DOI: 10.1590/S0037-86822011005000039

Article/Artigo

Nutritional assessment and lipid profile in HIV-infected children and adolescents treated with highly active antiretroviral therapy

Avaliação nutricional e do perfil lipídico em crianças e adolescentes infectadas pelo HIV tratadas com terapia antirretroviral de alta potência

Marina Hjertquist Tremeschin[1], Daniela Saes Sartorelli[2], Maria Célia Cervi[1], Bento Vidal de Moura Negrini[1], Roberta Garcia Salomão[1] and Jacqueline Pontes Monteiro[1]

ABSTRACT

Introduction: HIV-infected children and adolescents treated with highly active antiretroviral therapy (HAART) regimens that include a protease inhibitor (PI) can show significant improvements in clinical outcomes, nutritional status and quality of life. The study aimed to report nutritional and metabolic alterations for pediatric patients continuously exposed to HAART and for healthy controls for up to 1 year. **Methods:** Clinical, anthropometric, lipid profile and food intake data were collected prospectively over approximately 12-months for each patient. **Results:** Fifty-one individuals were studied, of these, 16 were healthy. After 12 months follow-up, HIV-positive individuals remained below the healthy control group parameters. No change was observed concerning food intake. Triglyceride serum levels were higher in patients using protease inhibitor at the onset of the study [PI groups: 114 (43 - 336), and 136 (63 - 271) *versus* control group: 54.5 (20 - 162); p = 0.003], but after twelve months follow-up, only the group using protease inhibitor for up to two months presented higher values [140 (73 - 273) *versus* 67.5 (33 - 117); p = 0.004]. HDL-cholesterol was lower in HIV-positive individuals [HIV-positive groups: 36 (27 - 58) and 36 (23 - 43); control 49.5 (34 - 69); p = 0.004]. **Conclusions:** HIV-infected children and adolescents treated with highly active antiretroviral therapy showed compromised nutritional parameters compared to a paired healthy control group. Individuals using protease inhibitor presented worse triglyceride serum levels compared to their healthy counterparts.

Keywords: Body composition. Dyslipidemia. Highly active antiretroviral therapy. HIV- positive children. Lipid profile. Nutritional status.

RESUMO

Introdução: Crianças e adolescentes infectadas pelo HIV e tratadas com terapia antirretroviral de alta potência (TAAP), que inclui inibidor de protease (IP) podem apresentar significante melhora clínica no estado nutricional e na qualidade de vida. O objetivo é relatar as alterações nutricionais e metabólicas em pacientes pediátricos expostos a TAAP e controles saudáveis durante 1 ano. **Métodos**: O perfil clínico, antropométrico e lipídico, bem como dados da ingestão alimentar foram coletados prospectivamente durante aproximadamente 12 meses. **Resultados**: Cinquenta e um indivíduos foram estudados. Dezesseis eram saudáveis. Após 12 meses de acompanhamento, indivíduos HIV-positivo permaneceram abaixo dos parâmetros do grupo controle saudável. Nenhuma mudança foi observada em relação à ingestão alimentar. Níveis séricos de triglicerídeos foram maiores em pacientes usando inibidor de protease no começo do estudo [IP grupo: 114 (43 - 336), e 136 (63 - 271) *versus* grupo controle: 54.5 (20 - 162); p = 0.003], porém após doze meses de acompanhamento, apenas o grupo que recebeu inibidor de protease por não mais do que dois meses apresentou maiores valores [140 (73 - 273) *versus* 67.5 (33 - 117); p = 0.004]. HDL-colesterol foi menor nos indivíduos HIV-positivos [grupo HIV-positivo: 36 (27 - 58) e 36 (23 - 43); controle 49.5 (34 - 69); p=0.004]. **Conclusões**: Crianças e adolescentes infectadas pelo HIV e tratadas com terapia antirretroviral de alta potência tiveram seus parâmetros nutricionais comprometidos quando comparados com o pareado grupo controle. Indivíduos usando inibidor de protease apresentaram piores níveis séricos de triglicerídeos quando comparados com os saudáveis.

Palavras-chaves: Composição corporal. Dislipidemia. Terapia antirretroviral de alta potência. Crianças HIV-positivas. Perfil lipídico. Estado nutricional.

1. Departamento de Puericultura e Pediatria, Disciplina de Nutrição e Metabolismo, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP. 2. Departamento de Medicina Social, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP.

Address to: Dra. Jacqueline Pontes Monteiro. Deptª Puericultura e Pediatria/FMRP/USP. Av. Bandeirantes 3900, Campus USP, 14049-900 Ribeirão Preto, SP, Brasil.

Phone: 55 16 3602-2806; Fax: 55 16 3602-2700

e-mail: jacque@fmrp.usp.br

Received in 03/09/2010

Accepted in 17/02/2011

INTRODUCTION

HIV-infected children and adolescents treated with highly active antiretroviral therapy (HAART) regimens that include a human immunodeficiency virus (HIV) protease inhibitor (PI) can exhibit significant improvements in clinical outcomes, nutritional status and quality of life[1]. HAART generally includes three or more antiretroviral agents used in combination. These drugs are selected from any of three well-recognized classes: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), or protease inhibitors (PI). However, HAART has also been associated with certain undesirable side effects, including gastrointestinal intolerance, high pill burden, mitochondrial toxicities and lipodystrophy.

The lipodystrophy syndrome has been clinically characterized by fat redistribution with an associated range of metabolic abnormalities[2]. The physical features include clinical evidence of at least one of the following: fat wasting (lipoatrophy) of the face, extremities, or buttocks and fat accumulation (lipohypertrophy) in the abdomen or over the dorsocervical spine. The metabolic features include at least one of the following: fasting hypertriglyceridemia and/or hypercholesterolemia, fasting C-peptide level elevation and evidence of abnormal glucose metabolism, including disorders ranging from abnormal fasting glucose levels to diabetes mellitus[2-4].

Although published studies have yielded valuable data on the characterization of lipodystrophy syndrome and metabolic changes and its association with PI-containing antiretroviral therapy among children and adolescents worldwide, very little data exist in Brazil concerning nutritional status, quality of life and lipid profile[5,6] after one year of HAART.

This study reports longitudinal clinical data for pediatric patients continuously exposed to HAART regimens and healthy controls groups for up to 1 year, and describes the nutritional and lipid profiles compared in both groups.

METHODS

Children attending the Pediatric Outpatient HIV Clinic at our center were studied. Every consecutive child who came to the teaching hospital of the School of Medicine of Ribeirão Preto, University of São Paulo, Brazil, over two years (2006 to 2007) was recruited and submitted to an interview to check their availability and inclusion criteria for participation. The institutional research ethics committee approved the research protocol and all the patients and their parents or legal guardians provided written informed consent to participate. The participants were divided into 4 groups of patients on the basis of the type of HAART being used: group 1, patients using nucleoside reverse transcriptase inhibitors or non-nucleoside reverse transcriptase inhibitors; group 2, patients using protease inhibitor (PI) for more than two months; group 3, patients using protease inhibitor for up to two months; and group 4, paired HIV-negative healthy children and adolescents.

The inclusion criteria were the ability to complete the anthropometry and absence of liver disease, chronic or acute pancreatitis, renal failure, or diarrhea that could interfere in the development of the child and their nutritional status. None of the patients was receiving vitamin supplementation or appetite stimulants and all were clinically stable.

The HIV-negative children and adolescents were selected from a Health Center in Ribeirão Preto, Brazil, and were paired for age and sex.

Data was collected prospectively over 12-months, for each patient. All HIV-positive patients received medical care according to the Pediatric Outpatient HIV Clinic protocol. Data obtained from medical records included age, sex, complete antiretroviral therapy history, Centers for Disease Control and Prevention classification, $CD4^+$ T lymphocyte counts and HIV-1 RNA levels.

Hypercholesterolemia was defined as a total fasting cholesterol level higher than 200mg/dl and a low-density lipoprotein cholesterol level higher than 130mg/dl. Hypertriglyceridemia was defined as a fasting triglyceride level above 140mg/dl[7]. Hyperlipidemia was defined as serum triglycerides ≥ 140mg/dl and/or serum cholesterol ≥ 200mg/dl.

Laboratory studies of total serum cholesterol and triglycerides were performed by commercial laboratories as part of routine clinical care. Lipid measurements were based on fasting blood samples.

The nutritional assessment of these children occurred at uniform intervals, generally every 6 months, as mandated by the service protocol of patients, and the data were recorded in a database (SPSS 15.0).

Weight and height were assessed according to the method described by Heymsfield et al[8] and determined by a dietitian who was trained to take all measurements. The reference data of the World Health Organization/National Center for Health Statistics/ Centers for Disease Control and Prevention[9] was used. For the estimation of fat-free mass and total body water, a bioelectrical impedance technique (BIA) was applied at the same time the weight was measured[10]. The midarm circumference, waist circumference, subscapular skinfold and triceps skinfold were also measured to reflect lean body mass and fat[11]. Body mass index (BMI) was calculated by the standard formula using height and weight and plotted on CDC BMI-for-age curves for 2 to 20 years of age for girls and boys[12]. Weight, height and BMI values were converted to age- and sex-adjusted Z scores using EPI INFO® software program and individuals < - 2 standard deviation for weight for age and or height for age were considered malnourished.

Usual dietary intake was assessed by an adapted semi quantitative food-frequency questionnaire. Individuals were asked to report which foods they had eaten during the preceding three months based on a fixed list. The standard portion sizes were presented to the respondent, who was asked how many times the portion size was eaten. The standard portion sizes for each food were those reported in a previous study[13,14]. Respondents were asked to report their consumption as daily, weekly, monthly and rarely. Nutrient intakes associated with each pattern of food consumption were determined according to Dietsys software®.

Quality of life was assessed by *Autoquestionnaire de qualité de vie enfant imagé* (AUQEI questionnaire)[15] which was validated by Assumpção Jr et al[16]. It is a generic tool applied to children aged between 4 and 12 years-old, based on children's subjective perspective of satisfaction regarding function, family, entertainment and autonomy. Values above 48 are indicative of good quality of life.

Statistical analyses

Continuous variables with normal distribution were expressed as mean ± standard deviation; in this case, comparison across groups was performed by analysis of variance (Post Hoc) and the non-paired t test. The nonparametric Kruskal-Wallis test was used to compare variables with non-normal distribution, which were expressed as median and range. The Wilcoxon test was used to compare longitudinal variables; this tests whether the distribution of two paired variables in two related samples is the same and takes into account the magnitude of the differences between two paired variables. The X^2 test or Fisher exact test was used to compare frequency distributions across groups. Linear regression analysis was used to determine whether alterations in weight and body composition were associated with changes in quality of life, since most commonly, linear regression refers to a model in which the conditional mean of y given the value of X is an affine function of X. Analysis of covariance (ANCOVA) was also applied for energy intake in two moments, adjusted for age and weight, to test the hypothesis that age and weight could interfere in the results of energy intake. $P < 0.05$ was considered statistically significant.

RESULTS

Fifty-one children and adolescents agreed to participate and met the criteria for inclusion in this study. They were distributed into four groups: group 1 (n = 17), group 2 (n = 9), group 3 (n = 9) and group 4 (n = 16). Stavudine, as part of a backbone NRTI regimen, and PI use, have both been associated with lipodystrophy syndrome[17]; however, in the present study, no statistical difference was verified in the proportion of individuals receiving stavudine among the groups (at the onset of the study: G1 17.6%, G2 33.3%, G3 33.3% p = 0.57; after twelve months: G1 23.5%, G2 22.2%, G3 33.3% p = 0.82).

At the onset of the study, the median duration of PI therapy was 27 months for group 2 and 1 month for group 3, and the median duration of prior NRTI or NNRTI therapy was 86 and 84 months, respectively. No significant differences between groups 1, 2 and 3 with respect to viral loads were noted at any time point, but CD4 cell counts and the CD4/CD8 ratio were worse for group 3 at the onset

of the study compared to group 2. Eight (47%) out of 17 patients in group 1 had prior AIDS, whereas five (55%) out of nine patients in group 2 and seven (78%) out of nine patients in group 3 had prior AIDS; this difference was not statistically significant ($p > 0.05$). No significant differences between any of the groups with respect to age and sex were observed (54.9% male *versus* 45.1% female, $p = 0.32$). Quality of life was similar between groups at all time points, according to the AUQEI questionnaire. There were also no statistical differences between groups 1, 2 and 3 concerning HIV infection classification at any time point. The demographic and clinical data for all patients are presented in **Tables 1** and **2**.

Triglycerides serum levels were higher in patients using protease inhibitor compared to healthy controls at the onset of the study, but after twelve months follow-up, only group 3 had higher values and HDL cholesterol serum levels were lower in group 1 and 3 compared to group 4 (**Table 1**). In spite of that there was no statistical differences between the groups concerning patients who exhibited hyperlipidemia: 12% (2) of patients in group 1, 33.3% (3) of patients in group 2, 44.4% (4) of patients in group 3, exhibited hyperlipidemia at any time point; 18.7% (3) and 6.2% (1) of patients exhibited hyperlipidemia at the study onset and after twelve months follow-up, respectively, for group 4.

At the beginning of the study, healthy controls subjects presented greater weight, height/age adequacy, Z scores for weight and height and triceps and subscapular skinfold thickness adequacy compared to HIV-positive individuals. Concerning body mass index adequacy, groups using protease inhibitor presented lower values compared to groups 1 and 4, but with statistically significant results only for group 2 (**Table 2**). After twelve months follow-up, group 2 showed the worst values for almost all the anthropometric parameters and group 4, the best values compared to HIV-positive individuals (**Table 2**).

At the onset of the study, malnourished individuals constituted 5.9% of group 1, 44.4% of group 2, 33.3% of group 3 and 0% of group 4 ($p = 0.007$). Individuals in PI groups presented greater malnourishment than individuals in group 4 ($p < 0.05$); and group 2 presented worse values compared to group 1 ($p = 0.03$) and group 4 ($p = 0.009$). After twelve months follow-up, only group 2 showed an increase in the number of malnourished individuals (55.5%). In group 1, overweight individuals constituted 11.8% at the onset of the study, while overweight individuals constituted 6.2% of group 4 at the end of the study. At the onset of the study, obese individuals constituted 5.9% and 12.5% of groups 1 and 4, respectively. A decrease in the rate of obesity occurred in group 4 by the end of the study (6.2%).

Bioelectrical impedance analyses were unable to detect any differences between the groups at any point during the study (**Table 3**).

Energy and macronutrient intakes were similar between the groups at all time points during the study, but a higher lipid intake (% of energy intake) occurred compared to the recommended intake in all groups. The mean energy intake at the onset of the study and at the end of study was, respectively, 2,413kcal (1,586 - 5,806) and 2,148kcal (1,289 - 4,166). The mean percentage of lipid calories at the onset and end of the study was, respectively, 37.8% (28.6 - 49.2) and 38.5% (28 - 48.6). Age and weight did not interfere with the energy intake results, according to ANCOVA analyses (at the onset: age $p = 0.39$, weight $p = 0.72$; at the end: age $p = 0.94$, weight $p = 0.49$).

An increase in CD4 cell count occurred in group 1 after twelve months follow-up ($p = 0.044$). Clinical improvement was not observed in groups 2 and 3 ($p > 0.05$ for all parameters).

An increase in weight ($p = 0.002$), height ($p = 0.001$), waist circumference ($p = 0.008$), triceps skinfold thickness ($p = 0.036$), subscapular skinfold thickness ($p = 0.003$), mid-arm-muscle circumference ($p = 0.006$), height/age ratio ($p = 0.018$) and lean body mass ($p = 0.001$) occurred in group 1 after twelve months follow-up.

TABLE 1 - Clinical and demographic data of children and adolescents distributed according to type and time of antiretroviral therapy (ART) in the beginning of the study and after twelve months follow-up.

Parameters	Group 1(n = 17)		Group 2(n = 9)		Group 3(n = 9)		Group 4(n = 16)		p-value	
	A	B	A	B	A	B	A	B	A	B
Age (months)	116 (82-180)	130 (92-192)	140 (73-187)	151 (86-202)	126 (60-195)	136 (74-208)	120.5 (48-192)	135 (60-204)	0.599	0.634
Viral load (cells/mm^3)	2,878 (49-2466)	2,399.5 (49-48,477)	556 (49-38,929)	49 (49-144,362)	12,775 (232-10,999)	3,904 (49-91,438)	-	-	0.210	0.290
CD4/CD8 (cells/mm^3)	0.425 (0.19-1.18)	0.53 (0.11-1.06)	0.72 (0.15-1.02)	0.63 (0.17-1.08)	0.33 (0.04-0.41)	0.37 (0.08-1.11)	-	-	0.019‡	0.217
CD4 (cells/mm^3)	574.5 (17-816)	730 (230-1,089)	681 (112-1,032)	821 (68-1,083)	396 (13-654)	406 (103-1,584)	-	-	0.047‡	0.530
CD8 (cells/mm^3)	1,466 (352-2,497)	1,262 (576-2,905)	936 (349-4,249)	1,316 (1,004-3,000)	1,182 (345-3,035)	1,105 (637-3,503)	-	-	0.314	0.782
Time of ATR (months)	102 (12-143)	115 (24-156)	86 (70-156)	100 (83-171)	84 (0.13-168)	93 (9-181)	-	-	0.613	0.575
Time of PI (months)	-	-	27 (5-86)	39 (20-100)	1 (0.13-2)	11 (9-14)	-	-	0.000‡	0.000*
Total cholesterol (mg/dl)	125 (100-202)	131 (91-209)	161 (129-236)	165 (110-215)	166 (103-213)	156.5 (107-202)	148.5 (101-200)	154 (95-203)	0.059	0.169
Triglycerides (mg/dl)	94 (40-197)	79 (55-286)	114 (43-336)	96 (42-216)	136 (63-271)	140 (73-273)	54.5 (20-162)	67.5 (33-117)	0.003**	0.004***
HDL cholesterol (mg/dl)	39 (21-59)	36 (27-58)	32 (26-47)	44 (19-54)	34 (21-52)	36 (23-43)	42 (32-68)	49.5 (34-69)	0.518	0.004****
LDL cholesterol (mg/dl)	69 (57-146)	74.5 (42-127)	74 (55-96)	100 (54-140)	109 (60-133)	100 (55-124)	85 (48-137)	83 (31-148)	0.302	0.219
AUQEI (counts)	58 (46-68)	56 (45-71)	56 (39-62)	54 (45-73)	54 (43-62)	57 (47-66)	53.5 (40-66)	54 (44-65)	0.280	0.564

Column A: dates at the onset of the study, column B: dates after twelve months follow-up, CD4: Lymphocyte T CD4 count, CD8: lymphocyte T CD8 count, serum HDL: high density lipoprotein, serum LDL: low density lipoprotein, AUQEI: Quality of life questionnaire, ‡ group 2 bigger than 3, *group 2 different from group 3, **group 4 different from groups 2 and 3, ***group 3 different from group 4, ****group 4 different from groups 1 and 3.

ATR: antiretroviral therapy; PI: protease inhibitor.

TABLE 2 - Anthropometric data of children and adolescents distributed according to type and time of antiretroviral therapy (ART) at the beginning of the study and after twelve months follow-up.

Parameters	Group 1(n = 17)		Group 2(n = 9)		Group 3(n = 9)		Group 4(n = 16)		p-value	
	A	B	A	B	A	B	A	B	A	B
Weight (Kg)	31.3 (19.6–49.8)	39 (21–55)	29.7 (14.5–45.6)	35.2 (16.6–51)	25 (16.6–50.9)	27.9 (20–53.1)	36.75 (16.9–73.8)	42.4 (9–70.3)	0.047*	0.531
Z score weight	-0.41 ±1.16	-0.51 ±1.21	-2.0±1.38	-1.97±1.32	-1.60±1.11	-1.35±0.84	0.19±0.91	0.2±0.95	0.001**	0.001**
Height (cm)	132 (114.5–166)	142.5 (118.5–170)	137 (105–159)	145.5 (110.5–163)	127.5 (105.5–158)	134 (112-163.5)	142.5 (104.5-164.5)	149.3 (111.5-66.5)	0.550	0.587
Z score height	-0.66 ±1.08	-0.66±0.94	- 1.36±0.93	-1.19±0.88	-1.6±1.1	-1.45±1.1	0.74±1.1	0.57±1.1	0.000**	0.000**
Body mass index (% of adequacy)	101 (80.22-141.46)	99 (80–148)	91.43 (74.70–99.87)	91 (67–100)	91.05 (85.6–101.5)	97 (82–109)	104.06 (79.8–151.5)	101 (79–156)	0.003†	0.036†
Waist circumference (cm)	61.5 (49–77)	65 (52–77)	57 (46.5–68.5)	63 (48–69)	61 (52–73.1)	60 (54.4–71.3)	62 (48.5–80)	62.75 (48.6–75.8)	0.509	0.516
Triceps skinfold thickness (% of adequacy)	68 (33.19–126.6)	77 (44–205)	45.49 (32.08–79.9)	60 (42–103)	60.41 (34.48–123)	84 (59.2–121)	121.73 (72.8-173.22)	106 (75–202)	0.000*	0.002††
Subscapular skinfold thickness (% of adequacy)	73.68 (33.33–250)	108 (71–250)	55.49 (38.46–125)	86 (56–133)	87.5 (41.6–107.69)	88 (80–167)	152.77 (57.1–400)	142 (85–367)	0.000**	0.001****
Mid-arm-muscle-circumference (% of adequacy)	100.5 (86.6–114.4)	96.1 (83–119)	94.4 (78.2–111.48)	91.4 (67.27-108.84)	89.7 (75.38–99.6)	86.76 (78.2-102.6)	94.24 (54.39–143.3)	100.3 (79.76–133)	0.125	0.006****
Height/age (%)	98.76 (92.4–107.0)	98 (89–104)	94.9 (88.1–101.57)	94 (89–102)	95.04 (87.46-98.55)	96 (86–102)	105.33 (95–115.34)	102 (95–114)	0.000**	0.001**
Weight/height (%)	99.0 (85.59-149.18)	100 (84–147)	91.58 (78.2–99.16)	91 (73–99)	97 (87.9–108.3)	99 (85–112)	91.53 (82.5–135)	98 (85–140)	0.093	0.033***

Column A: dates at the onset of the study, Column B: dates after twelve months follow-up, †group 2 different from groups 1 and 4, ††group 4 different from groups 1 and 2, *The four groups are statistically different, **group 4 different from groups 1, 2 and 3, ***group 2 different from group 1, ****group 4 different from groups 2 and 3.

An increase in weight (p = 0.008), height (p = 0.008), triceps skinfold thickness (p = 0.035), subscapular skinfold thickness (p = 0.034) and lean body mass (p = 0.008) also occurred in group 2 after twelve months follow-up.

Group 3 showed an increase in weight (p = 0.008), height (p = 0.008), subscapular skinfold thickness (p = 0.034) and lean body mass (p = 0.017) after twelve months follow-up.

Group 4 also showed progress in nutritional status, with an increase in weight (p = 0.003), height (p = 0.001), height/age index (p = 0.008), Z score for height (p = 0.01), body mass index (p = 0.032), mid-arm-muscle circumference (p = 0.008) and lean body mass (p = 0.002) after twelve months follow-up.

No differences were observed concerning food intake after twelve months follow-up in groups 1, 2 and 3 (p > 0.05 for all parameters). Group 4 presented a decrease in food intake in relation to energy (p = 0.020), protein (p = 0.030) and carbohydrate (p = 0.044).

After twelve months follow-up, no change was observed concerning the lipid profiles in all groups (p > 0.05 for all parameters), except for an increase in HDL cholesterol in group 4.

Linear regression analysis showed that an increase in fat mass in HIV-positive individuals is associated with quality of life (p = 0.026; adjusted for age and sex p = 0.042; adjusted for time using protease inhibitor PI p = 0.047; adjusted for time in antiretroviral therapy p = 0.034) (**Table 4**). No other variable was statistically associated with quality of life.

TABLE 3 - Bioelectrical impedance analyses of children and adolescents distributed according to type and time of antiretroviral therapy (ART) at the beginning of the study and after twelve months follow-up.

Parameters	Group 1(n = 17)	Group 2(n = 9)	Group 3(n = 9)	Group 4(n = 16)	p-value
At the beginningof study					
lean body mass (Kg)	24.1 (14.3–39.3)	24.2 (12.6–34.5)	20.1 (12.7–36.4)	28 (14.2–49.3)	0.544
fat mass (Kg)	6.6 (3.1–16.3)	5.3 (1.9–11.1)	4.9 (3.8–15.1)	6.9 (1.8–24.5)	0.444
body cell mass (Kg)	11.95 (7.6–19.3)	11.1 (6.4–16.4)	9.7 (6.5–18.2)	13.95 (7–24.1)	0.460
total body water (Liters)	18.2 (10.6–28.8)	17.7 (10.2–25.1)	15.2 (9.6–27.3)	20.45 (11.5–34.9)	0.431
After 12 months of study					
lean body mass (Kg)	26.6 (15.7–44.9)	28.4 (14–35.9)	23 (15.5–46.1)	32.55 (15.5–48)	0.636
fat mass (Kg)	7.1 (3.9–13.7)	4.9 (2.6–15.1)	5.75 (3.2–13.3)	7.05(2.7–22.9)	0.588
body cell mass (Kg)	13 (8.2–22.8)	13.1 (7.1–17.5)	11.35 (7.9–23.9)	15.6 (7.9–25.8)	0.489
total body water (Liters)	20 (11–33)	21(11–25.3)	17.15 (11.9–34.2)	23.9 (12.2–36)	0.608

TABLE 4 - Regression coefficients β 1 (95% confidence interval) for the difference in quality of life according to fat mass alteration in HIV positive children after twelve months follow-up.

	Alteration in quality of life		
Difference in fat mass	β	CI 95%	p
Model 1*	0.406	0.195 - 2.848	0.026
Model 2**	0.410	0.059 - 3.018	0.042
Model 3 ***	0.041	0.025 - 3.049	0.047
Model 4 †	0.433	0.129 - 3.104	0.034

*Model 1: crude analysis, **Model 2: adjusted for age and sex, ***Model 3: model 2 + Time using protease inhibitor, †Model 4: model 2 + time using antiretroviral therapy.

DISCUSSION

Analysis of the data obtained showed that clinically stable HIV-positive children and adolescents still present greater compromise regarding nutritional status compared to healthy controls paired for age, sex and quality of life, in the HAART era. The most compromised were the individuals using protease inhibitor. Despite adequate nutritional improvement after twelve months follow-up, HIV-positive individuals remained below the healthy control group parameters. An increase in fat mass in HIV-positive individuals improves quality of life predictions. No change was observed concerning food intake and only the group using NRTI and/or NNRTI showed a statistically significant increase in CD4 cell count after twelve months follow-up. Triglyceride serum levels were higher in patients using protease inhibitor compared to healthy controls at the onset of the study, but after twelve months follow-up, only the group using PI for up to two months presented triglyceride serum levels higher than healthy controls, while HDL cholesterol serum levels were lower in groups 1 and 3 compared to group 4. A proportion of hyperlipidemia occurred in individuals using protease inhibitor, though this was not statistically significant. Despite the small sample size, the results obtained were similar to those reported by Aldrovandi et al in a larger cross-sectional multicenter study in the United States[18].

Despite worse nutritional status compared to controls, HIV-positive individuals presented an increase in weight, height, fat mass and fat-free mass after twelve months follow-up. Longitudinal follow-up monitoring HIV-positive children with HAART also showed an increase in lean mass[19]. The study by Verweel et al indicates that virology respondent children with HIV-infection show an increase in height and weight following the initiation of HAART[20].

It seems that HAART had a positive effect on height and weight in the children and adolescents with HIV-infection in this study, though not sufficient to achieve healthy control values. This effect was sustained for at least 12 months (48 weeks) and can last up to 96 weeks according to Verweel et al[20]. These sustained effects on fat

mass may positively influence the child's quality of life, as shown by the present results and will predictably contribute to improved prognosis. The positive effect of HAART on nutritional parameters has been extensively reported[21-25].

Group 4 showed the best values for z scores compared to the HIV-positive groups. After twelve months follow-up, only group 4 showed an increase in the height-for-age Z score. In contrast, group 2 presented more malnourished individuals compared to groups 1 and 4 at the onset of the study. After twelve months follow-up, only group 2 presented an increase in the number of malnourished individuals, which can be attributed to poorer clinical evolution in one patient. Similar results were reported by Verweel et al[20].

In the present study, triceps and subscapular skinfold thickness and mid-arm muscle circumference showed no detectable statistical differences, comparing individuals using NRT/NNRT and PIs, and fat redistribution was not an important feature in these individuals, corroborating the results obtained by Santos et al[26]. Melvin et al[27] suggested that dyslipidemia occurs prior to body changes in the lipodystrophy syndrome, especially in individuals in Tanner stages 1 and 2. This study did not analyze Tanner classification stage, but the median age of the children was compatible with stages 1 and 2. Metabolic abnormalities and fat redistribution are more likely to occur in post-pubertal children, especially those who are receiving protease inhibitor treatment[28-30].

The period of follow-up and age were statistically similar between the groups, but might have affected the results, since the control group presented 14.5 months of follow-up compared to 14, 11 and 10 months for groups 1, 2 and 3, respectively. Since statistically significant differences for weight, height, triceps and subscapular skinfold thickness were verified at the onset of the study, this shows that HIV-positive individuals continue to present poorer nutritional parameters than the healthy control group.

In the present study, HIV-infected individuals showed worse nutritional evolution compared to healthy controls, despite similar food intake. HIV-1-infected children in developed countries present similar birth weights compared to non-infected groups, but quickly diverge in both weight and height within the first few months of life[31]. This fact is difficult to explain because in children who fail to gain weight, identifying a single factor, which, when corrected, results in normal growth in the course of HIV infection is uncommon. Evidence of significantly less lean body mass (as assessed by midarm circumference and triceps skinfold thickness) has been verified among very young HIV-infected children compared to control children of similar age[32]. At present, the pathogenesis of weight loss or growth failure in HIV infection is largely speculative. Many factors, including poor oral intake, malabsorption, and hypermetabolism may be involved[33]. Disturbances in the growth hormone insulin-like growth factor axis that have been described in HIV infection could also play a role in the growth and body composition abnormalities observed here[34].

The fact that there were more malnourished individuals among HIV-infected children compared to controls in the present study suggests that the nutritional characteristics of Brazilian HIV-infected children may not become similar to their uninfected counterparts as they become healthier with HAART, a fact that is in disagreement with the results of some studies[20,35].

Many reports regarding clinically evaluated lipodystrophy syndrome suggest that peripheral atrophy is often accompanied by an increase in central obesity in HIV-infected individuals using HAART. In the present study, waist circumference does not permit precise characterization of any increase in central obesity in HIV-positive individuals. It is possible that waist circumference cannot easily distinguish changes in fat from lean and may not be suitable for this purpose in children.

In contrast to the increase in the body mass index (BMI) in adults on HAART, BMI did not increase in all children effectively treated with HAART after twelve months follow-up in the present study. These result corroborates similar findings reported by Verweel et al[20]. It is possible that BMI increases more in children with an advanced stage of infection and poor nutritional status at baseline[36].

Bioelectrical impedance was unable to detect any differences between the groups. BIA has been used to assess body composition in HIV-infected children, but interpretation of the results is difficult due to the lack of standards for children[37-39]. The accuracy of bioelectric impedance may vary not only in relation to the equations used, but by sex and percentage of body fat[40]. In addition, BIA measures only whole-body fat and lean body mass, thus it cannot diagnose abnormalities in fat redistribution and may be inaccurate in the setting of lipodystrophy[41].

Food intake was similar between the groups and no changes were observed after twelve months follow-up, except for a decrease in energy, protein and carbohydrate intake in the control group. Despite this fact, a higher proportion of lipid intake than carbohydrate was verified in all groups.

Decreased nutrient intake is not encountered in children with HIV infection. The dietary intake among children with HIV infection is reported to be equal to or greater than those in non-infected children[42] and additional variables, such as metabolic abnormalities, could be involved in lipodystrophy syndrome[43].

Nutritional concerns in HIV-infected children have evolved, from wasting to obesity and insulin resistance. Excessive caloric intake and a shift in dietary composition toward lipids suggest that continued dietary monitoring in HIV-infected children is important to avoid increased risk of cardiovascular disease.

The present study showed that an increase in fat mass is associated with better quality of life. The AUQEI questionnaire seemed to be appropriate in pediatric and adolescent populations with HIV[44,45]. Preliminary evidence in pediatric HIV-1 research suggests that combination antiretroviral therapies have a positive effect on mean weight, height, growth velocity, appetite, and well-being[21,23,45,46].

Studies on the tolerability and efficacy of PI containing regimens have mentioned alterations in serum lipids ranging from dyslipidemia in 20% to 50% of children on single PI to > 90% on dual PI containing regimens[45,47-49]. The present data showed a lower proportion of hyperlipidemia compared to the study by Taylor et al[50], who reported 58.3% and the study by Werner et al, who verified 88.3%[51]. In addition, the proportion of hyperlipidemia among HIV-positive individuals was similar to the healthy control group, suggesting that the HAART regimen alone could not be associated with an increased risk of dyslipidemia. Taylor et al[50] also confirmed that some patients using protease inhibitor may not develop dyslipidemia.

Genetic, pharmacokinetic, virological and/or immunological factors may protect these children after longer treatment duration, the differences could be associated with drug dosing and may be more pronounced in children with higher PI levels[52].

The study failed to detect higher dyslipidemia in the group using PIs, and the the occurrence of hypertrygliceridemia among HIV-positive individuals from groups 2 and 3 could have preceded the use of protease inhibitor[53]. Although initial reports implicate protease inhibitors, more recent studies have suggested that nucleoside analogues could play a role in the development of lipodystrophy syndrome, including dyslipidemia[2,54].

The study also failed to detect any association between PI duration and dyslipidemia. Cheseaux et al[55] and Krause et al also reported no significant increase even after 24 and 30 months of antiretroviral therapy[56]. The stabilizing relation with extended durations of PI usage may explain why most cross-sectional studies have failed to detect this association.

The study has limitations. The assessment of the physical abnormalities of lipodystrophy was not possible, because assessment of the phenotypic manifestations of lipodystrophy with physical examinations is inherently subjective and may differ among different providers. In addition, sex differences in growth and body composition in children in response to infection have been described[39].

The study design does not permit any conclusions regarding whether PI alone may be associated with dyslipidemia or whether a potentiating effect occurs when combining PI with nucleoside inhibitors. Processes that lead to changes in metabolic parameters are likely to be multifactor, and dyslipidemia occurs in patients who have never received PI[57-59]. Furthermore, the fact that patients were not randomized to PI therapy and that the study was based on a small number of HIV-infected children must be taken into account.

Since body composition shows a wide variation in growing children according to age, sex and pubertal status, inter-individual variability was minimized by comparing each HIV-infected patient with a matched healthy control. In addition, each child was used as his or her own control by capturing data after twelve months follow-up.

Further studies, mainly longitudinal cohort studies, are required to precisely describe the time course of body-composition changes in HIV-infected children and, because they will probably survive for longer periods in adulthood, the long-term risks for the development of premature cardiovascular disease attributable to prolonged dyslipidemia associated with antiretroviral therapy warrant additional studies.

ACKNOWLEDGMENTS

The authors would like to state that the coauthors have contributed to the conception and design of the study, generation, collection, assembly, analysis and interpretation of data, and to the revision and final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FINANCIAL SUPPORT

UNESCO, Ministério da Saúde - Secretaria de Vigilância em Saúde - Departamento de DST, Aids e Hepatites Virais - PN-DST/AIDS; Unidade de Pesquisa e Desenvolvimento Tecnológico.

REFERENCES

1. Gortmaker S, Hughes M, Cervia J, Brady M, Johnson G, Seage G, et al. Effect of Combination Therapy Including Protease Inhibitors on Mortality Among Children and Adolescents Infected with HIV-1. N Engl J Med 2001; 345:1522-1528.
2. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. Lancet 1999; 353:2093-2099.
3. Mauss S. HIV-associated lipodystrophy syndrome. AIDS 2000; 14:S197-S207.
4. Yanovski JA, Miller KD, Kino T, Friedman TC, Chrousos GP, Tsigos C, et al. Endocrine And Metabolic Evaluation Of Human Immunodeficiency Virus-Infected Patients With Evidence Of Protease Inhibitor-Associated Lipodystrophy. J Clin Endocrinol Metab 1999; 84:1925-1931.
5. Battistini TRB, Sarni RO, Souza FIS, Pitta TS, Fernandes AP, Hix S, et al. Lipodystrophy, lipid profile changes, and low serum retinol and carotenoid levels in children and adolescents with acquired immunodeficiency syndrome. Nutr 2010; 26: 612-616.
6. Sarni ROS, de Souza FIS, Battistini TRB, Pitta TS, Fernandes AP, Tardini PC, et al. Lipodystrophy in children and adolescents with acquired immunodeficiency syndrome and its relationship with the antiretroviral therapy employed. J Pediatr. 2009; 85:329-334.
7. National Institute of Health. National Cholesterol Education Program. ATP III Guidelines At-A-Glance Quick Desk Reference. Bethesda, MD: National Heart, Lung, and Blood Institute; 2001.
8. Heymsfield SB, Tighe A, Wang ZM. Nutritional assessment by anthropometric and biochemical methods. *In*: Shils ME, Olson JA, Shike M, editors. Modern Nutrition in Health and Disease. 8th ed. Philadelphia: Lea & Febiger; 1994. p. 812.
9. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Center For Disease Control And Prevention 2000 Growth Charts For The United States: Improvements To The 1977 National Center For Health Statistics Version. Pediatrics 2002; 109:45-60.
10. Kushner RF, Schoeller DA. Estimation of total body water by bioelectrical impedance analysis. Am J Clin Nutr 1986; 44:417-424.
11. Heller LS. Nutrition support for children with HIV/AIDS. J Am Diet Assoc 1997; 97:473-474.
12. Center for Disease Control and Prevention. CDC advance data nº 314. [Cited 200 December 4]. Available from: www.cdc.gov/.
13. Cardoso MA, Stocco PR. Desenvolvimento de um questionário quantitativo de frequência alimentar em imigrantes japoneses e seus descendentes residentes em São Paulo, Brasil. Cad Saude Publica 2000; 16:107-114.
14. Cardoso MA, Kida AA, Tomita LY, Stocco PR. Reproducibility and validity of a food frequency questionnaire among women of Japanese ancestry living in Brazil. Nut Res 2001; 21:725-733.
15. Manificat S, Dazord A. Evaluation de la Qualité de Vie de l'enfant: validation d'un questionaire, premier résultats. Neuropsichiatr Enfance Adolesc 1997; 45:106-114.
16. Assumpção Jr FB, Kuczynski E, Sprovieri MH, Aranha EMG. Escala de avaliação de qualidade de vida (AUQEI - Autoquestionnaire qualité de Vie Enfant Imagé): Validade e confiabilidade de uma escala para qualidade de vida em crianças de 4 a 12 anos). Arq Neuropsiquiatr 2000; 58:119-127.
17. Apardi SM, Cuff A, Horlick M, Wan 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 Aquir Immune Defic Syndr 2001; 27:30-34.
18. Aldrovandi GM, Lindsey JC, Jacobson DL, Zadzilka A, Sheeran E, Moye J, et al. Morphologic and Metabolic Abnormalities in Vertically HIV-infected Children and Youth. AIDS 2009; 23:661-672.
19. 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. JAIDS 2003; 32:482-489.
20. Verweel G, Rossum AMC, Hartwig NG, Wolfs TFW, Scherpbier HJ, Groot R. Treatment with highly active antiretroviral therapy in human immunodeficiency

virus type 1-infected children is associated with a sustained effect on growth. Pediatrics 2002; 109:25.

21. Darasteanu J, Petra S, Luminos M, Mardarescu M. Comparison of two antiretroviral triple combinations including the inhibitors in children infected with HIV/AIDS. Paper presented at the 3trd International Conference on Nutrition and HIV infection. 1999; Cannes, France.
22. Mueller BU, Sleasman J, Nelson RP, Smith S, Deutsch PJ, Ju W, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. Pediatrics 1998; 102:101-109.
23. Dollfus C, Vaudre G, Clairon C, Courpotin C. Height and weight growth in HIV infected children treated with antiretroviral combination therapy including protease inhibitors. Paper present at the third international conference on nutrition and HIV infection. 1999; Cannes, France.
24. Chantry C, Hughes M, Alvero C, Cervia J, Hodge J, Borum P, et al. Insulin-Like Growth Factor-1 and Lean Body Mass in HIV-Infected Children. JAIDS 2008; 48:437-443.
25. Miller TL, Mawn BE, Orav EJ, Wilk D, Weinberg GA, Nicchitta J, et al. The effect of protease inhibitor therapy on growth and body composition in human immunodeficiency virus type 1-infected children. Pediatrics 2001; 107:1-6.
26. Santos FS, Rangel LGG, Saucedo GP, Rosales GV, Novales MGM. Hypertriglyceridemia and Hypercholesterolemia in Human Immunodeficiency Virus-1-Infected Children Treated with Protease Inhibitors. Arch Med Res 2006; 37:129-132.
27. Melvin AJ, Lennon S, Mohan KM, Purnell JQ. Metabolic abnormalities in HIV type 1-infected children treated and not treated with protease inhibitors. AIDS Res Hum Retroviruses 2001; 17:1117-1123.
28. Beregszaszi M, Dollfus C, Levine M, Faye M, Deghmoun S, Bellal N, et al. Longitudinal evaluation ad risk factors of lipodystrophy and associated metabolic changes in HIV-infected children. J Acquir Immune Defic Syndr 2005; 40:161-168.
29. Carter RJ, Wiener J, Abrams EJ, Farley J, Nesheim S, Palumbo P, et al. Dyslipidemia among perinatally HIV-infected children enrolled in PACTS-HOPE cohort, 1999-2004: A longitudinal analysis. J Acquir Immune Defic Syndr 2006; 41:453-460.
30. Chantry CJ, Hughes MD, Alvero C, Cervia JS, Meyer WA, Hodge J, et al. Lipid and glucose alteration in HIV-infected children beginning or changing antiretroviral therapy. Pediatrics 2008; 122:129-138.
31. Moye J, Richk C, Kalish LA, Sheon AR, Diaz C, Cooper ER, et al. Natural history of somatic growth in infants born to women infected by human immunodeficiency virus. Woman and infants transmission study group. J Pediatr 1996; 128:58-69.
32. Miller TL, Evans SJ, Orav EJ, Morris V, Mcintosh K, Winter HS. Growth and body composition in children infected with the human immunodeficiency virus -1. Am J Clin Nutr 1993; 7:588-592.
33. Fontana M, Zuin G, Plebani A, Bastoni K, Visconti G, Principi N. Body composition in HIV-infected children: relations with disease progression and survival. Am J Clin Nutr 1999; 69:1282-1286.
34. Frost RA, Lang CH, Celato MC. Growth hormone/insulin-like growth factor axis in human immunodeficiency virus-associated disease. Endocrinol 1997; 7:23-31.
35. Ferrando SJ, Rabkin JG, Lin S, Mcelhiney M. Increase in body cell mass and decrease in wasting are associated with increasing potency of anti-retroviral therapy for HIV infection. AIDS Patient Care 2005; 19:216-223.
36. Beau JP, Imboua-Coulibaly L. Body mass index: a prognosis factor among HIV seropositive malnourished children. J Trop Ped 1997; 43:301-303.
37. American Dietetic Association. HIV/AIDS medical nutrition therapy protocol: medical nutrition therapy across the continuum of care. Chicago, IL: American Dietetic Association; 1998.
38. Apardi SM, Cuff PA, Kotler DP, Wang J, Bamji M, Lnge M, et al. Growth velocity, fat-free mass and energy intake are inversely related to viral load in HIV-infected children. J Nutr 2000; 130:2498-2502.
39. Parraga IM, Assis AMO, Prado MS. Gender differences in growth of school-aged children with schistosomiasis and geohelminth infection. Am J Trop Med Hyg 1996; 55:150-156.
40. Corcoran C, Anderson EJ, Burrows B, Stanley T, Walsh M, Poulos AM, et al. Comparison of total body potassium with other techniques for measuring lean body mass in men and women with AIDS wasting. Am J Clin Nutr 2000; 72:1053-1058.
41. Knox TA, Zafonte-Sanders M, Fields-Gardner C, Moen K, Johansen D, Paton N. Assessment of nutritional status, body composition, and human immunodeficiency virus-associated morphologic changes. Clin Infect Dis 2003; 36:S63-S68.
42. Miller T, Evans S, Orav J. Growth and nutrient intake in HIV-infected children. Clin Res 1992; 40:380.
43. Henderson RA, Saavedra JM, Perman JA, Hutton N, Livingston RA, Yolken RH. Effect of enteral tube feeding on growth of children with symptomatic human immunodeficiency virus infection. J Pediatr Gastroenterol Nutr 1994; 18:429-434.
44. Garvie PA, Lawford J, Banet MS, West RL. Quality of life measurement in paediatric and adolescent populations with HIV: a review of the literature. Child Care Health Dev 2009; 35:440-453.
45. Thoni GJ, Lalande M, Bachelard G, Vidal P, Manificat S, Fedou C, et al. Quality of life in HIV-infected children and adolescents under higly active antiretroviral therapy: change over time, effets of age and familial context. Arch Pediatr 2006; 13:130-139.
46. Mueller BU, Nelson RP, Sleasman J, Zuckerman J, Heath-Chiozzi M, Steinberg SM, et al. A Phase I/II Study Of The Protease Inhibitor Ritonavir In Children With Human Immunodeficiency Virus Infection. Pediatrics 1998; 101:335-343.
47. Duiculescu D, Ball E, Mihai E. Influence of anti-retroviral therapy on growth parameters in HIV-infected children. Paper presented at the third international conference on nutrition and HIV infection. 1999; April 22-25; Cannes, France.
48. Lainka E, Oezbek S, Falck M, Ndagijimana J, Niehues T. Marked dyslipidemia in human immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. Pediatrics 2002; 110:56.
49. Nadal D, Steiner F, Cheseaux JJ, Lazarevitch CA, Aebi C, Kind C, et al. Long-Term Responses To Treatment Including Ritonavir Or Nelfinavir In HIV-1-Infected Children. Infection 2000; 28:287-296.
50. Amaya RA, Kozinetz CA, Mcmeans A, Schwarzwald H. Lipodystrophy Syndrome In Human Immunodeficiency Virus-Infected Children. Pediatr Infect Dis J 2000; 21:405-410.
51. Taylor P, Worrel C, Steinberg SM, Hazra R, Jankelevich S, Wood LV. Natural History Of Lipid Abnormalities And Fat Redistribution Among HIV-Infected Children Receiving Long-Term, Protease Inhibitor-Containing, Highly Active Antiretroviral Therapy Regimens. Pediatrics 2004; 114:235-242.
52. Werner MLF, Pone MVS, Fonseca VM, Chaves CRMM. Lipodystrophy syndrome and cardiovascular risk factors in children and adolescents infected with HIV/AIDS receiving highly active antiretroviral therapy. J Pediatr 2010; 86:27-32.
53. 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; 13:1659-1667.
54. Dube M, Fenton M. Lipid abnormalities. Clin Infect Dis 2003; 33:S79-S83.
55. Nolan D, Mallal S. Complications associated with NRTI therapy: update on clinical features and possible pathogenic mechanisms. Antivir Ther 2004; 9:849-863.
56. Cheseaux JJ, Jotterand V, Aebi C, Gnehm H, Kind C, Nadal D, et al. Hyperlipidemia in HIV-infected children treated with protease inhibitors: relevance for cardiovascular diseases. J Acquir Immune Defic Syndr 2002; 30:288-293.
57. Krause JC, Toye MP, Fisher DJ, Stechenberg BW, Reiter EO, Allen HF. Metabolic abnormalities in human immunodeficiency vírus-infected children: two-year follow-up. J Pediatr Endocrinol Metab. 2009; 22:345-351.
58. Brinkman K, Smeitink JA, Romijin JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse transcriptase inhibitors is key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. Lancet 1999; 354:1112-1115.
59. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. AIDS 2000; 14:25-32.