL

demia. The pattern of dyslipidemia was not stable. In most children, the abnormal lipid profiles were found transiently and changed in pattern (Table 3). There were only 3 children who had persistent dyslipidemia through 24 months of treatment.

The association of HAART regimens and dyslipidemia are displayed in Table 4. The incidence of dyslipidemia was 76-100% in all regimens. There was no significant difference in the incidence of dyslipidemia found between each regimen.

Other factors such as W/A gain, H/A gain, BMI gain, and CD4% gain were not different among those with and without dyslipidemia (Table 5). How-

ever, there was a trend of increase cholesterol level associated with CD4% gain over time of HAART (Fig. 3) and a correlation of increased cholesterol level with CD4% gain at 18-24 months of HAART ($r = 0.596$, $p = 0.007$).

Lipodystrophy feature

There were two children who had visible peripheral fat wasting based on physical examination. The first child was a 6-year-old boy in stage B3 (#22 in Table 2). He had experienced dual NRTIs for 5.2 years; 2.5 years exposure to didanosine and stavudine. His baseline CD4 count before HAART was 14 cells/

Table 3. Pattern of dyslipidemia detected after HAART

Dyslipidemia		Baseline n = 10	6 mo. n = 10	12 mo. n = 13	18 mo. n = 5	24 mo. n = 8
HyperCH	Isolate	1	-	-	-	2
	Mixed	-	3	4	1	2
HyperLDL	Isolate	-	-	2	1	3
	Mixed	-	4	4	1	3
HypoHDL	Isolate	9	4	5	3	-
	Mixed	-	3	2	-	-
HyperTG	Isolate	-	1	1	-	4
	Mixed	-	2	3	-	1

n = number of children with dyslipidemia detected
Isolated hyperTG was not count because the blood samples were non-fasting

Table 4. Frequency of dyslipidemia by ARV regimens

	Baseline and at 6 mo.of Rx	At 12 mo.	At 18 mo.*	At 24 mo.	Number of children (%) with dyslipidemia
2NRTI+EFV	18	20	17*	17	13 (76%)
2NRTI+IDV	3	2	1	1	1 (100%)
2NRTI+RTV	2	1	-*	-	-
2NRTI+IDV/r	-	-	2	2	2 (100%)

*Loss F/U 2 and dead 1

Table 5. Factors associated with dyslipidemia at 6, 12, 18 and/or 24 months of HAART

	6 mo.		12 mo.		18 mo.		24 mo.	
	DL+	DL-	DL+	DL-	DL+	DL-	DL+	DL-
Mean age (year)	4.5	4.9						
Sex (male: female)	13:6	1:3						
No.Children at each F/U	19	4	19	4	16*	4	16*	4
Median								
CD4% gain	2.66	6.18	5.98	6.3	7.62	5.36	11.77	3.74
z-W/A gain	0.29	-0.19	0.35	0.10	0.38	0.16	0.35	0.00
z-H/A gain	0.01	-0.10	0.05	-0.16	0.23	0.15	0.15	0.20
BMI gain	+0.64	+0.42	+0.84	+0.03	+0.17	-0.31	+0.16	-0.56

* Some children did not come to follow up
 DL+ = children with dyslipidemia
 DL- = children without dyslipidemia
 All p > 0.05 between DL+ and DL-

mm^3 (0.26%) and BMI was 13.77kg/m². The HAART regimen was AZT/3TC/IDV for 12 months, after that was changed to AZT/3TC/EFV due to PI intolerance. After 24 months of the new regimen, he had a CD4 count gain of 6 cells/mm³, CD4% gain of 0.33% and BMI gain of 0.16 kg/m². He had hypoHDL at 6, 12 months of HAART and had hyperTG at 24 months of HAART.

The second child was a 7.5 -year-old girl in stage B3 (#15 in Table 2). She had experienced dual NRTIs for 3.7 years; 1year exposure to didanosine and stavudine. Her baseline CD4 count before HAART
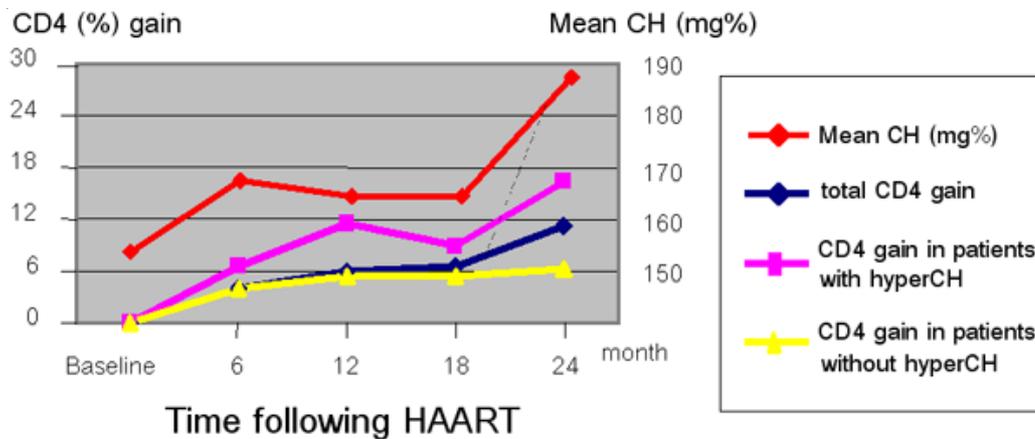
r = 0.596, p = 0.007

Fig. 3 CD4% gain and cholesterol change after HAART

was 59 cells/mm^3 (3.09%) and BMI was 13.70 kg/m^2. The HAART regimen was ddI/d4T/EFV for 18 months, after that was changed to AZT/3TC/IDV/r due to clinical and immunological failure. After 24 months of HAART, she had a CD4 count gain of 339 cells/mm^3, CD4% gain of 7.44% and BMI gain of -0.46 kg/m^2. She had hyperTG at 12 months of ddI/d4T/EFV.

Discussion

During the course of HIV infection, disturbances of lipid metabolism were observed long before the introduction of ART. HyperTG and a decrease in total cholesterol and HDL cholesterol occurring in advanced phases of HIV infection were considered as markers of chronic inflammation[6,25-27]. Abnormalities of lipid metabolism had been increasingly recognized among HIV-infected patients after the introduction of HAART. The characteristic pattern of dyslipidemia induced by HAART includes elevated total cholesterol (10-50%), LDL cholesterol (40-80%) and triglyceride (40-80%)[28]. Onset of lipid changes occurs within 3 months of the initiation of HAART and plateau after 6-9 months[28].

Farley et al reported 22% of the HIV-infected children had a cholesterol level > 200 mg/dl, compared with 9% of the non-infected children. Hyperlipidemia was also more prevalent in children of 4-6 years of age than in the groups aged 6-12 years and 12-19 years[29]. Additional factors associated with hyperCH were the use of two or more PIs, greater than 3 years exposure to PI, adherence to medication, and white or hispanic race[29]. A cross sectional study in 37 vertically infected children from an outpatient clinic found more dyslipidemia in children receiving PI containing regimen than non-PI regimens. In children on the PI-containing regimens, 8 (32%) had hyperCH, 13 (52%) had hyperTG, and 2 (8%) had hypoHDL, while only 2 (17%) who on non PI- regimens had hyperTG. The results in nonfasting and fasting conditions were similar[20]. Another cross sectional study in 40 HIV-infected children found the incidence of hyperlipidemia of 73%; 18 (45%) had hyperCH, 2 (5%) had hyperTG,

Table 6. Factor associated with hypercholesterolemia (hyperCH)

	With hyperCH	Without hyperCH	p value
Sex (male:female)	6:2	8:7	0.29
Mean age (year)	4.40+2.8	4.60+2.0	0.378
Mean baseline BMI (kg/m^2)	15.14+2.41	14.44+1.88	0.378
Mean duration ARV (month)	47.00+9.84	50.41+16.42	0.445
Median baseline CD4 (cell/mm^3)	87	369	0.549
Median CD4% gain at 24 mo.	15.87	9.41	0.179
Median z- W/A gain at 24 mo.	-0.21	0.58	0.552

and 9 (23%) had hyperCH plus hyperTG[19]. Similar to the present study that about half of dyslipidemia were isolated types of dyslipidemia. However, the present study found isolated hypoHDL more than hyperCH and hyperTG. The result from the present study showed that dyslipidemia is commonly found within 6-12 months of HAART. Dyslipidemia found in the present study was usually transient and changes in pattern with only a few had persistent dyslipidemia beyond 18 months. This has not been described in other studies.

The DAD study and the Anti-proteases Cohorte (APROCO) Study in HIV-infected adults found hypercholesterolemia associated with a greater age, higher BMI, a higher CD4 cell count, and a longer cumulative exposure to stavudine[12,30]. The present study did not find the difference of HAART regimen, treatment duration, or host factor (age, sex, BMI gain) between children with and without dyslipidemia; probably because of the small number of subjects in the non-dyslipidemia group. However, considering that 20 children received NRTI for more than 2 years, there was only one child who developed hyperCH. After HAART, 10 developed hyperCH or hyperLDL within 6-24 months of treatment. This confirmed that HAART induced the development of hyperlipidemia. The present study has shown that both the NNRTI and PIs-containing regimens could induce dyslipidemia, however the authors were unable to find the difference in magnitude of the effect due to a limited number of patients on PI regimen. The authors found that the children with hypercholesterolemia had a trend of higher baseline BMI than those without hypercholesterolemia patients. There seemed to be less BMI gain in the children without dyslipidemia. There was a correlation of elevated total cholesterol following HAART corresponding with the CD4% gain particularly at 18-24 months of treatment. It is possible that increased cholesterol level is a marker of clinical response. Many prospective cross sectional cohort studies in HIV- infected patients were unable to find the association between CD4 lymphocyte counts or HIV viral load and serum lipid abnormalities[31]. However, one study showed a significant correlation between the lower last viral load and higher HDL level [32]. Similar to the present results, HDL level continued to increase up to 24 months during CD4% gain following HAART.

Hyperlipidemia and lipodystrophy were probably related; however, it has been observed that metabolic abnormalities usually precede the body fat redistribution[33,34]. Pediatric data remain observational. A cross-sectional study evaluated 39 HIV-infected children; 13 (33%) children had clinical lipodystrophy (LD). Another cross sectional study evaluated 40 HIV-infected children; 7 (18%) children had clinical LD. In this study, lipohypertrophy and mixed LD were more common than peripheral fat wasting alone[19]. This was different from the present result that found only clinical peripheral fat wasting in 2 (8.6%) children. The prevalence of fat redistribution syndrome was varied, due to the study population, duration, method and different diagnostic criteria of lipodystrophy syndrome. Moreover there was difficulty in assessing body fat abnormalities because of some similarity between abnormal body habitus and normal physical growth and development in children. A longitudinal observational study of 28 HIV infected children that assessed the changes in regional fat by comparison of individual from baseline dual-energy X-ray absorptiometry (DEXA) scans found 8 (29%) children had LD. Children with LD had significant higher levels of HIV RNA and lower CD4 level at baseline. LD was associated with the use of PIs or stavudine[35]. The latest prospective study in adults found that there was no significant association between the use of, or the duration on any ARV and lipoatrophy. The strongest associations with an incidence of lipoatrophy were host factors (white race and less BMI) and previous or current low CD4 count.[36]. From the present study, the two children who had obvious peripheral lipoatrophy evaluated from physical examination had experienced previous dual treatment with didanosine and stavudine. They also had low baseline CD4 count, low baseline BMI and had isolated hyperTG. The present study concurred with the preliminary results of the LIPOCO study in adults which found a significantly elevated level of plasma triglycerides in the lipoatrophy groups[37]. The authors did not perform MRI or DEXA scan and therefore may have missed many cases of LD with less obvious presentation. The authors were unable to find the associated risk foctors due to a limited number of patients.

To date, there has been no recommendation of how to treat dyslipidemia induced by HAART in children. The long-term effects of lipid lowering agents and their impact on cardiovascular outcomes in treatment of ART-associated elevations of blood lipids are unknown. Therefore, the potential of deleterious dyslipidemia side effects remain the dominant concern. The effect of LD is mainly on adverse

appearance. However, in some cases, the appearance of severe LD could be a stigma of HIV infection. Changing d4T to other NRTI may be helpful to stop further LD.

The authors acknowledge several limitations to the present study, a lack of standardized definition of lipodystrophy, and limited case numbers. Because it was very hard for young children to fast overnight before drawing blood samples for lipid assessment, the present study did not count hyper TG that was found. With this, however, the authors may have underestimated the frequency of hyperTG dyslipidemia. The isolated type of hyperTG was found in 5 occasions, of these only one case had isolated hyperTG without other type of dyslipidemia, therefore probably did not affect the conclusion.

Conclusion

The present preliminary study showed an 83% incidence of dyslipidemia, mostly within 6-12 months on HAART in Thai children. Most of the cases of dyslipidemia were transient and changed in pattern over time. None of the baseline characteristics or the immunological or clinical response to HAART was associated with dyslipidemia. Dyslipidemia was found in all of the antiretroviral regimens used (most of the children in the present study were on EFV, a few were on PIs). Abnormal fat redistribution syndrome was also found in two cases of peripheral lipoatrophy. The cardiovascular disease risk associated with these changes should be assessed and monitored. The long-term complications of dyslipidemia were of major concern in the growing HIV-infected child. A larger population and long-term follow up are needed to evaluate the trend, the association factors, and clinical consequences. The availability of further data is necessary for consideration of the appropriate interventions.

References

1. Walli R, Herfort O, Michl GM, Demant T, Jager H, Dieterle C, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1 infected patients. AIDS 1998; 12: 167-73.

2. Carr A, Cooper DA. Lipodystrophy associated with an HIV-protease inhibitor. N Engl J Med 1998; 339: 1296.

3. Vigouroux C, Gharakhanian S, Salhi Y, Nguyen TH, Chevenne D, Capeau J, et al. Diabetes, insulin resistance and dyslipidemia in lipodystrophic HIV-infected patients on highly active antiretroviral therapy (HAART). Diabetes Metab 1999; 25: 225-32.

4. Periard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond MJ, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. Circulation 1999; 100: 700-5.

5. Hadigan C, Meigs JB, Corcoran C, Rietschel P, Piecuch S, Basgoz N,et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. Clin Infect Dis 2001; 32: 130-9.

6. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ,et al. A syndrome of peripheral lipodystrophy, hyperlipidemia, and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998; 12: 51-8.

7. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal fat accumulation associated with the use of indinavir. Lancet 1998; 351: 871-5.

8. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction and natural course of lipodystrophy, hyperlipidemia and diabetes mellitus. Lancet 1999; 353: 2093-9.

9. Behrens G, Dejam A, Schmidt H, Balks HJ, Brabant G, Korner T, et al. Impaired glucose tolerance and beta cell function and lipid metabolism in HIV-patients under treatment with protease inhibitors. AIDS 1999;13:63-70.

10. Moyle GJ, Baldwin C. Lipid elevations during non-nucleoside RTI (NNRTI) therapy: a cross sectional analysis. Antiviral Ther 1999; 4: 58.

11. Behrens GM, Meyer-olson D, Stoll M, Schmidt RE. Clinical impact of HIV-related lipodystrophy and metabolic abnormalities on cardiovascular disease. AIDS 2003; 17: 149-54.

12. Friis-Mller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, et al. Cardiovascular disease risk factors in HIV patients-association with antiretroviral therapy: results from DAD study. AIDS 2003;17: 1179-93.

13. Saint-Marc T, Partisani M, Poizot-Martin I, Bruno F, Rouviere O, Lang JM, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long term nucleoside analogue therapy. AIDS 1999;13: 1659-67.

14. Madge S, Kinloch-de-Loes S, Mercey D, Johnson MA, Weller IV. Lipodystrophy in patients na ve to HIV protease inhibitors. AIDS 1999; 13: 735-7.

15. Passalaris D, Sepkowitz A, Glesby J. Coronary artery disease and human immunodeficiency virus infection. Clin Infect Dis 2000; 31: 787-97.

16. van der Valk M, Gisolf EH, Reiss P, Wit FW, Japour A, Weverling GJ,et al. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. AIDS 2001; 15: 847-55.

17. Carr A. HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management. AIDS 2003; 17: 141-8.

18. Jaquet D, Levine M, Ortega-Rodriguez E, Faye A, Polak M, Vilmer E, et al. Clinical and metabolic presentation of the lipodystrophic syndrome in HIV-infected children. AIDS 2000; 14: 2123-8.

19. Amaya RA, Kozinetz CA, McMeans A, Schwarzwald H, Kline MW. Lipodystrophy syndrome in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2002; 21: 405-10.

20. Lainka E, Oezbek s, Falck M. Marked dyslipidemia in human immunodeficiency virus infected children on protease inhibitor-containing antiretrovirus therapy. Pediatrics 2002; 110: 1-7.

21. Vigano A, Mora S, Testolin C, Beccio S, Schneider L, Bricalli D, et al. Increased lipodystrophy is associated with increased exposure to highly active antiretroviral therapy in HIV- infected children. J Acquir Immune Defic Syndr 2003; 32: 482-9.

22. Leonard EG, Mc Comsey GA. Metabolic complications of antiretroviral therapy in children. Pediatr Infect Dis J 2003; 22: 77-84.

23. Executive Summary, "Executive Summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II)". JAMA 2001; 285: 2486-513.

24. Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children < 13 years of age. MMWR 1994; 43 (RR-12):1-19.

25. Sav s M, Ch ne G, Ducimeti re P, Leport C, Le Moal G, Amouyel P. Distribution of cardiovascular risk factors in French HIV-infected men started on a protease inhibitor-containing regimen compared to the general population. Antivir Ther 2001; 6: 74.

26. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab 1992; 74: 1045-52.

27. Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN. Hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med 1989; 86: 27-31.

28. Sherer R. HIV, HAART, and hyperlipidemia: balancing the effects. J Acquir Immune Defic Syndr 2003; 34: 123-9.

29. Farley J, Gona P, Crain M. Hypercholesterolemia and associated risk factors among perinatally HIV infected children (4-19 years) in PACTG 219C. 10th Conference of Retroviruses and Opportunistic Infections, Boston, MA, USA2003 (Abstract 773).

30. Saves M, Raffi F, Capeau J, Rozenbaum W, Ragnaud JM, Perronne C, et al. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. Clin Infect Dis 2002; 34: 1396-405.

31. Green ML. Evaluation and management of dyslipidemia in patient with HIV infection. J Gen Intern Med 2002; 17: 797-810.

32. Vergis EN, Paterson DL, Wagener MM, Swindells S, Singh N. Dyslipidemia in HIV-infected patients: association with adherence to potent antiretroviral therapy. Int J STD AIDS 2001; 12: 463-8.

33. Kamin D, Hadican C. Hyperlipidemia in children with HIV infection: an emerging problem. Expert Rev Cardiovasc Ther 2003; 1: 143-50.

34. Calza L, Manfredi R, Chiodo F. Hyperlipidemia in patients with HIV-1 infection receiving highly active antiretroviral therapy: epidemiology, pathogenesis, clinical course and management. Int J Antimicrob Agents 2003; 22: 89-99.

35. Arpadi SM, Cuff PA, Horlick M, Wang J, Kotler DP. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4+ -lymphocyte count and CD4+ -lymphocyte percentage at baseline and use of protease inhibitors and stavudine. J Acquir Immune Defic Syndr 2001; 27: 30-4.

36. Lichtenstein KA, Ward DJ, Moorman AC, Delaney KM, Young B, Palella FJ Jr, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. AIDS 2001; 15: 1389-98.

37. Saint-Marc T, Partisani M, Poizot-Martin I, Rouviere O, Bruno F, Avellaneda R, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. AIDS 2000; 14: 37-49.

ภาวะไขมันในเลือดผิดปกติ และไขมันผิดปกติทางรูปร่างลักษณะในผู้ป่วยเด็กไทยที่ติดเชื้อเอชไอวี ที่ได้รับยาต้านไวรัสสูตรยา 3 ตัว

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ที่มา: จากการศึกษาในเด็กที่ได้รับยาต้านไวรัสเอดส์ พบอุบัติการณ์ของภาวะไขมันในเลือดผิดปกติ ประมาณร้อยละ 50-70 ยังไม่มีข้อมูลเหล่านี้ในเด็กในประเทศกำลังพัฒนา ซึ่งอาจมีความแตกต่างในแง่ของภาวะทางโภชนาการ

วัตถุประสงค์: เพื่อประเมินอุบัติการณ์ และปัจจัยเสี่ยงที่สัมพันธ์กับภาวะไขมันในเลือดผิดปกติ และเพื่อประเมิน อุบัติการณ์ของอาการไขมันสะสมผิดปกติโดยปรากฏชัดทางรูปร่างในผู้ป่วยเด็กไทยที่ติดเชื้อเอชไอวีที่ได้รับ ยาต้านไวรัสสูตรยา 3 ตัว

วัสดุและวิธีการ: เด็กติดเชื้อเอชไอวี 23 คน ที่เริ่มรับยาต้านไวรัส สูตรยา 3 ตัว ในโครงการ Access to Care ในช่วง เดือนตุลาคม พ.ศ. 2544 จะถูกเจาะเลือดตรวจระดับไขมันในเลือดก่อนเริ่มยาต้านไวรัสสูตรยา 3 ตัว และทุก 6 เดือน และจะได้รับการติดตามประเมินอาการทางคลินิกของภาวะไขมันสะสมผิดปกติ ทุก 1-2 เดือน

ผลการศึกษา: เมื่อถึงเดือนตุลาคม พ.ศ. 2546 มีเด็กจำนวน 19 คน (83%) ที่มีภาวะไขมันในเลือดผิดปกติ โดยเด็ก 10 คน, 13 คน, 5 คน, และ 8 คน มีภาวะไขมันในเลือดผิดปกติหลังได้รับยาต้านไวรัสสูตรยา 3 ตัว นาน 6 เดือน, 12 เดือน, 18 เดือน, และ 24 เดือน ตามลำดับ ระดับโคเลสเตอรอล, LDL และHDL เพิ่มขึ้นชัดเจน เมื่อได้รับยาต้านไวรัสสูตรยา 3 ตัว ตั้งแต่ 6 เดือน ไปจนถึง 24 เดือน พบมีความสัมพันธ์ของระดับโคเลสเตอรอลที่เพิ่มขึ้นกับ CD4 % ที่เพิ่มขึ้น โดยเฉพาะในช่วง 18-24 เดือนของการรักษา (r = 0.596, p = 0.007) เด็กที่มีภาวะไขมันผิดปกติส่วนใหญ่เป็นเพียง ชั่วคราวมีเพียง 3 รายที่พบผิดปกติโดยตลอด 24 เดือน เด็ก 2 คน มีภาวะไขมันบริเวณแขนขาฝ่อ ไม่พบปัจจัยเสี่ยง ที่สัมพันธ์กับภาวะไขมันในเลือดผิดปกติ

สรุป: ภาวะไขมันในเลือดผิดปกติ พบส่วนใหญ่ในช่วง 6-12 เดือนของการเริ่มยาต้านไวรัสสูตรยา 3 ตัว และส่วนใหญ่ จะพบชั่วคราว พบภาวะไขมันบริเวณแขนขาฝ่อในเด็ก 2 คน การติดตามต่อไป จะช่วยให้ทราบถึงอุบัติการณ์ในระยะยาว ปัจจัยที่เกี่ยวข้อง และผลกระทบที่จะเกิดในภายหลัง