International Journal of Contemporary Pediatrics
Sanjeeva GN et al. Int J Contemp Pediatr. 2016 Feb;3(1):41-51
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20151482

Research Article

Prevalence and predictors for lipodystrophy syndrome among HIV infected children on anti-retroviral therapy

Sanjeeva G. N.*, Pavithra H. B., Sukanya V., Shobha S., Govindaraj M.

Pediatric Centre of Excellence for HIV, Indira Gandhi Institute of Child Health, Karnataka, Bangalore, India

Received: 03 December 2015
Accepted: 05 December 2015

***Correspondence:**
Dr. Sanjeeva G.N.,
E-mail: sanju_gn@rediffmail.com

ABSTRACT

Background: With the widespread use of ART and prolonged survival of CLHIV, toxicities like lipodystrophy are increasingly evident. There are limited pediatric data on the prevalence of Lipodystrophy syndrome (LDS). The aim of this study was to determine the prevalence and predictors associated with LDS among HIV-infected children on ART.
Methods: A cross-sectional study of 320 CLHIV aged between 2-18 years on ART were enrolled. Fat redistribution (FR) was assessed clinically and fasting blood sample was taken for lipid profile. LDS was defined as FR or metabolic abnormalities or both. We conducted univariate, multivariate and adjusted analysis to determine factors predisposing to LDS.
Results: Median age of the participants was 13 years. Mean duration on ART was 3.7±1.9 years. Prevalence of LDS, FR, and metabolic abnormalities was 60%, 46% and 36% respectively. We found significant association between FR and age less than 5 yrs at the time of ART initiation, d4T exposure and duration of ART exposure of > 3yrs. Children who were moderately malnourished before ART initiation were less likely to develop FR and LDS (p=0.03). A significant association was also seen between metabolic abnormalities and female gender, advanced sexual maturity and hypertriglyceridemia at the time of ART initiation.
Conclusions: Prevalence of LDS is high among HIV-infected children on ART and likelihood of developing FR increases with prolonged exposure of ART as well as early age of initiation of ART. Advanced sexual maturation and hypertriglyceridemia at the time of ART initiation were associated with increased prevalence of metabolic abnormalities.

Keywords: Lipodystrophy, Prevalence, CLHIV, Antiretroviral therapy

INTRODUCTION

Worldwide, increased accessibility to antiretroviral therapy (ART) has resulted in its widespread use including in children, improving their survival and longer duration of exposure to ART. Consequently, there is increased risk of long-term toxicities like lipodystrophy syndrome (LDS) associated with such long-term ART. LDS is a poorly defined condition associated with fat redistribution (FR) and metabolic abnormalities. This was first described in HIV-infected adults in 1989.[1] The exact pathogenesis of these changes is unknown. Even though these changes are attributed to the long-term exposure to ART, many factors like individual susceptibility, HIV virus itself influences the manifestation.

The prevalence of LDS ranges from as low as 23% to as high as 56%.[2-4] This wide variation in the prevalence of the LDS could be due to lack of consensus on the definition of LDS, ethnic, sociocultural and nutritional variation and variable number and duration of ART regimen exposure among the study subjects from the

different parts of the world. The normal dynamic childhood alteration in the body fat composition pose a greater challenge in the assessment of ART-associated FR.

Most of the data about lipodystrophy is from middle-/high-income countries, and sub-Saharan Africa. Inspite of India being home for substantial number of children living with HIV with nearly 1.45 lakhs children estimated to be infected with HIV in 2011,[5] there are no data on the pediatric LDS. The National pediatric initiative was started in 2006 in India and rapidly scaled to reach children living with HIV across the country through pediatric ART services. The initial stavudine (d4T) based regimen has been phased out from 2013. This has led to a large cohort across the country who have exposed to d4T based ART for varying period of time. Even after phase out, due to limited options of drugs for the children, d4T still holds its relevance in the context of failure of first-line regimen. Also, zidovudine (AZT), used as substitute for d4T, being another thymidine analogue nucleoside reverse transcriptase inhibitor (NRTI), could potentially lead to LDS.

The aim of our study is to assess the prevalence of LDS among the HIV-infected children on NRTI-based ART and also to determine predictors of LDS in our population.

METHODS

The study was conducted at Pediatric Centre of Excellence for pediatric HIV, Indira Gandhi Institute of Child health, referral and teaching hospital at Bangalore, India between January to June 2013. As of January 2013, 1170 children were enrolled in HIV care (Figure 1). We studied 320 children on first-line ART regimen which was either AZT or d4T. Lamivudine (3TC) being common across all the regimen and either Nevirapine (NVP) or efavirenz (EFV) is being used as third drug. The dosage of the ART drugs is based on the children's body weight. The clinic ART policies are based on the National AIDS control Organization (NACO) guidelines.[6,7]

We conducted a cross-sectional study of HIV-infected children (CLHIV) on first-line ART regimens. Children were eligible for this study if: (1) aged between 2-18 years at the time of ART initiation, (2) on first-line ART regimen for atleast one year and (3) those whose caretakers provided written informed consent. We excluded children with diabetes mellitus, renal disease, cardiac disease, severe malnutrition and severe clinical illness at the time of study. We also excluded those children who have switched between d4T and AZT-based regimen before recruitment.

Data including clinical history, physical exam and laboratory results was collected using a standardized data collection form. Cross-sectional data at the time of ART initiation including date and age of diagnosis of HIV infection, date of ART initiation, previous history of opportunistic infections, WHO staging, anthropometric data and nutritional status, CD4 count and percentages, lipid profile and ART treatment history was extracted from the chart. The physical assessment for fat redistribution and pubertal maturity was done by the principal investigator or a co-investigator who was an experienced pediatrician. A trained nutritionist measured the weight, height, mid-upper arm circumference, waist and hip circumference. A fasting blood sample (over-night) was obtained for blood glucose and lipid profile. Blood glucose and lipid profile were measured by semi-automated analyser (Star 21 plus, E12029, Chennai, India). This study was approved by IRB/ethical committee of Indira Gandhi Institute of Child Health.

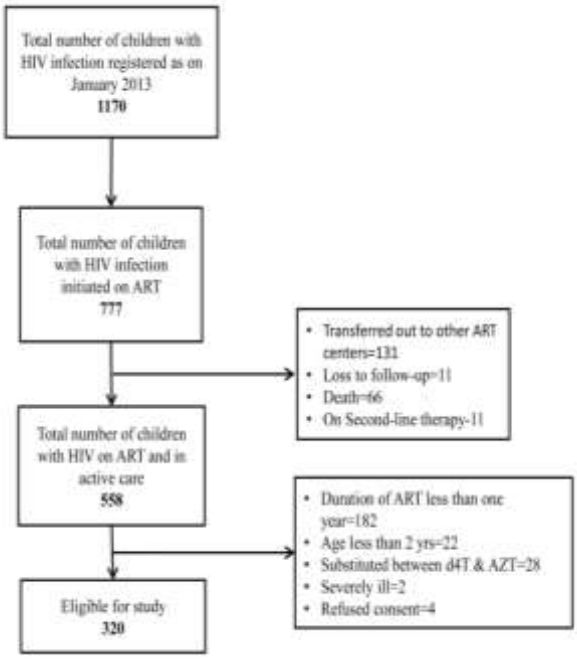

Figure 1: Study profile.

Definitions

Fat redistribution (FR) was defined clinically by physical findings of any fat wasting of extremities, face or buttocks; with the presence of prominent vessels or fat accumulation in the abdomen and dorsocervical spine (buffalo hump). The fat redistribution was scored separately for limbs, face, buttocks, abdomen, thorax and neck on a scale of 0 to 3 based on an adult scoring system.8 Where 0 represented the absence of fat changes, 1-minor changes (changes noticeable only when specifically inspected), 2-moderate changes (changes readily obvious to even caretakers/patients) and 3-major changes (changes noticeable by other people, such as family or classmates). The presence of a score 1 in any part of the body was considered as abnormal FR. Hyperglycaemia was defined as fasting blood glucose ≥126 mg/dl.

Serum cholesterol levels and serum triglycerides of children were classified as follows:[9]

- Serum cholesterol - <200 mg/dl – Normal cholesterol levels.
- Serum cholesterol - >200 mg/dl – Hypercholesterolemia.
- Serum triglycerides - <150 mg/dl – Normal triglycerides levels.
- Serum triglycerides - >150 mg/dl – Hypertriglyceridemia.

Metabolic abnormalities were defined as the presence of hyperlipidemia and/or hyperglycaemia.

LDS was defined as the presence of FR or metabolic abnormalities or both. Further, the children with LDS were classified into two overlapping subgroups: Fat redistribution group which includes children with FR with or without metabolic abnormalities and second subgroup, metabolic abnormalities group which includes children with metabolic abnormalities with or without FR.

Following nutritional status classification was done using WHO reference centile charts (Table 1).[10,11]

Table 1: Classification of nutritional status.

Nutritional status classification	Wt/Ht in Children <5years	BMI in Children >5years
Severe malnutrition	Less than -3SD	Less than -3SD
Moderate malnutrition	Between – 2 SD and -3SD	Between – 2 SD and -3SD
No malnutrition	More than -2SD	More than -2SD

Statistical analysis

Primary outcomes of the study were the proportion of children with FR and metabolic abnormalities. We evaluated patient characteristics including age, gender, BMI, Tanner stage, WHO clinical stage, laboratory parameters, ART regimen and duration on ART. Statistical significance of differences between proportions was evaluated by chi-square test. Multivariable logistic regression analysis was done to determine factors independently associated with LDS, FR and metabolic abnormalities. All the variables with p-value <0.05 at univariate analysis were included in the model. To determine whether one predictor variable confounds the other predictor variables, the crude odds ratio was compared with the adjusted odds ratio. If these two odds ratio differed by 10% or more, then it was concluded that confounding was present. Statistical analysis was performed using the statistical software SPSS (version 16.0, USA).

RESULTS

We studied 320 CLHIV aged between 2-18 years (mean age: 12±4 years; median age: 13years). Majority, 231(72%) were on d4T based regimen. Two third of the participants had advanced HIV disease (WHO Stage-III-54% and IV-9%) at ART initiation. At the time of initiation of ART, 34% of the children had hypertriglyceridemia. The characteristics of the children at the time of ART initiation are as shown in Table 2.

Table 2: Characteristics of the children at the time of analysis.

Characteristics	Frequency, % (n=320)
Age	
2-5yrs	16 (5%)
5-10yrs	87 (27%)
>10yrs	217 (68%)
Gender	
Male	173 (54%)
Female	147 (46%)
Regimen	
d4T based regimen	231 (72%)
AZT based regimen	89 (28%)
WHO Stage at ART initiation	
WHO 1	23 (7%)
WHO 2	95 (30%)
WHO 3	173 (54%)
WHO 4	29 (9%)
S. cholesterol (mg/dl)	
Normal	294 (92%)
Hypercholesterolemia	26 (8%)
S. triglycerides(mg/dl)	
Normal	211 (66%)
Hypertriglyceridemia	109 (34%)
Mean CD4 cell count ± SD	513 ±389
Mean CD4 percentage ± SD	17±9

Prevalence of Lipodystrophy

The overall prevalence of LDS was 59.7% (Figure 2). Among children with LDS, 76(39.8%) had only FR, 44(23%) had metabolic abnormalities only and 71(37%) children had both FR as well as metabolic abnormalities Figure 2). Among children who had LDS, 85% were on d4T based regimen whereas among the children who developed metabolic abnormalities alone 64% and 36% were on d4T and AZT-based regimen respectively.

Factors associated with lipodystrophy

Male: female ratio of children who developed LDS was 1.2:1. Nearly 43% of girls developed metabolic abnormalities as compared to 30% of boys which was statistically significant (OR=1.75 (95%CI: 1.10-2.77;p=0.02). There was no statistically significant gender difference in those who developed FR or LDS.

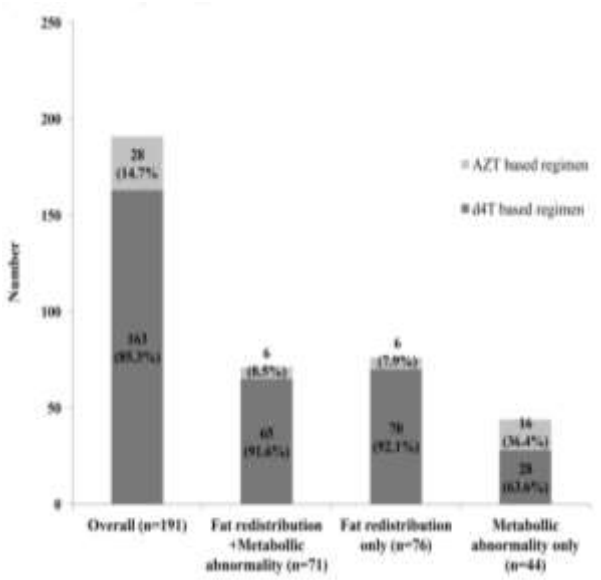

Figure 2: Prevalence of lipodystrophy.

Fifty-eight percent of children under 5 years of age at the time of ART initiation developed FR as compared to 47% and 35% among the age-group of 5-10years and >10years. This was statistically significant [OR=2.55 (95% CI: 1.41-4.60) p= 0.01]. Similarly, 74% of the children <5 years of age and 58% of children between 5-10 years at ART initiation developed lipodystrophy. This was statistically significant [OR= 2.75 (95% CI: 1.47-5.14; p=0.01]. There was no statistically significant age difference among who developed metabolic abnormalities (Table 3).

Nutritional status of these children at ART initiation was assessed and classified using the WHO growth charts. Only 29% of the children who had moderate malnutrition at the time of ART initiation developed FR as against 50% and 48% of the children with normal nutrition and severe malnutrition respectively. This was statistically significant [OR = 0.42 (95% CI: 0.22-0.82;p=0.03]. Similarly, 43% of children who had moderate malnutrition at the time of ART initiation developed LDS as against 62.8% of children with normal nutrition and severe malnutrition each. This was statistically significant [OR=0.45 (95%CI: 0.24-0.84) p=0.03]. However, there was no statistically significant difference in the nutritional status among the children who developed metabolic abnormalities (Table 3).

Significant number of children on d4T-based regimen developed LDS (71%), FR (58%) and metabolic abnormalities (40%) when compared to children on AZT-based regimen (32%, 14 % and 25%respectively) [OR 5.22 (95% CI: 3.08-8.87);p=<0.001 for LDS; OR= 9.02 (95% CI: 4.65-17.05) p=<0.001) for FR and OR= 2.05 (95% CI: 1.19-3.55) p=0.01 for metabolic abnormalities] (Table 3).

The mean duration of exposure to d4T-based regimen was 4.29 ±1.73 years and AZT-based regimen was 2.45±1.68 years. This mean difference in duration of ART exposure was found to be statistically significant (p=0.01).

There was a linear relationship between duration of ART and prevalence of LDS and FR (Figure 3). Metabolic abnormalities were seen among 20%, 42% and 42% of the children who had 1-2 years, 2-3years and > 3years of ART exposure respectively. FR was seen among 12%, 34% and 64% of the children who had 1-2 years, 2-3years and > 3 years of ART exposure respectively. Similarly, LDS was seen among 29%, 53% and 76% of children who had 1-2 years, 2-3years and > 3 years of ART exposure respectively. The mean duration of exposure to ART was 3.7 ±1.9 years.

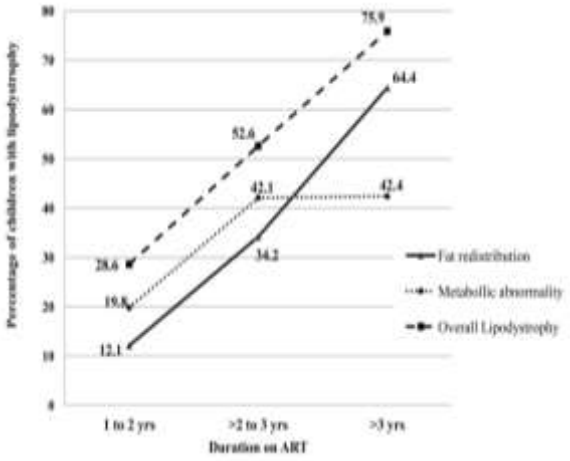

Figure 3: Relationship between duration of ART and prevalence of LDS, FR and metabolic abnormalities.

Metabolic abnormalities were noted in 64% and 34% of children with hypercholesterolemia and normal serum cholestrol at the time of ART initiation respectively, which was statistically significant[OR= 3.52 (95% CI: 1.50-8.26) p=< 0.01]. Similarly 48% and 31% of the children with hypertriglyceridemia and normal serum triglyceride at the time of ART initiation respectively developed metabolic abnormalities. This was statistically significant [OR= 2.08 (95% CI: 1.25-3.47) p=< 0.01]. However, there was no association between metabolic abnormalities at ART initiation and children developing FR and LDS. None of our children had abnormal glucose level.

The prevalence of metabolic abnormalities was significantly higher with advanced sexual maturity (p=0.02). The risk of developing metabolic abnormalities were significantly higher in children with Tanner stage IV and V as against children with Tanner stage I (Tanner stage IV vs. I –OR = 2.61 (95% CI: 1.21-5.64); p =0.02); Tanner stage V vs. I - OR = 3.17 (95% CI: 1.11-9.08); p=0.03). Though the risk of developing FR and LDS

increases with advanced sexual maturation, this was not found to be statistically significant (Table 4).

Table 3: Factors associated with Lipodystrophy.

	Fat redistribution		Metabolic abnormality		Lipodystrophy syndrome	
	Yes (n=147)	**No (n=173)**	**Yes (n=115)**	**No (n=205)**	**Yes (n=191)**	**No (n=129)**
Age at the time of ART initiation						
2 to 5 yrs	47 (58.0%)	34 (42.0%)	33 (40.7%)	48 (59.3%)	60 (74.1%)	21 (25.9%)
5 to 10 yrs	62 (47.3%)	69 (52.7%)	45 (34.4%)	86 (65.6%)	76 (58.0%)	55 (42.0%)
>10 yrs	38 (35.2%)	70 (64.8%)	37 (34.3%)	71 (65.7%)	55 (50.9%)	53 (49.1%)
	Chi-sq=9.90; OR=2.55 (95%CI:1.41-4.60) p=0.01		Chi-sq=1.09; OR=1.32 (95%CI:0.73-2.39) p=0.58		Chi-sq=10.56; OR=2.75 (95%CI:1.47-5.14) p=0.01	
Gender						
Male	86 (49.7%)	87 (50.3%)	52 (30.1%)	121 (69.9%)	100 (57.8%)	73 (42.2%)
Female	61 (41.5%)	86 (58.5%)	63 (42.9%)	84 (57.1%)	91 (61.9%)	56 (38.1%)
	Chi-sq=2.16; OR=0.72 (95%CI:0.46-1.12) p=0.14		Chi-sq=5.65; OR=1.75 (95%CI:1.10-2.77) p=0.02		Chi-sq=0.56; OR=1.19 (95%CI:0.76-1.86) p=0.46	
Nutritional status at the time of ART initiation						
No malnutrition	91 (49.7%)	92 (50.3%)	68 (37.2%)	115 (62.8%)	115 (62.8%)	68 (37.2%)
Moderate malnutrition	15 (29.4%)	36 (70.6%)	15 (29.4%)	36 (70.6%)	22 (43.1%)	29 (56.9%)
Severe malnutrition	41 (47.7%)	45 (52.3%)	32 (37.2%)	54 (62.8%)	54 (62.8%)	32 (37.2%)
	Chi-sq=6.77; OR=0.42 (95%CI:0.22-0.82) p=0.03		Chi-sq=1.12; OR=0.70 (95%CI:0.36-1.38) p=0.57		Chi-sq=6.91; OR=0.45 (95%CI:0.24-0.84) p=0.03	
ART Regimen						
AZT based regimen	12 (13.5%)	77 (86.5%)	22 (24.7%)	67 (75.3%)	28 (31.5%)	61 (68.5%)
d4T based regimen	135 (58.4%)	96 (41.6%)	93 (40.3%)	138 (59.7%)	163 (70.6%)	68 (29.4%)
	Chi-sq=52.29; OR=9.02 (95%CI:4.65-17.05) p=<0.001		Chi-sq=6.74; OR=2.05 (95%CI:1.19-3.55) p=0.01		Chi-sq=40.83; OR=5.22 (95%CI:3.08-8.87) p=<0.001	
Serum Cholesterol (mg/dl) at the time of ART initiation						
Normal	125 (45.1%)	152 (54.9%)	93 (33.6%)	184 (66.4%)	162 (58.5%)	115 (41.5%)
High	15 (60.0%)	10 (40.0%)	16 (64.0%)	9 (36.0%)	19 (76.0%)	6 (24.0%)
	Chi-sq=2.04; OR=1.82 (95%CI:0.79-4.20) p=0.15		Chi-sq=9.20; OR=3.52 (95%CI:1.50-8.26) p=<0.01		Chi-sq=2.93; OR=2.25 (95%CI:0.87-5.80) p=0.09	
Serum Triglycerides (mg/dl) at the time of ART initiation						
Normal	100 (46.9%)	113 (53.1%)	66 (31.0%)	147 (69.0%)	127 (59.6%)	86 (40.4%)
High	40 (44.9%)	49 (55.1%)	43 (48.3%)	46 (51.7%)	54 (60.7%)	35 (39.3%)
	Chi-sq=0.10; OR=0.92 (95%CI:0.56-1.52) p=0.75		Chi-sq=8.17; OR=2.08 (95%CI:1.25-3.47) p=<0.01		Chi-sq=0.03; OR=1.05 (95%CI:0.63-1.74) p=0.86	

pISSN 2349-3283 | eISSN 2349-3291

Multivariate logistic regression

The LDS model included age at ART initiation, nutritional status at ART initiation, ART regimen and duration on ART. The FR model included age at ART initiation, nutritional status at ART initiation, ART regimen and duration on ART. Metabolic abnormalities model included gender, metabolic abnormalities at ART initiation, ART regimen, duration on ART and sexual maturation.

LDS was independently associated with d4T-based regimen (OR= 2.10 (95% CI: 1.11-3.99) p=0.02) and duration of ART of more than 3 years (OR= 5.46 (95% CI: 2.80-10.62) p=<0.001). No significant independent association was found between LDS and age at ART initiation and nutritional status at ART initiation.

FR was independently associated with d4T-based regimen (OR = 3.56 (95% CI: 1.67-7.62) p=<0.01) and duration of ART of more than 3 years (OR= 7.48 (95% CI: 3.47-16.15) p=<0.001). Also children with moderate malnutrition at ART initiation were less likely to develop fat redistribution when compared to children with normal nutrition [OR = 0.45 (95% CI: 0.21-0.97) p= 0.04]. No significant independent association was found between fat redistribution and age of ART initiation. Female gender (OR =1.72 (95% CI: 1.02-2.91) p=0.04), duration of ART of more than 3 years (OR =2.33 (95% CI: 1.06-5.12) p=0.03) and hypertriglyceridemia at ART initiation (OR =2.03 (95% CI: 1.14-3.61)) p=0.02) was independently associated with metabolic abnormalities. However, ART regimen, hypercholesterolemia at the time of ART initiation and advanced sexual maturation was not independently associated with metabolic abnormalities (Table 5).

Adjusted analysis

Since age below 5 years at ART initiation was not found to be independently associated with the prevalence of LDS and FR, an adjusted analysis was done to find out confounding factors. When age at ART initiation was adjusted against duration of ART, there was no statistically significant difference between crude OR and adjusted OR for LDS [crude OR = 2.35 (95% CI: 1.35-4.12) and AOR=2.06 (95% CI: 1.13-3.75)] and for FR (crude OR = 1.92 (95% CI: 1.15-3.20) and AOR=1.62 (95% CI: 0.92-2.86)]. When age less than 5 years at ART initiation was adjusted to the type of ART regimen, there was statistically significant difference between crude OR and adjusted OR for LDS[crude OR = 2.35(95% CI:1.35-4.12) and AOR = 1.78 (95% CI:0.99-3.21)] and for FR(crude OR = 1.92 (95% CI:1.15-3.20) and AOR = 1.38 (95% CI: 0.80-2.39)]. When children with age < 5 years at ART initiation was adjusted to duration of d4T-based ART regimen and duration of AZT-based ART regimen, there was statistically significant difference between crude OR and adjusted OR for LDS [crude OR = 4.76 (95% CI:2.78-8.15) and AOR = 2.48 (95% CI:1.35-4.55)] and for FR (crude OR = 8.52 (95% CI:4.37-16.63) and AOR = 4.16 (95% CI:2.00-8.65)](Table 6).

Table 4: Tanner staging.

Characteristics	Fat redistribution		Metabolic abnormality		Lipodystrophy syndrome	
Tanner Stage	**Yes (n=147)**	**No (n=173)**	**Yes (n=115)**	**No (n=205)**	**Yes (n=191)**	**No (n=129)**
I	47 (45.6%)	56 (54.4%)	32 (31.1%)	71 (68.9%)	62 (60.2%)	41 (39.8%)
II	39 (41.1%)	56 (58.9%)	31 (32.6%)	64 (67.4%)	51 (53.7%)	44 (46.3%)
II	29 (45.3%)	35 (54.7%)	19 (29.7%)	45 (70.3%)	35 (54.7%)	29 (45.3%)
IV	20 (54.1%)	17 (45.9%)	20 (54.1%)	17 (45.9%)	27 (73.0%)	10 (27.0%)
V	9 (52.9%)	8 (47.1%)	10 (58.8%)	7 (41.2%)	13 (76.5%)	4 (23.5%)
	Chi-sq=2.23; p=0.69		Chi-sq=11.78; p=0.02		Chi-sq=6.79; p=0.15	
	ODDS RATIO (95% CI)	**p-Value**	**ODDS RATIO (95% CI)**	**p-Value**	**ODDS RATIO (95% CI)**	**p-Value**
II vs I	0.83 (0.47-1.46)	0.52	1.07 (0.59-1.96)	0.81	0.77 (0.44-1.35)	0.36
III vs I	0.99 (0.53-1.85)	0.97	0.937 (0.48-1.85)	0.85	0.80 (0.43-1.50)	0.48
IV vs I	1.40 (0.66-2.98)	0.38	2.61 (1.21-5.64)	0.02	1.79 (0.78-4.08)	0.17
V vs I	1.34 (0.48-3.75)	0.58	3.17 (1.11-9.08)	0.03	2.15 (0.66-7.05)	0.21

Table 5: Multivariate analysis.

Characteristics	ODDS RATIO (95% CI)	p-Value
Independent variables for Lipodystrophy syndrome		
Age at the time of ART initiation		
2-5yrs vs >10yrs	1.59 (0.77-3.27)	0.21
5-10yrs vs >10yrs	0.88 (0.48-1.61)	0.68
Nutritional status at the time of ART initiation		
Moderate under nutrition vs no malnutrition and severe malnutrition	0.51 (0.25-1.04)	0.06
Initial Regimen		
d4T based regimen vs AZT based regimen	2.10 (1.11-3.99)	0.02
Duration on ART		
2-3 yrs vs 1 to 2 yrs	2.28 (0.99-5.24)	0.05
>3 yrs vs 1 to 2 yrs	5.46 (2.80-10.62)	<0.001
Independent variables for fat redistribution		
Age at the time of ART initiation		
2-5yrs vs >10yrs	1.30 (0.64-2.66)	0.47
5-10yrs vs >10yrs	1.10 (0.58-2.06)	0.79
Nutritional status at the time of ART initiation		
Moderate under nutrition vs no malnutrition	0.45 (0.21-0.97)	0.04
Initial Regimen		
d4T based regimen vs AZT based regimen	3.56 (1.67-7.62)	<0.01
Duration on ART		
>2 to 3 yrs vs 1 to 2 yrs	2.68 (1.01-7.10)	0.05
>3 yrs vs 1 to 2 yrs	7.48 (3.47-16.15)	<0.001
Independent variables for metabolic abnormality		
Gender		
Female vs Male	1.72 (1.02-2.91)	0.04
Baseline S. Cholesterol (mg/dl) at the time of ART initiation		
High (>200 mg/dl) vs Normal (< 200 mg/dl)	2.02 (0.78-5.22)	0.15
Baseline S. Triglycerides (mg/dl) at the time of ART initiation		
High (>150 mg/dl) vs Normal (< 150 mg/dl)	2.03 (1.14-3.61)	0.02
Initial Regimen		
d4T based regimen vs AZT based regimen	1.43 (0.68-3.02)	0.34
Duration on ART		
>2 to 3 yrs vs 1 to 2 yrs	2.51 (0.99-6.38)	0.05
>3 yrs vs 1 to 2 yrs	2.33 (1.06-5.12)	0.03
Tanner stage		
II vs I	1.14 (0.59-2.20)	0.70
III vs I	0.83 (0.40-1.75)	0.63
IV vs I	1.76 (0.72-4.30)	0.23
V vs I	1.97 (0.62-6.21)	0.25

Table 6: Adjusted analysis.

	Lipodystrophy syndrome		Fat redistribution	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Age <5 years at initiation of ART adjusted for duration on ART < 3 years	2.35 (1.35-4.12)	2.06 (1.13-3.75)	1.92 (1.15-3.20)	1.62 (0.92-2.86)
Age < 5 years at initiation of ART adjusted for type of ART regimen	2.35 (1.35-4.12)	1.78 (0.99-3.21)	1.92 (1.15-3.20)	1.38 (0.80--2.39)
Age < 5 years at initiation & regimen adjusted for duration on ART < 3years	4.76 (2.78-8.15)	2.48 (1.35-4.55)	8.52 (4.37-16.63)	4.16 (2.00-8.65)
Type of regimen adjusted for duration on ART < 3 years	5.22 (3.07-8.87)	2.72 (1.49-4.96)	9.02 (4.65-17.50)	4.41 (2.14-9.08)

When type of regimen was adjusted to duration of d4T-based ART regimen and duration of AZT-based ART regimen, there was statistically significant difference between crude OR and adjusted OR for LDS [crude OR = 5.22 (95% CI: 3.07-8.87) and AOR = 2.72 (95% CI: 1.49-4.96)] and for FR (crude OR = 9.02 (95% CI: 4.65-17.50) and AOR = 4.41 (95% CI: 2.14-9.08)].

DISCUSSION

This study is the one of the largest assessment of lipodystrophy syndrome in CLHIV from a single center to date. All other studies involving larger numbers are a multicentric cross-sectional study which makes the study population as well as assessment heterogeneous. Another, strength of our study was that study subjects were on either d4T- or AZT-based ART regimen exclusively and children who were switched between d4T and AZT-based regimen before the study were excluded. All the available studies included children who were exposed to multiple regimens making the assessment complex and confusing. In our study FR was assessed by the experienced pediatricians however, objective methods like DEXA, skin fold thickness were not used due to lack of consensus in the definition of FR based on these methods as well as non-availability of norms in our population so that it can be compared. Children with LDS were classified into two overlapping subgroups: Fat redistribution group children has FR as a predominant manifestation and may also be associated with or without metabolic abnormalities and similarly metabolic abnormalities group children manifests predominantly with metabolic abnormalities with or without FR. The impact of these features on the clinical outcome are diverse with FR is associated with issues of body image and growth in the children and metabolic abnormalities are associated with increased cardiovascular risk. Hence, this classification was done to study the factors associated with these subgroups separately.

In our study, 231(72%) children were on d4T-based regimen and mean duration of ART exposure was 3.7±1.9 years. The prevalence of LDS was 59.7%% in our study. FR was found among 45.9% of children and metabolic abnormalities in 35.9% of children. Various studies from both developing and developed countries have shown the prevalence of LDS to be varying from 23% to 56% [2-4] and that of FR was between 25% and 42% .This wide-ranging variation in the prevalence of LDS and FR could be due to lack of consensus in the definition of the LDS or FR, heterogeneity of the study group indicating ethnic predisposition, variable duration of ART exposure before the assessment, varying duration of ART exposure at the time of analysis and many subjects receiving multiple ART regimens before assessment. However, metabolic abnormalities were found in 34% to 42% of children which is comparable to our study.[12-17]

In our study significant number of children developed LDS and FR when ART was initiated below 5 years of age as compared to older age. A similar correlation was not found among the children who developed metabolic abnormality. Dynamic alteration in the body fat composition during childhood may predispose the younger children for the development of LDS and FR. Another reason for this increased prevalence could be the longer duration of ART exposure in these children. But multivariate regression analysis found no independent association between age of ART initiation and development of FR, metabolic abnormalities, and LDS.

To analyze the role of confounding factors like duration of ART and type of ART regimens adjusted analysis was done. In the adjusted analysis, first, age less than 5 years at the time of ART initiation was adjusted against the duration of ART and we found that duration of ART is not a confounding factor for increased prevalence of LDS and FR in these children. However, when the age of ART initiation was adjusted to ART exposure, it was found to be significant. This shows that the development of LDS and FR in children younger than 5 years is determined by the ART initiation rather than the duration of ART.

Children under five years of age when initiated on d4T-based ART, found to have a higher prevalence of LDS and FR, but the duration of ART was longer in these children when compared to the duration of AZT-based regimen. To determine the confounding factor among type of ART regimen and duration of ART, contributing to increased prevalence of LDS and FR in children under 5 years of age at the time of ART initiation, two step adjusted analysis was done which showed duration of d4T-based ART was a confounding factor. This analysis shows that children under five years likely to develop FR and LDS when exposed to ART for sufficient duration of time irrespective of regimen. This finding is important in the context of implementation of universal ART for the children under 5 years of age as a strategy for retention in care recommended recently by the WHO.[18] None of the studies available till now have considered the role of age of initiation of ART in the development of LDS, especially FR.

In our study, we found that significant numbers of girls are more likely to develop metabolic abnormality compared to boys. The female gender is also found to be independently associated with the development of metabolic abnormalities (OR =1.75 (95% CI: 1.10-2.77) p=0.02). A similar correlation between genders was not found among the children who developed FR and LDS. Europen Pediatric Lipodystrophy group also found a significant number of girls developing metabolic abnormalities and FR than boys.[13] However, other studies found no significant difference among genders in the prevalence of metabolic abnormalities and FR.[14, 17]

In our study children with moderate malnutrition at ART initiation are less likely to develop FR and LDS when compared to children with normal nutritional status. There was no significant association between nutrition and development of metabolic abnormalities. Multivariate analysis also found that children with moderate malnutrition at ART initiation are less likely to develop FR, but no significant independent association was found between nutritional status at ART initiation and LDS. As other studies analyzed the nutritional status of the children at time of cross-sectional data collection rather at the time of ART initiation, no comparable data is available. Prospective longitudinal studies are needed to elucidate the factors interplaying between nutrition and LDS.

The children who have received d4T-based ART are nine times more likely to develop FR, twice more likely to develop metabolic abnormalities and five times more likely to develop LDS as compared to AZT-based regimen. But the children on d4T-based regimen were exposed to significantly longer duration of ART than the children on AZT-based regimen. When adjusted analysis was done, this longer duration of d4T was found to be a confounding factor indicating the fact that AZT-based regimen when given for longer duration is also associated with significantly increased risk of developing LDS and FR.

When the children were divided into cohorts based on duration of ART exposure, the prevalence of FR and LDS increases with duration of exposure to ART whereas the prevalence of metabolic abnormalities was found to be nearly same in children after 2 years of ART exposure. During initial 2 years after ART initiation, more children developed metabolic abnormalities than FR. But after 2 years of ART initiation significantly higher number of children developed FR than metabolic abnormalities. Several studies have shown the increased incidence of LDS and FR associated with d4T-based regimen. But many of these study subjects were switched to other NRTI like AZT before analysis. The risk of developing lipodystrophy with d4T is strongly related to the dosage and duration of exposure to antiretroviral agents.[12,13,16,19]

Children at the time of ART initiation with hypercholesterolemia are 3.5 times more likely and with hypertriglyceridemia levels are twice more likely to developed metabolic abnormalities. In our analysis, hyper triglyceridemia at ART initiation was found to be independently associated with metabolic abnormalities. But no such independent association was found with hypercholesterolemia at ART initiation. In a longitudinal study from France, found no significant association between baseline serum cholesterol and triglyceride levels and prevalence of metabolic abnormalities after 2 years.[15]

The children with advanced sexual maturation are 2.6-3 times more likely to develop metabolic abnormality than children with prepubertal sexual maturation. Multivariate analysis found no significant independent association between stage of sexual maturation and prevalence of metabolic abnormalities. Also, in our univariate analysis, no association was found between different stages of sexual maturation and prevalence of FR and LDS. But several studies have found an association between puberty and LDS and FR. Alam et al., in their study found subjects undergoing puberty or with completed puberty had a 2- to 3-fold increased risk of fat abnormality.[12] Vigano et al., found that puberty appears to worsen peripheral fat loss using an objective method of DEXA-scan.[20] Several studies have reported sexual maturation to be significantly associated with abnormal fat redistribution.[16, 21, 22] Few studies also found significant association between advanced sexual maturity and metabolic changes. Piloya et al in their Ugandan study found fat redistribution and hyperlipidemia to be significantly associated with advanced sexual maturity.[14] Lipid levels increase throughout the childhood and reaches adult levels by puberty.[23] Hence, this increased prevalence of metabolic abnormalities at the time of puberty could be an exaggerated physiological response. Longitudinal studies are required to understand its implication, role of hormonal changes and its reversibility.

Although large sample size from a single center is beneficial, our study is limited by its cross-sectional design. We are also limited by the non-availability of Indian norms for the various lipid levels and insulin resistance assessment. We are also collecting longitudinal data and objective assessment using various anthropometric measurements to address the gaps like duration of ART before the development of LDS or FR and also metabolic changes. Also further studies are needed to study the optimal and safe regimen customized to individual children based on these factors before ART initiation.

CONCLUSION

Lipodystrophy syndrome among CLHIV is a significant morbidity. Furthermore, the associations between LDS and FR and younger age of ART initiation irrespective of ART regimen suggest that the problem may worsen with time in the context of recent WHO and National guidelines adopting universal ART for children under five years as a strategy for retention in care. The main predictors of LDS being the longer duration of d4T-based regimen, baseline lipid abnormalities, and onset of puberty. Moderate malnutrition was found to have a protective effect on the prevalence of LDS.

ACKNOWLEDGEMENTS

We wish to acknowledge National AIDS Control Organisation (NACO), Dr. B.B. Rewari, WHO National Consultant, NACO and Karnataka State AIDS Prevention Society (KSAPS) for reviewing this article. We

acknowledge the contribution of ART Team at PCOE. We are thankful to the children and their parents who participated in this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Grunfeld C, Kotler D, Hamadeh R. Hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med. 1989;86:27–31.
2. Babl FE, Regan AM, Pelton SI. Abnormal body-fat distribution in HIV-1-infected children on antiretrovirals. Lancet. 1999;353(9160):1243-4.
3. Bockhorst JL, Ksseiry I, Toye M, Chipkin SR, Stechenberg BW. Evidence of human immunodeficiency virus-associated lipodystrophy syndrome in children treated with protease inhibitors. Pediatr Infect Dis J. 2003;22:463–65.
4. Jaquet D, Levine M, Ortega-Rodriguez E, Faye A, Polak M. Clinical and metabolic presentation of the lipodystrophic syndrome in HIV-infected children. AIDS. 2000;14:2123–8.
5. National AIDS Control Organisation. Technical report India HIV Estimates. 2012. Available:http://www.naco.gov.in/upload/Surveillance/Reports%20&%20Publication/Technical%20Report%20-%20India%20HIV%20Estimates%202012.pdf. Accessed 10 December 2014.
6. National AIDS Control Organisation. Guidelines for HIV care and treatment in infants and children. 2006. Available:http://www.naco.gov.in/upload/Publication/Treatment%20Care%20and%20support/Guidelines%20for%20HIV%20care%20and%20treatment%20in%20Infants%20and%20children.pdf. Accessed 20 December 2014.
7. National AIDS Control Organisation. Pediatric antiretroviral therapy (ART) guidelines. 2013. Available: http://www.naco.gov.in/upload/2014%20mslns/CST/Pediatric_14-03-2014.pdf. Accessed 10 December 2014.
8. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. Lancet. 1999;353(9170):2093-9.
9. Yip PM, Chan MK, Nelken J, Lepage N, Brotea G. Pediatric reference intervals for lipids and apolipoproteins on the VITROS 5,1 FS Chemistry System. Clin Biochem. 2006;39:978–83.
10. World Health Organization. United Nations Children's Fund WHO child growth standards and the identification of severe acute malnutrition in infants and children A joint statement. 2009. Available: http://www.who.int/nutrition/publications/severemalnutrition/9789241598163/en/. Accessed 20 December 2014.
11. World Health Organization. Growth reference 5-19 years. 2007. Available: www.who.int/growthref/who2007_bmi_for_age/en/. Accessed 10 December 2014.
12. Alam N, Cortina-Borja M, Goetghebuer T, Marczynska M, Vigano A. Body fat abnormality in HIV-infected children and adolescents living in Europe: prevalence and risk factors. J Acquir Immune Defic Syndr. 2012;59:314–24.
13. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. Aids. 2004;18:1443–51.
14. Piloya T, Bakeera-kitaka S, Kekitiinwa A, Kamya MR. Lipodystrophy among HIV-infected children and adolescents on highly active antiretroviral therapy in Uganda : a cross sectional study. J Int AIDS Soc. 2012;15:1–7.
15. Children H, Beregszaszi M, Dollfus C, Levine M, Faye A. Longitudinal Evaluation and Risk Factors of Lipodystrophy and Associated Metabolic Changes in. J Acquir immune Defic Syndr. 2005;40:161–8.
16. Kinabo GD, Sprengers M, Msuya LJ, Shayo AM, van Asten H. Prevalence of lipodystrophy in HIV-infected children in Tanzania on highly active antiretroviral therapy. Pediatr Infect Dis J. 2013;32:39–44.
17. Ene L, Goetghebuer T, Hainaut M, Peltier A, Toppet V. Prevalence of lipodystrophy in HIV-infected children: a cross-sectional study. Eur J Pediatr. 2007;166:13–21.
18. World Health Organization Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach. 2013. Available: http://www.who.int/hiv/pub/guidelines/arv2013/en/. Accessed 20 December 2014.
19. Amaya RA, Kozinetz CA, Mcmeans ANN, Schwarzwald H, Kline MW. Lipodystrophy syndrome in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2002;21:405-10.
20. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. Aids. 2004;18:1443–51.
21. Torres AMS nchez, Muniz RM, Madero R, Borque C, Garcı´a-Miguel MJ s. Prevalence of fat redistribution and metabolic disorders in human immunodeficiency virus-infected children. Eur J Pediatr. 2005;164:271–6.
22. Hartman K, Verweel G, de Groot R, Hartwig NG. Detection of lipoatrophy in human

immunodeficiency virus-1-infected children treated with highly active antiretroviral therapy. Pediatr Infect Dis J 2006;25:427–31.
23. Daniels SR, Greer FR. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122:198–208.

Cite this article as: Sanjeeva GN, Pavithra HB, Sukanya V, Shobha S, Govindaraj M. Prevalence and predictors for lipodystrophy syndrome among HIV infected children on anti-retroviral therapy. Int J Contemp Pediatr 2016;3:41-51.