Original Article

Lipodystrophy and Metabolic Complications of Highly Active Antiretroviral Therapy

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ABSTRACT

Objective. To assess the metabolic drug toxicities of first-line, World Health Organization (WHO)-recommended generic highly active antiretroviral therapy (HAART) regimens, to estimate the prevalence of body fat redistribution and to identify associated risk factors.

Methods. Cross- sectional observational study. During 3 month period, 52 HIV infected children (25 on HAART; 27 not on HAART) were assessed. Their sociodemographic, clinical, and immunological data was recorded. Children were examined or the signs of fat redistribution (peripheral lipoatrophy and central lipohypertrophy). Liver function tests, fasting blood sugar, lipid profile, serum amylase, serum lactate, blood pH and bicarbonate levels were done in all patients.

Results. Twenty-two patients were on stavudine and three on zidovudine based HAART. None of the patients ever received any protease inhibitor. There were no cases of clinical or immunological failure. Children on HAART had significantly lower weight for age and body mass index but the mean height for age was similar between study groups. Only two cases of peripheral lipoatrophy were observed. Hypercholesterolemia was observed in four children on HAART but none without therapy. Hypertriglyceridemia was observed in three children on HAART and seven without therapy. Four cases of asymptomatic mild hyperlactatemia were observed. No case of any hyperglycemia or liver impairment was observed.

Conclusion. Metabolic abnormalities and lipodystrophy are emerging complications of HAART in Indian children and needs very close follow up. Future studies with larger sample size and longitudinal model are recommended. **[Indian J Pediatr 2009; 76 (10) : 1017-1021]** *E-mail: ankitparakh102@rediffmail.com*

Key words: *Children; Dyslipidemia; HAART; India; Lipodystrophy*

Drug toxicities are an emerging problem as access to highly active antiretroviral therapy (HAART) improves in the developing world with the aid of World Health Organization (WHO) and National AIDS Control Organization (NACO) of India. Morphologic and metabolic complications associated with long-term HAART use have been widely described in adults from the developed world[1-6] and resource limited countries including India.[7,8] Pediatric studies are limited in number and have small sample sizes.[9-20] The largest cross-sectional experience in pediatric age group comes from the European Pediatric Lipodystrophy Group[11] and longitudinal data from the PACTSHOPES trial.[17] The prevlance of these complications in Indian children remains unknown.

This study was carried out to assess the prevalence of morphological and the metabolic complications of WHO recommended first line HAART in Indian children naïve to any anti-retroviral drugs and to identify associated risk factors.

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MATERIAL AND METHODS

During 3-month period starting from August 2007 to November 2007, 52 HIV infected children in a pediatric HIV clinic of a tertiary care teaching hospital of North India were assessed. Twenty-five children were on WHO recommended fixed-dose combinations (FDC) of HAART provided by the NACO [stavudine (D4T)/ lamivudine (3TC)/nevirapine (NVP) or zidovudine (ZDV)/ lamivudine (3TC)/nevirapine (NVP)].

Only HIV-infected children naïve to any retroviral drugs and now on first line drugs were included. Children were assessed at their first clinic visit during this data collection period. Exclusion criteria were:

AIDS-defining events or severe illness within one month of the evaluation, and severe encephalopathy or cachexia secondary to HIV infection. Any patient who had switched therapy was excluded from the study.

Data collection: Clinical, immunological data and epidemiological data (age, sex) was recorded including mode of transmission, date of confirmed HIV test, WHO clinical stage at diagnosis/ at beginning of HAART[21], present CD4 cell count, if on HAART duration/regimen and family status. Previous medical records were reviewed to obtain height and weight before treatment, previous immunological status, the ART administered, and WHO clinical stage. A routine physical examination and anthropometric measurements was performed. The CDC 2000 body mass index (BMI) reference centiles were used in assessing BMI. Puberty was rated according to Tanner criteria.[22] Children were examined for the signs of fat redistribution (peripheral lipoatrophy and central lipohypertrophy) on a standard checklist. [23, 24]

In addition to lipodystrophy, metabolic complications of HAART therapy were assessed. Liver function tests [serum bilirubin, aspartate aminotransferase (ALT), alanine aminotransferase (AST)], fasting venous blood sugar, lipid profile [total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides], serum amylase, serum lactate, blood pH and bicarbonate levels were done in all patients after an overnight fast (minimum 6 h). Blood for lactic acid determination was drawn at rest with minimal venous constriction and after voiding. Blood glucose, serum cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured by automated enzymatic methods. CD4 counts were measured by flow cytometry (Becton Dickinson, CA, USA).

Outcome definitions: Assessment of fat redistribution included the detection of fat accumulation in the abdominal and thoracic region, the presence of a buffalo hump and fat loss in the face, limbs and buttocks. Based on an adult scoring system[23, 25], the fat redistribution was scored separately for limbs, face, buttocks, abdomen, thorax and neck on a scale of 0 to 3 [0= absent, 1= mild (noticeable on close inspection), 2= moderate (readily noticeable by patient/physician), 3= severe (readily noticeable to a casual observer)]. Children were considered to have fat redistribution if they had one or more of the signs listed above. To be classed as having the combined subtype of fat redistribution, a child needed to have at least one sign of peripheral lipoatrophy and at least one of central lipohypertrophy.

Children with plasma total cholesterol levels of > or = 200 mg/dl were considered to have hypercholesterolaemia (HC)[25] and those with triglycerides levels of > or = 150 mg/dl were considered to have hypertriglyceridemia (HT) and hyperglycemia at values over 110 mg/dl. Lactic acid level under 2.0 mmol/l was taken as normal, 2-5 mmol/l as mild hyperlactatemia (HL), 5-10 mmol/l as moderate hyperlactatemia and >10 mmol/l as severe hyperlactatemia. Adverse events were graded according to the US National Institutes of Health Division of AIDS.[26] Children were divided into two groups: those receiving HAART and those not receiving HAART.

Informed consent was taken from the parents of children participating in the study. Approval from the institutional ethical committee was taken. Any specific questionnaire to be completed by the patients or their legal guardians could not be used because of the poor educational status. The examiners were not bound to the cases and controls.

Statistical analyses

A descriptive study was made and statistical tests such as Fisher's exact test and U-Mann Whitney were performed for categorical and continuous variables respectively. Statistical significance was considered as $P < 0.05$ and all tests were two sided. Data were analyzed using the SPSS 11.0. No logistic regression multivariate analysis of risk factors was performed because of the low numbers of patients in each group. Z-scores were calculated using the Epi-Info version 3.3.2 (CDC, Atlanta).

RESULTS

A total of 52 children were included (males= 34, females=18), of these, 22 were taking d4T/3TC/NVP and 3 patients ZDV/3TC/NVP. All children were currently on WHO recommended first line HAART regimens. The median age was 6.0 years (range, 2–12). All patients were pre-pubertal. Children on HAART had significantly lower weight for age and body mass index (BMI) but the mean height for age was similar between study groups. Study entry characteristics of patients are summarized in table 1. 48 children had acquired HIV infection through mother-to-child transmission, with 3 having acquired infection through contaminated blood transfusions or blood products and 1 with mode of acquisition unknown.

The average age at initiation of ART was 4.75 years (range, 1.5 to 10.0 years) and the median duration of ART was 1.75 years (range, 3 months to 6 years). At the time of evaluation, mean CD_4 counts in the children off HAART were 525.56 cells/mm3, and in children on HAART 367.69 cells/mm3, respectively. According to the WHO clinical classification, 31 children (60%) were in class I, 6 (11.5 %) in class II, 12 (23 %) in class III and

Table 1. Study Entry Characteristics of Patients

		HAART Cases (n=25)	Non-HAART Cases (n=27)	Total Cases (n=52)	P value
Age (years)	Mean (SD)	6.29 (2.16)	5.68 (2.62)	5.96 (2.41)	0.338
Sex	Males	15	18	33	0.57
	Females	8	9	1 7	
Weight- for-age z-score	Mean (SD)	-4.077 (2.18)	-2.41 (1.59)	-3.18 (2.04)	0.004
Height for-age z-score	Mean (SD)	-2.009 (1.95)	-1.66 (1.16)	-1.82 (1.57)	0.069
BMI for-age z-score	Mean (SD)	-4.066 (3.43)	-2.05 (2.61)	-2.97 (3.15)	0.016
	Stage I	13	18	31	
	Stage II	1	5	6	
WHO Clinical Stage	Stage III	9	3	12	0.06
	Stage IV	2	1	3	
CD_4 counts	Mean (SD)	367.69 (262.67)	525.56 (392.19)	452.92(344.84)	0.102

Table 2 . Metabolic abnormalities in the study groups [mean (+ SD)]

	HAART (n=25)	Non-HAART (n=27)	Total Cases (n=52)	P value
FBS (mg/dl)	83.3(12.7)	79.1(12.1)	81.0(12.5)	0.300
TC (mg/dl)	142.7(45.2)	107.7(25.8)	123.8(39.8)	0.003
HDL (mg/dl)	41.0(9.3)	37.8(9.0)	39.3(9.2)	0.130
TG (mg/dl)	97.2(56.3)	117.4(57.6)	108.1(57.3)	0.100
Serum amylase (U/L)	78.1(82.4)	56.5(18.0)	66.4(57.8)	0.500
Serum lactate (mmol/L)	1.57(0.64)	1.26(0.57)	1.49(0.61)	0.010
Blood pH	7.385(4.77)	7.382(3.90)	7.383(4.18)	0.790
Bicarbonate levels (mmol/l)	22.31(2.38)	21.65(2.80)	21.95(2.61)	0.280
Serum Bilirubin (mg/dl)	.473(.117)	0.44 (.145)	.458(.132)	0.170
AST (U/L)	51.4 (40.5)	42.8(40.3)	46.8(40.2)	0.120
ALT (U/L)	44.0(37.3)	42.3(19.0)	43.1(28.6)	0.260

FBS- fasting Blood sugar; TC- Total cholesterol; HDL- high-density lipoprotein cholesterol; TG- triglycerides; ALT - aspartate aminotransferase; AST - alanine aminotransferase

3 (5.5 %) in class IV.

Fat redistribution was observed in 2 male children. The incidence of lipodystrophy was 0.0337 per 100 person years. Both had only peripheral lipoatrophy [score 4 (sunken cheeks and prominent zygomatic arch; buttocks had loss of contour and loose skin folds)] noticed readily both by the doctor and the parents. There was consistent improvement in the CD 4 counts with HAART. Both the children were maintaining weight and BMI as per previous records. Duration of HAART was 26 and 72 months respectively. Age at start of HAART was 4.8 and 8.5 years. One child was on ZDV and other on d4t. Both were WHO Stage I with CD4 counts of 235 and 256 cells/mm3. One child had HC, rest no metabolic abnormality were found.

Among lipid abnormalities, only the prevalence of HC was significantly higher in patients on HAART (4 in Group A, none in Group B; P = 0.038). The incidence of HC was 0.0674 per 100 person years. Mean total cholesterol was also significantly higher in children on HAART (Group A 142.7 + 45.2, Group B 107.7 + 25; P = 0.003). The results of the metabolic profile are shown in table 2.

Mean serum triglycerides and HDL cholesterol were similar in both groups. Although HT was observed in 4 patients on HAART and 7 patients off HAART, the results did not reach statistical significance (P = 0.309). The incidence of lipodystrophy was 0.0674 per 100 person years. The mean serum lactate was raised statistically in children on HAART [Group A 1.57(0.64); Group B 1.26(0.57); P =0.01] although none were clinically symptomatic. Asymptomatic mild hyperlactatemia was observed in 4 children on HAART.

There were no significant differences in the mean serum bilirubin, ALT, AST, fasting venous blood sugar, serum amylase, blood pH and bicarbonate levels between the study groups.

DISCUSSION

As access to HAART improves with the aid of WHO "scale up" programmes increasing number of children are being started on WHO prequalified first line FDC [mainly d4T/3TC/NVP and occasionally ZDV/3TC/NVP as the FDC preparations available for ZDV based therapy are only for > 20 kg at present in India]. With increasing numbers of years on HAART more morphological [abnormalities in fat distribution i.e. lipodystrophy including central lipohypertrophy and peripheral lipoatrophy and mixed forms) and metabolic abnormalities (dyslipidemia, insulin resistance/ diabetes, hyperlactatemia and osteopenia are gaining importance.

Lipodystrophy and metabolic complications of HAART are emerging complications in children.[9-20] Unlike the situation in adults[23,24], the case definition of

lipodystrophy syndrome has not been validated in children. Also the assessment of fat redistribution in HIV-infected children is complicated by the normal, dynamic alterations in body composition during childhood and puberty. As there are no standardized reference parameters in children, diagnosis is usually difficult and based on subjective aspects.

The prevalence of lipodystrophy syndrome hence has been variable and has been estimated to range from 18 to 33% in cross sectional studies.[9-16] Disturbances in lipid/ glucose metabolism have been reported in HIV-infected children around 20-30 %.[11-13,16] Most of the longitudinal studies have shown lipid abnormalities to be very stable over time.[18-20] Although lipodystrophy syndrome and metabolic abnormalities are associated not all children with lipodystrophy have metabolic abnormalities and vice versa. Limited pediatric data is available from developing countries[19] and none from India.

Identified risk factors for lipodystrophy include severe HIV disease, female gender, increasing age and use of PI's /d4t. Risk factors for HC include female gender, PI use, HAART and central lipohypertrophy. Risk factors for HT includes severe HIV disease, PI use, HAART and stavudine. Central lipohypertrophy is found to be associated with HC and peripheral lipoatrophy with HT.[11]

Two children in our study had features of fat redistribution, with both having peripheral lipoatrophy. No patient had central lipohypertrophys and mixed forms, which have been reported to be more common phenotypes as compared to peripheral lipoatrophy in most studies.[11,12,16] The incidence of metabolic complications was also lower as compared to other studies but significant. HC and HL although were statistically significant the clinical significance is unclear especially in view of borderline raised values. These children need regular follow up. The significance of HT in HIV patients without drugs is unclear. Whether it is due to the disease or some other factor remains to be seen.

The absence of PI use, younger age of the included subjects as compared to other studies, lower number of girls and non-inclusion of adolescents could explain the lower incidence of these complications. Also none of the children had reached puberty, which had also been found to an independant risk factor.[17] Racial and genetic differences also could be contributory. Prevlance of high rates of malnutrition in the developingc ountries could also influence the development of these complications.

Limitations of our study include the small sample size, unicenteric, crosssectional design; controls were not matched, variable duration of ART and disproportionately smaller number of patients in the ZDV/3TC/NVP arm. Lack of blinding of the physician to the treatment status of the child might introduce bias. No patient questionnaire could be used due to the poor educational status of the population. Lack of an objective model for case definition of lipodystrophy in children compounded the problem. Viral loads and their association with these complications also could not be determined due to poor availability and financial constraints.

In summary, our study demonstrates a significant prevalence of morphologic and metabolic complications among children taking WHO-recommended first-line generic HAART regimens at present. These abnormalities appear to be emerging complications and need very close follow up as they would worsen with time as the duration of HAART increases and PI are used as second line therapy.

Many questions still remain unanswered such as how it develops /progresses in childhood, clinical significance of the different types of fat redistribution and lipid/glucose abnormalities, need and frequency of routine lipid monitoring, long term complications with dyslipidemia especially cardiovascular, negative psychosocial impact and optimum clinical management. In future, long-term cohort or case-control (matched for age, sex, CD4) studies should be undertaken with a larger sample size to further clear these issues.

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