Diabetes Metab (Paris)
2002, 28, 397-404

ORIGINAL ARTICLE

REDUCTION OF FAT ACCUMULATION AND LIPID DISORDERS BY INDIVIDUALIZED LIGHT AEROBIC TRAINING IN HUMAN IMMUNODEFICIENCY VIRUS INFECTED PATIENTS WITH LIPODYSTROPHY AND/OR DYSLIPIDEMIA

G.J. THÖNI (1, 2), C. FEDOU (2), J. F. BRUN (2), J. FABRE (3), E. RENARD (4), J. REYNES (3), A. VARRAY (1), J. MERCIER (2)

SUMMARY - **Background:** The management of abdominal fat accumulation and metabolic disorders in HIV1-infected patients, by an aerobic training program, is considered.
Methods: Seventeen lipodystrophic and 2 dyslipidemic (without body modification) adults were studied before and after 4 months of training. The training load was individualized on a ventilatory threshold basis, determined during a maximal exercise test on cycle ergometer. Total (TAT), Visceral (VAT) and Subcutaneous Adipose Tissue (SAT) were assessed by CT-scan. Total (TC) and High Density Lipoprotein (HDL-C) Cholesterol, Triglycerides (TG), lactate (La), insulin and glucose were measured after a 12-hour-overnight fast. LDL, TC/HDL, TG/HDL, HOMA-insulin resistance index and coronary heart disease (CHD) relative risk (RR_{CHD}) were calculated.
Results: Besides a significant improvement of aerobic fitness, trained patients exhibited a reduction in TAT (-12.8%, $p < 0.001$), specially at the visceral level (– 12%, $p < 0.01$) and in TC, TG and La (– 23%, – 43% and – 19% respectively, $p < 0.01$). HDL-C was increased (+ 6%, $p < 0.01$). All these effects were above changes that could be expected by a possible regression to the mean artefact. Both TC/HDL and TG/HDL were reduced ($p < 0.01$) and the estimated RR_{CHD} decreased by $\sim$13% ($p < 0.01$). No significant training effect was observed on the 9 available HOMAs. Significant correlations were found between changes in blood lipid values and baseline measures (r range – 0.55 to – 0.79, $p < 0.05$), indicating a larger improvement when baseline lipid parameters were higher.
Conclusion: Aerobic training reduced visceral fat, lipid disorders, basal blood lactate and CHD markers in HIV patients. Training effects were particularly important for patients with marked dyslipidemia.

Key-words: HIV, fat redistribution, aerobic training, CT-scan, metabolic disorders.

RÉSUMÉ - **Réduction de l'accumulation adipeuse et des désordres lipidiques par l'entraînement aérobie individualisé de faible intensité chez les patients infectés par le VIH présentant une lipodystrophie et/ou une dyslipidémie.**
Contexte : La place d'un entraînement aérobie dans la prise en charge de l'accumulation adipeuse abdominale et des désordres métaboliques, observés chez les personnes infectés par le VIH, est envisagée.
Méthode : Dix-sept adultes lipodystrophiques et deux dyslipidémiques sans modification corporelle ont été explorés avant et apres 4 mois d'entraînement aérobie au seuil ventilatoire. Un test d'effort maximal sur cyclo-ergometre permettait d'individualiser la charge d'entraînement. Les surfaces du tissu adipeux (abdominal) total, viscéral et sous-cutané (respectivement TAT, VAT et SAT) ont été évaluées par tomodensitométrie. Les concentrations sériques de Cholestérol Total (TC), de HDL-Cholestérol, des triglycerides (TG), du lactate (La), de l'insuline et du glucose ont été mesurées apres 12 heures de jeune. Le LDL, les rapports CT/HDL, TG/HDL, l'index d'insulino-résistance (HOMA) et le risque relatif d'incident cardio-vasculaire ont été calculés.
Résultats : Parallèlement a une amélioration significative de l'aptitude physique, les patients entraînés bénéficient d'une réduction du TAT (– 12,8 % ; $p < 0,001$), notamment du VAT (– 12 % ; $p < 0,01$), du Cholestérol Total, des Triglycérides et de la lactatémie (– 23 %, – 43 % and – 19 % respectivement, $p < 0,01$). Le HDL Cholestérol augmente de + 6 % ($p < 0,01$). Tous ces effets sont supérieurs a ceux qu'une éventuelle régression vers la moyenne aurait pu occasionner. Les rapports CT/HDL et TG/HDL s'abaissent apres entraînement ($p < 0,01$) ainsi que le risque estimé d'incident cardio-vasculaire ($\sim$13 % ; $p < 0,01$). Le HOMA n'est pas significativement modifié apres entraînement pour les 9 patients pour qui il est disponible. Des corrélations significatives ont été mise en évidence entre l'évolution des parametres lipidiques et les valeurs initiales (r compris entre – 0,55 et – 0,79 ; $p < 0,05$), indiquant une évolution plus importante lorsque les désordres lipidiques initiaux sont plus importants.
Conclusion : L'entraînement aérobie réduit donc le tissu adipeux viscéral, les désordres lipidiques, la lactatémie basale et les marqueurs du risque cardio-vasculaire des patients infectés par le VIH. Les effets de l'entraînement sont particulierement marqués chez les patients présentant initialement de larges perturbations lipidiques.

Mots-clés : redistribution adipeuse liée au VIH, entraînement aérobie, CT-scan, désordres métaboliques, risques cardio-vasculaires.

: G. Thöni, UPRES EA 2991, Laboratoire "Sports, Performance, Santé", Faculté des Sciences du Sport, 700 av. du pic St Loup, 34090 Montpellier, France.
e-mail: gilles.thoni@sc.univ-montp1.fr

Received : May 13th, 2002 ; *revised :* June 18th, 2002

(1) UPRES EA 2991, "Sports, Performance, Health" Laboratory, Faculty of Sport Sciences
(2) The central dpt. of Clinical Physiology, CERAMM, Lapeyronie University Hospital
(3) The department of Infectious and Tropical diseases, Gui de Chauliac Hospital
(4) Endocrinology Department, Lapeyronie Hospital, Montpellier, France.

Different morphologic changes, described as 'lipodystrophy', and metabolic disorders were widely and recently described in HIV-infected patients. In addition to peripheral and/or facial fat loss (lipoatrophy), a high proportion of patients are concerned by fat accumulation (lipohypertrophy) in the central and the dorso-cervical areas and/or by dyslipidemia, insulin resistance and elevated blood lactate [1]. The intra abdominal fat is known to be highly predictive of metabolic disorders (cardio-vascular disease [CVD] and type 2 diabetes) in uninfected people [2-4]. The abnormal high Visceral Adipose Tissue (VAT), Visceral to Total (abdominal) Adipose Tissue ratio (VAT: TAT) [1, 5], and elevated blood lipids have generated legitimate fears about long-term cardiovascular risks in HIV-infected patients [6, 7] whereas current antiretroviral therapies succeeded in greatly improving the infectious disease control. Numerous recent studies have also shown vascular alterations in these patients [8-11].

In addition, physical activity is well-known to reduce VAT, blood lipid and carbohydrate disorders in uninfected subjects. Some authors have reported positive effects of various training programs in seropositive persons [12-15]. Few of them have used the aerobic exercise, although often proposed in the uninfected people for the management of central obesity and metabolic disorders. Likewise, few have succeeded in improving these two latter disorders, and imaging technique able to distinguish intra abdominal fat, such the CT-scan, has never been considered to evaluate training effects. Hence, our objective was i) to evaluate effects of an individualized aerobic training program in reducing fat accumulation, especially visceral one, and lipid disorders of HIV-infected patients, ii) to estimate Coronary Heart Disease (CHD) risk and to evaluate how it is altered by the training, iii) to determine parameters having an influence on training results.

■ PATIENTS AND METHODS

Subjects

All HIV1-infected adults with lipodystrophy, i.e., either with clinical evidence of body shape changes including one of those described in introduction (self reported by the patient, confirmed by a doctor's physical examination), and/or dyslipidemia, followed in our department were proposed to participate to our study.

Patients were included in the study if they were not classified as wasted, if they did not change their treatment in the three months before the study and if they received neither corticosteroids, androgen, lipid lowering nor insulin sensitizing drug during the same period. All were able to give informed consent. Moreover, patients were not included if they presented cardiovascular, articular, neuromuscular, or respiratory disorders contra-indicating exercise testing or physical training.

TABLE I. *Baseline anthropometric and immuno-virologic characteristics.*

Characteristics	Trained Patients (n = 19)
Age	44.2 ± 2.3 years
Height	171 ± 1.9 cm
sex ratio	12 men/5 women
CD4	514.4 ± 60.1 cells.μl^{-1}
CD4	22.4 ± 3.5 %
HIV RNA	2.1 ± 0.2 $\log_{10}$copies.ml^{-1}
Time since HIV diagnosis	6.7 ± 0.8 years
Lipodystrophic since	12 ± 1.7 months

The duration of lipodystrophy (in the 17 patients with perceived clinical signs) corresponded to the mean time from the first clinically perceived physical symptom of fat redistribution. Data are expressed as mean ± SEM.

Nineteen volunteers, who agreed and were available to closely follow the supervised sessions, with clinically noticeable changes in the distribution of adipose tissue (since 12±1.7 month) or with dyslipidemia, decided to participate in our protocol and completed the program. Measurement of plasma CD4-lymphocyte cell counts and plasma HIV1- RNA levels were obtained from the last medical records before training. The main baseline characteristics are shown in *Table I*.

Exercise testing and training protocol

All trained individuals were evaluated before and after 4 months of a light individualized aerobic training program. It consisted in 2 supervised sessions a week on cycle ergometer, lasting 45 minutes each. Heart rate (HR) was continuously monitored (Sport Tester PE3000, Polar Electro, Kemple, Finland) and the patients were asked to maintain a HR corresponding to the ventilatory threshold ($\dot{V}O_{2VTh}$). The latter, determined for each subject by using the Beaver method [16], and the maximal oxygen uptake ($\dot{V}O_{2max}$) was evaluated during a progressive exercise test, led to exhaustion on an electromagnetically-braked cycle ergometer (Ergometrics 800, Ergoline, Bitz, West Germany). During the baseline and the final exercise test, the main cardiac, ventilatory and metabolic outcomes were continuously monitored by a metabolic system CardioO_2 (CPX, Medical Graph-

ics, St Paul, MN, USA). All patients were advised to perform, by their own, an unsupervised aerobic session with a similar intensity.

Pre- and post- training evaluations

Every subject underwent before and after training a determination of the whole body composition (tetrapolar bioelectrical impedance analysis BIA 101s. Akern-RJL Systems. Frankfurt. Germany). Total abdominal Adipose Tissue (TAT), Visceral Adipose Tissue (VAT) and Subcutaneous Adipose tissue (SAT) were obtained by CT-scan (General Electric HiSpeed helical scanner, GE Medical Systems. Milwaukee. WI. USA) as previously described by Miller *et al.* [5]. The VAT/TAT ratio was then calculated.

Blood was collected after a 12-hour-overnight fast for measurement of plasma glucose (G), insulin (I) – Insulin Resistance was then estimated using the homeostasis model assessment calculated as IR HOMA = (G*I)/22.5 [17]. These data were available for 9 patients. Fasting triglycerides, total and high-density lipoprotein cholesterol (respectively TG, TC, and HDL-C), lactate and pyruvate were also analysed. The TC/HDL-C and TG/HDL-C ratio were calculated and used as atherogenesis indexes. The 10-year relative risk for coronary heart disease (RR_{CHD}) was calculated through the algorithm proposed by Wilson [18] for uninfected people which includes cholesterol lipoprotein subclasses categories.

Statistical analysis

Differences between before- and after-training variables were analysed by using a paired t-test analysis or Wilcoxon test when appropriate. A possible effect of "regression to the mean" (RTM) that could explain a part of our results was considered. This is the tendency of values, far from average ones (e.g. high TG or low HDL-C level), to be less extreme on re-testing, even without an intervention program. The Pearson's r coefficient for correlation between pre- and post- measurement variables with normal distribution was calculated. Our experimental group was compared (unpaired t-test) with a reference population constituted of 100 lipodystrophic patients followed in our department during the last 3 years. At last, the method proposed by Yudkin and Stratton [19] was used to estimate the magnitude of RTM effect. In order to realise the simulation, we assumed that patient were selected for inclusion because of elevated baseline CT scan values (TAT > 220 cm^2 or VAT > 110 cm^2) or abnormal biological values (TC > 200 $mg.dL^{-1}$, HDL-C < 35 $mg.dL^{-1}$, TG > 200 $mg.dL^{-1}$ or La > 2.1 $mmol.L^{-1}$). Some of these latter can be considered as appropriate values for intervention. The possible extent of RTM was then compared with the observed training effects. The pre-to-post difference (delta) was calculated for each value and a Pearson's r coefficient was calculated to analyse the relations between observed changes over the training period and baseline values. A $p < 0.05$ was considered as statistically significant. Values were expressed by their mean ± standard error of the mean (SEM).

■ RESULTS

The clinical profiles of lipodystrophy were the following: 15 patients showed peripheral lipoatrophy associated with hypertrophy; among them 1 developed a buffalo neck. One patient was only lipoatrophic and one woman was only hypertrophic (increased breast and abdominal girth). Two dyslipidemic patients did not show any discernable clinical signs of fat redistribution.

All 19 patients were under nucleoside reverse transcriptase inhibitor (NRTI) either 1 (n = 3) or 2 (n = 13) or 3 (n = 3) molecules. Eleven patients were also under protease inhibitor (PI). Five patients were under non nucleoside reverse transcriptase inhibitor (NNRTI).

All patients realised at least 85% or more of the supervised sessions. The baseline, the post-training values and statistical significance for cardiorespiratory fitness, body composition and biological parameters are respectively shown in *Tables II, III and IV*. The training program induced a significant improvement of whole-body- aerobic ($\dot{V}O_{2max}$) and peripheral oxidative (as indirectly explored by $\dot{V}O_{2VTh}$) capacities, making values closer to theoretical ones. A decrease in Respiratory Equivalent (significant for RE O_2, $p = 0.06$ for RE CO_2) was also underlined. Lipodystrophic patients profited also by a significant reduction in VAT, leading to a reduction of total abdominal fat (without any change on whole-body fat determined by bio-impedancemetry). Positive effects of aerobic training were also noticed on TC, HDL-C, TG, TC/HDL-C and TG/HDL-C *(Table IV)*. The 10 yr relative risk for CVD significantly decreased from 1.12 (± 0.12) to 0.97 (± 0.12) ($p = 0.004$) throughout the study period. No modification in basal glucose, insulin and IR-HOMA were found. When the two dyslipidemic patients without clinical sign of body shape change were ruled out from statistical analysis, no modification of the results (especially those concerning lipid parameters) was underlined (pre- and post- TC values: 256 ± 11 *vs* 210 ± 8 $mg.dL^{-1}$; HDL-C: 36.5 ± 2.1 *vs* 38.8 ± 1.5 $mg.dL^{-1}$; TG: 256 ± 42 *vs* 151 ± 18 $mg.dL^{-1}$ and La: 2.68 ± 0.2 *vs* 2.2 ± 0.2 mM, $p < 0.01$ for all).

The parameters used to estimate the potential artefact of regression to the mean are shown in *Table V*. The correlation coefficient between pre- and post training values ranged between .71 and .86, except for TG (.64). The mean total cholesterol of trained pa-

TABLE II. *Pre- and post-training values for aerobic fitness.*

	Before training mean ± Sem	After training mean ± Sem	p
$\dot{V}O_{2max}$ ($ml.min^{-1}$)	1751 ± 90	1950 ± 104	0.001
$\dot{V}O_{2max}$ ($ml.kg^{-1}.min^{-1}$)	25.2 ± 1.2	27.8 ± 1.5	0.005
$\dot{V}O_{2max}/th\dot{V}O_{2max}$ (%)	80.4 ± 2.7	91.1 ± 2.9	0.004
W_{max} (watts)	147.4 ± 9.2	156.7 ± 8.8	0.01
$\dot{V}O_{2VTh}$ ($ml.min^{-1}$)	855.9 ± 45.5	1000.3 ± 64.4	0.004
$\dot{V}O_{2VTh}/th\dot{V}O_{2max}$ (%)	39.8 ± 2	46.7 ± 1.6	0.004
RE O_{2max}	47.4 ± 2.4	40.7 ± 2.2	0.04
RE CO_{2max}	41.2 ± 1.9	35.8 ± 2.2	0.06

$\dot{V}O_{2max}$, absolute maximal oxygen uptake, W_{max}, maximal workload; $\dot{V}O_{2VTh}$, oxygen uptake at ventilatory threshold, $\dot{V}O_{2max}/th\dot{V}O_{2max}$ and $\dot{V}O_{2VTh}/th\dot{V}O_{2max}$, respectively $\dot{V}O_{2max}$ and $\dot{V}O_2$ at ventilatory threshold, both expressed as a percentage of theoretical $\dot{V}O_{2max}$; RE O_{2max} and RE CO_{2max}, respiratory equivalent for O_2 and CO_2 at maximal exercise (i.e. respectively $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$). Data are mean ± SEM. P value for pre- to post-comparison.

TABLE III. *Pre- and post-training values for body composition and abdominal fat distribution.*

	Before training mean ± Sem	After training mean ± Sem	P
Weight (kg)	68.6 ± 1.7	68.4 ± 1.8	NS
BMI ($kg.m^{-2}$)	23.5 ± 0.5	23.5 ± 0.5	NS
FFM (kg)	57 ± 2	56 ± 2.1	NS
FFM (%)	82.4 ± 1.5	81.2 ± 1.5	NS
FM (kg)	11.7 ± 0.9	12.7 ± 0.9	NS
FM (%)	17.6 ± 1.5	18.8 ± 0.9	NS
TAT (cm^2)	242 ± 23.9	211.3 ± 22.9	0.0005
VAT (cm^2)	100.6 ± 15.4	88.7 ± 14.3	0.004
SAT (cm^2)	129.8 ± 20.3	122.4 ± 16.2	NS
VAT/TAT	0.41 ± 0.05	0.41 ± 0.05	NS

BMI, body mass index; FFM, fat free mass; FM, fat mass by bio impedancemetry; TAT, total (abdominal) adipose tissue; SAT, subcutaneous (abdominal) adipose tissue; VAT, visceral adipose tissue, by CT scan analysis. Data are expressed as mean ± SEM. P value for pre- to post-comparison.

tients was the only value significantly higher than the reference population's mean ($p < 0.01$). The genuine training effect was above effect likely to be attributable to RTM for any tested value and especially for blood TC, TG and lactate.

The *Figure 1* represents the pre-to-post change (delta) of different variables in relation to their respective baseline values. The modification rate during training of physical fitness, metabolic disorders and fat distribution, were correlated (significantly for both formers) with the extent of respective baseline disorders. Significant strong relations were especially found for delta Ventilatory Threshold, TC, TG, TC/HDL-C and TG/HDL-C and their respective baseline values.

■ DISCUSSION

The prolonged individualized aerobic training at an intensity corresponding to the ventilatory threshold, followed by HIV infected subject with fat redistribution and/or metabolic disorders, induced a significant reduction of abdominal adipose tissue by a specific decrease of VAT. The blood lipid profile also improved and resting blood lactate decreased during the training period.

The simulation realised to estimate the potential extent of RTM showed that such an effect would be less than the training changes. Furthermore and because no spontaneous decrease in either fat accumulation or lipid disorders could be expected in HIV infected patients over the study period [20-22], the observed modifications can be widely considered as genuine intervention effects.

The change in aerobic fitness observed in the present study, characterised by both $\dot{V}O_{2max}$ and ventilatory threshold, was similar to the 10-15% change obtained in uninfected elderly people [23], obese patients [24], patients with cardiac [25-27] or pulmonary diseases [28], after endurance trainings (rehabilitation programs) with similar intensities, frequencies and duration. A greater evolution in ventilatory threshold than in whole body $\dot{V}O_{2max}$ was expected considering the mild exercise load used in our study. A more intensive training (higher intensity and/or frequency) should be more effective to improve $\dot{V}O_{2max}$ in higher fit subjects [29] but it did not seem compatible neither with professional constraints of subjects with previous sedentary habits nor with muscle weakness and fatigue often met in these patients.

TABLE IV. *Change in Pre- and post-training biological values.*

	Before training mean ± Sem	After training mean ± Sem	P
TC ($mg.dL^{-1}$)	254.4 ± 11.8	195.1 ± 8.1	0.005
HDL-C ($mg.dL^{-1}$)	36.9 ± 2.3	39.2 ± 1.8	0.01
LDL-C ($mg.dL^{-1}$)	166.5 ± 10.2	148.9 ± 7.1	NS
TG ($mg.dL^{-1}$)	237 ± 39.4	134 ± 18	0.003
TC/HDL-C	7.22 ± 0.53	5.76 ± 0.3	0.0007
TG/HDL-C	3.59 ± 0.97	1.8 ± 0.21	0.003
La_0 (mM)	2.58 ± 0.2	2.08 ± 0.21	0.005
La/Pyr_0	30.3 ± 4.5	25.6 ± 2.6	NS
G (mM)	4.86 ± 0.18	4.84 ± 0.17	NS
I ($\mu U.mL^{-1}$)	12.1 ± 2.4	9.2 ± 3.1	NS
IR-HOMA	2.56 ± 0.6	2.04 ± 0.7	NS

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, Triglycerides; La_0 and Pyr_0, resting blood lactate and pyruvate; G glucose and I insulin, all in fasting conditions; HOMA, Insulin resistance index. Data are mean ± SEM. P value for pre- to post-comparison.

Our results confirmed and completed the findings preliminary published in previous studies about training in the management of lipodystrophic defining disorders. Physical training was described to diversely reduce abdominal fat in HIV infected patients. A 16wk resistance training did not succeed in reducing central fat as evaluated by DEXA scan [15]. Nevertheless, all the studies which have demonstrated significant effect on this parameter included an aerobic component in their program suggesting the specificity of this training modality. This result was estimated or evaluated with different means of measurement such as simple techniques (BMI, abdominal girth, waist to hip ratio [13, 30]) or imaging techniques (DEXA [12]). Our study was the first one using CT-scan in a large HIV seropositive sample. Furthermore, the visceral adipose tissue (VAT) of HIV lipodystrophic patients decreased by about 20 cm^2 after training, while subcutaneous abdominal adipose tissue (SAT) did not change significantly. A similar VAT modification was previously described in obese children [31] or adults [32] after training. That is often associated with a significant 15-30% decrease in SAT [32-34] which is usually found also higher in uninfected obese than in HIV infected patients.

Besides, our study confirmed Jones' promising but preliminary results [13] on Total Cholesterol and Triglycerides obtained after 10 weeks of aerobic training. The tendency outlined by Jones about the decrease in TC/HDL-C ratio reached here significant threshold possibly either because of a higher number of studied patients, or the use of different training modalities (duration and intensity), perhaps more efficient in our study. In addition, we described a significant decrease in TG/HDL-C ratio – known to be inversely correlated with LDL particle size in uninfected subjects – and a significant reduction in the calculated 10yr RR_{CHD} showing a fundamental importance of such training in HIV patients.

TABLE V. *Estimate of regression to the mean.*

	TAT	VAT	TC	HDL-C	TG	La_0
Correlation between repeated measurements	0.73***	0.73***	0.72***	0.73***	0.64**	0.71***
Mean values in the reference population (n=100)	244.3 ± 10.8	112.6 ± 5.9	217 ± 5	38 ± 1	207 ± 16	2.27 ± 0.1
Trained group *vs* Reference population difference	NS	NS	p<0.01	NS	NS	NS
Expected RTM difference (%)	– 7.9	– 10	– 6.8	+ 4.8	– 14.7	– 7.1
Observed mean difference (%)	– 13	– 12	– 23	+ 6	– 43	– 19

TAT, total (abdominal) adipose tissue; VAT, visceral adipose tissue both in cm^2. TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, Triglycerides all in $mg.dL^{-1}$; La_0, resting blood lactate (mM). ** $p < 0.01$, *** $p < 0.001$ for significant correlation between pre- and post-training values. 100 lipodystrophic patients studied in our department were used as a reference population, their values are mean ± SEM. NS: non significant for comparison between trained patients and the reference population. RTM: regression to the mean, i.e. the estimated percentage of change that could be expected if we assume that values could be less extreme at retesting than at baseline, even without any intervention. The genuine training effects are all above this possible statistical artefact.

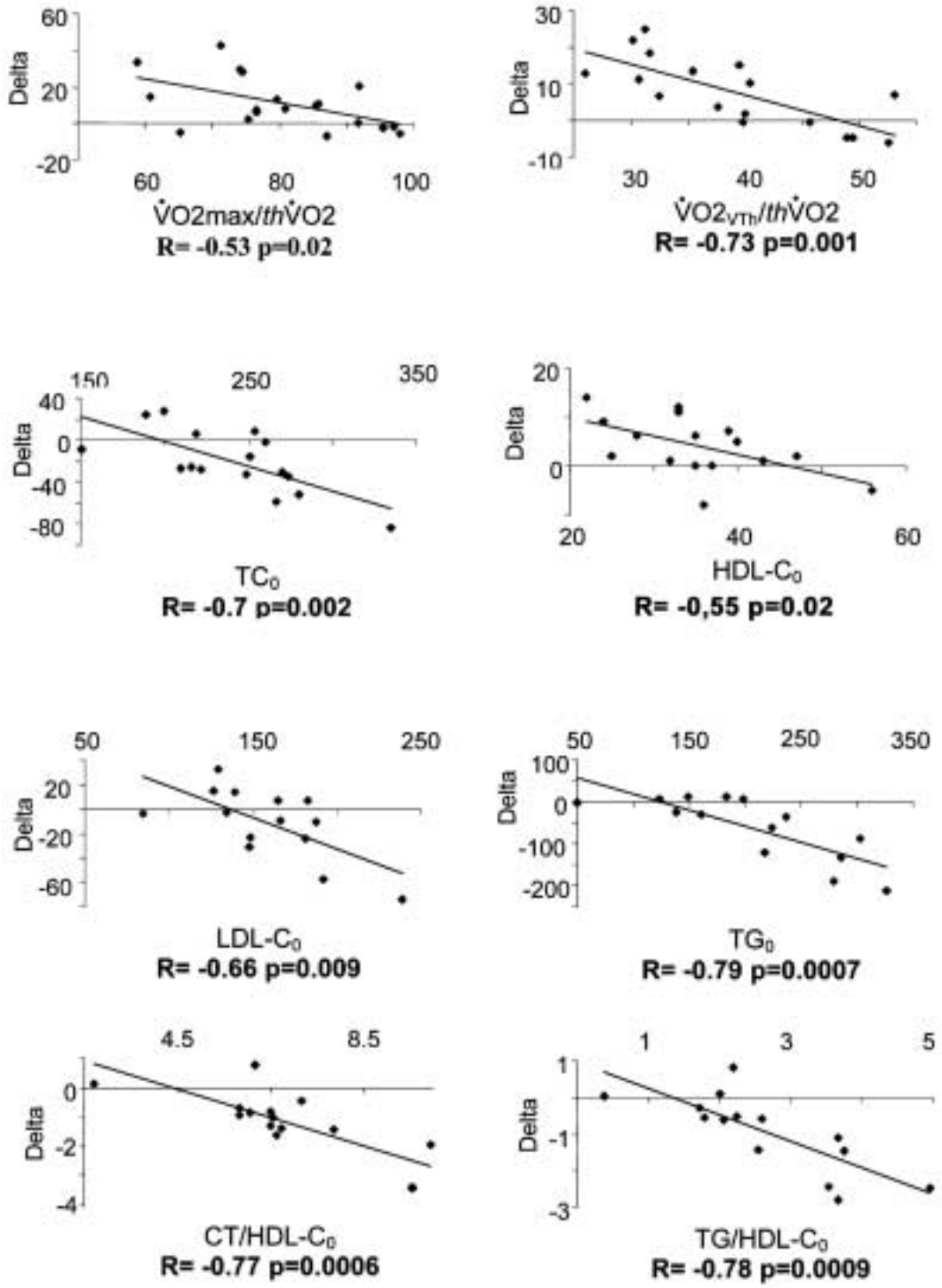

FIG. 1. *Relation between Delta values of aerobic, CT scan, biological features and their respective baseline values.*

Pearson's R coefficients and p values. $\dot{V}O_{2max}$, maximal oxygen uptake, $\dot{V}O_{2VT}$, $\dot{V}O_2$ at ventilatory threshold, both expressed as a percentage of theoretical $\dot{V}O_{2max}$. TC_0, total cholesterol; HDL-C_0, high density lipoprotein cholesterol, LDL-C_0, low density lipoprotein cholesterol, TG_0, triglycerides; all at baseline ($mg.dL^{-1}$). The beneficial effects of aerobic training was higher in patients who showed more elevated baseline disorders (significant correlation between change and baseline values for physical fitness index, lipid features and atherogenicity index).

Nevertheless, some restrictions could limit the use of classical algorithms in HIV-infected patients for risk calculation. Both ratio (TC/HDL-C and TG/HDL-C) are usually considered as good indexes for atherosclerosis risk in a long term. But, using algorithms proposed for uninfected people in the RR_{CHD} calculation may bring several problems. Indeed, on the one hand, this method does not take into account the independent effects of infection itself [10] or protease inhibitor use [9, 11, 35] on cardiac and vascular health: that could induce an underestimation of the real CHD risk in infected patients. On the other hand, the extent of positive training effects on long-term cardiovascular risks could be also underestimated because the change in the way of life (diet habits and daily physical activity) was not considered by Wilson's algorithm.

Furthermore, if the training results on infected patients' total Cholesterol and LDL subclass seemed to be found specifically with aerobic protocols (results not described for example by Yarasheski after a resistance training [15]), on the opposite, TG seemed widely affected by both resistance and aerobic training, indicating that its decrease could be induced by other processes than an improvement of peripheral oxidative capacities. This finding reinforced the hypothesis developed by this last author about improvement of the LPL activity by repeated muscle contractions realised during each training bout.

After training, the absolute increase in HDL-C, observed in uninfected hypercholesterolemic or hypertriglyceridemic subjects, is usually modest [36, 37]. The 6%-increase described here coincided with results obtained by Crouse *et al.* [38] and Couillard *et al.* [39], but was higher than the modifications (+ 3.6%) induced by a 20wk supervised exercise program led in a large heterogeneous population, issued from the HERITAGE Family study [40]. On the opposite, the beneficial effect of an individualised training on both total cholesterol (– 23%) and triglycerides (– 43%) level was widely more pronounced in HIV infected patients than in uninfected subjects with metabolic disorders. Indeed, in these latter patients, the decrease reach most often 10% for TC and 10-to-15% for TG [38, 39].

Our study was the first one to outline, in HIV^+ patients, the decrease of resting blood lactate after a physical training. This interesting modification may result from the cumulative effects of both reduced lactate production and improved removal abilities linked to the improvement of peripheral oxidative capacities observed after training. The decrease in both central adiposity and circulating blood lipids, that could lead to a reduction of hepatic steatosis, may also be hypothesized to indirectly favour blood lactate removal. The lack of significant effects of aerobic training either on fasting glucose and insulin or on insulin resistance index may be partly explained by the low number of patients with real glucoregulation disorders in our study group at baseline.

The significant relationship observed between the change of aerobic fitness, change of lipid disorders over the training period and the respective baseline values also constituted a positive result. These data suggest that variation in training responsiveness exists, and that individuals who have higher disorders are most likely to be high responders. The relation between baseline lipid levels and lipid change to physical training was already shown in seropositive patients by Yarasheski [14] who found greater reduction in TG level in subjects with higher pre-training values. A similar result was observed in HIV^-, during cholesterol lowering intervention [41] even after control for regression to the mean, or after a 20wk training program followed by people with various baseline TG, TC, and HDL levels [39]. Surprisingly, an acute exercise session was also likely to induce greatest reduction in TG in subjects with higher pre-exercise TG values [42]. Nevertheless, further studies are needed to determine the best exercise intensity for HIV-infected patients who were low responders in our work. The concept of individualized training (rather than standardized one) is thus reinforced in these patients. Our study did not outline any critical value in lipid features above which the training could not induce effects anymore. Nevertheless our patients presented relatively moderate disorders. Patients with major dyslipidemia, preferentially treated by an intensive pharmacological therapy, could not be included in the study. If we consider the slow progressive degradation in blood lipid profile of HIV^+ patients over time [20], people can start training even if such disorders are widely developed, but the prevention against CVD will be improved if patients start it as soon as possible.

In conclusion, our study demonstrated the positive effects of a light aerobic training on central adipose accumulation, lipid disorders and basal blood lactate in HIV-infected patients. The proposed intervention led to a sharp reduction of several markers for cardiovascular disorders. In addition, our results indicated that a large extent of patients can take advantage of the training benefits, even and above all, patients with the most important pre-training disorders. Indeed, the higher the baseline disorders were, the more efficient the training were. These results reinforce the interest of individualized physical exercise in the induction of a lifestyle modification and in the early management of infected patients for their long-term follow-up. It could be accurately associated with diet, smoking reduction, pharmacological treatment against type-2 diabetes or against major dyslipidemia, and with the optimization of the antiretroviral therapy.

Acknowledgements – The authors thank all the physicians from the infectious disease department who have widely participated to the recruitment and to the motivation of patients.

We acknowledge also patients for their contribution and Magali Faure, Marie-Jeanne Alemany, Marie-Chantal Granat and Colette Sagnes for their helpful technical support.

REFERENCES

1 Carr A, Samaras K, Burton S *et al.* A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *Aids,* 1998, *12,* F51-58.

2 Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism,* 1987, *36,* 54-59.

3 Bjorntorp P. Abdominal obesity and the development of noninsulin-dependent diabetes mellitus. *Diabetes Metab Rev,* 1988, *4,* 615-622.

4 Matsuzawa Y, Nakamura T, Shimomura I, Kotani K. Visceral fat accumulation and cardiovascular disease. *Obes Res,* 1995, *3,* 645S-647S.

5 Miller KD, Jones E, Yanovski JA *et al.* Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet,* 1998, *351,* 871-875.

6 Hadigan C, Meigs JB, Corcoran C *et al.* Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis,* 2001, *32,* 130-139.

7 Mercie P, Tchamgoue S, Thiebaut R *et al.* Atherogen lipid profile in HIV-1-infected patients with lipodystrophy syndrome. *Eur J Intern Med,* 2000, *11,* 257-263.

8 SoRelle R. Vascular and lipid syndromes in selected HIV-infected patients. *Circulation,* 1998, *98,* 829-830.

9 Periard D, Telenti A, Sudre P *et al.* Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. *Circulation,* 1999, *100,* 700-705.

10 Depairon M, Chessex S, Sudre P *et al.*Premature atherosclerosis in HIV-infected individuals--focus on protease inhibitor therapy. *Aids,* 2001, *15,* 329-334.

11 Stein JH, Klein MA, Bellehumeur JL *et al.* Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation,* 2001, *104,* 257-262.

12 Roubenoff R, Weiss L, McDermott A *et al.* A pilot study of exercise training to reduce trunk fat in adults with HIV-associated fat redistribution. *Aids,* 1999, *13,* 1373-1375.

13 Jones SP, Doran DA, Leatt PB, Maher B, Pirmohamed M. Short-term exercise training improves body composition and hyperlipidaemia in HIV-positive individuals with lipodystrophy. *Aids,* 2001, *15,* 2049-2051.

14 Yarasheski KE, Roubenoff R. Exercise treatment for HIV-associated metabolic and anthropomorphic complications. *Exerc Sport Sci Rev,* 2001, *29,* 170-174.

15 Yarasheski KE, Tebas P, Stanerson B *et al.* Resistance exercise training reduces hypertriglyceridemia in HIV-infected men treated with antiviral therapy. *J Appl Physiol,* 2001, *90,* 133-138.

16 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol,* 1986, *60,* 2020-2027.

17 Matthews DR, Hosker JP, Rudenski AS *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia,* 1985, *28,* 412-419.

18 Wilson PW, D'Agostino RB, Levy D *et al.* Prediction of coronary heart disease using risk factor categories. *Circulation,* 1998, *97,* 1837-1847.

19 Yudkin PL, Stratton IM. How to deal with regression to the mean in intervention studies. *Lancet,* 1996, *347,* 241-243.

20 Carr A, Samaras K, Thorisdottir A *et al.* Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet,* 1999, *353,* 2093-2099.

21 Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. *Arch Intern Med,* 2000, *160,* 2050-2056.

22 Ruiz L, Negredo E, Domingo P *et al.* Antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with hiv-associated lipodystrophy: 1-year prospective follow-up of a multicenter, randomized, controlled study. *J Acquir Immune Defic Syndr,* 2001, *27,* 229-236.

23 Fabre C, Masse-Biron J, Ahmaidi S, Adam B, Prefaut C. Effectiveness of individualized aerobic training at the ventilatory threshold in the elderly. *J Gerontol A Biol Sci Med Sci,* 1997, *52,* B260-266.

24 Van Aggel-Leijssen DP, Saris WH, Wagenmakers AJ, Senden JM, Van Baak MA. Effect of exercise training at different intensities on fat metabolism of obese men. *J Appl Physiol,* 2002, *92,* 1300-1309.

25 Kiilavuori K, Sovijarvi A, Naveri H, Ikonen T, Leinonen H. Effect of physical training on exercise capacity and gas exchange in patients with chronic heart failure. *Chest,* 1996, *110,* 985-991.

26 Lampert E, Mettauer B, Hoppeler H *et al.* Skeletal muscle response to short endurance training in heart transplant recipients. *J Am Coll Cardiol,* 1998, *32,* 420-426.

27 Nieuwland W, Berkhuysen MA, van Veldhuisen DJ *et al.* Differential effects of high-frequency *versus* low-frequency exercise training in rehabilitation of patients with coronary artery disease. *J Am Coll Cardiol,* 2000, *36,* 202-207.

28 Vallet G, Ahmaidi S, Serres I *et al.* Comparison of two training programmes in chronic airway limitation patients: standardized *versus* individualized protocols. *Eur Respir J,* 1997, *10,* 114-122.

29 Swain DP, Franklin BA. VO(2) reserve and the minimal intensity for improving cardiorespiratory fitness. *Med Sci Sports Exerc,* 2002, *34,* 152-157.

30 Smith BA, Neidig JL, Nickel JT *et al.* Aerobic exercise: effects on parameters related to fatigue, dyspnea, weight and body composition in HIV-infected adults. *Aids,* 2001, *15,* 693-701.

31 Gutin B, Owens S, Okuyama T *et al.* Effect of physical training and its cessation on percent fat and bone density of children with obesity. *Obes Res,* 1999, *7,* 208-214.

32 Lynch NA, Nicklas BJ, Berman DM, Dennis KE, Goldberg AP. Reductions in visceral fat during weight loss and walking are associated with improvements in VO(2 max). *J Appl Physiol,* 2001, *90,* 99-104.

33 Schwartz RS, Shuman WP, Larson V *et al.* The effect of intensive endurance exercise training on body fat distribution in young and older men. *Metabolism,* 1991, *40,* 545-551.

34 Owens S, Gutin B, Allison J *et al.* Effect of physical training on total and visceral fat in obese children. *Med Sci Sports Exerc,* 1999, *31,* 143-148.

35 Sullivan PS, Dworkin MS, Jones JL, Hooper WC. Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. *Aids,* 2000, *14,* 321-324.

36 Tran ZV, Weltman A, Glass GV, Mood DP. The effects of exercise on blood lipids and lipoproteins: a meta-analysis of studies. *Med Sci Sports Exerc,* 1983, *15,* 393-402.

37 Thompson PD, Cullinane EM, Sady SP *et al.* Modest changes in high-density lipoprotein concentration and metabolism with prolonged exercise training. *Circulation,* 1988, *78,* 25-34.

38 Crouse SF, O'Brien BC, Grandjean PW *et al.*Training intensity, blood lipids, and apolipoproteins in men with high cholesterol. *J Appl Physiol,* 1997, *82,* 270-277.

39 Couillard C, Despres JP, Lamarche B *et al.* Effects of endurance exercise training on plasma HDL cholesterol levels depend on levels of triglycerides: evidence from men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. *Arterioscler Thromb Vasc Biol,* 2001, *21,* 1226-1232.

40 Leon AS, Rice T, Mandel S *et al.* Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the HERITAGE Family Study. *Metabolism,* 2000, *49,* 513-520.

41 Denke MA, Frantz ID, Jr. Response to a cholesterol-lowering diet: efficacy is greater in hypercholesterolemic subjects even after adjustment for regression to the mean. *Am J Med,* 1993, *94,* 626-631.

42 Crouse SF, O'Brien BC, Rohack JJ *et al.* Changes in serum lipids and apolipoproteins after exercise in men with high cholesterol: influence of intensity. *J Appl Physiol,* 1995, *79,* 279-286.