Bioelectrical impedance analysis in HIV-infected patients treated with triple antiretroviral treatment[1,2]

Achim Schwenk, Alexander Beisenherz, Gisela Kremer, Volker Diehl, Bernd Salzberger, and Gerd Fätkenheuer

ABSTRACT

Background: Triple antiretroviral treatment including protease inhibitors (PIs) delays the clinical progression of HIV infection and may thus reduce the risk of malnutrition. However, fat redistribution (lipodystrophy) was recognized recently as a metabolic side effect of PIs.

Objective: The study aimed to assess the effect of triple antiretroviral treatment on body composition and on the prevalence of malnutrition.

Design: Two cross-sectional studies, 1 in 1996 (t96; *n* = 247) and 1 in 1997 (t97; *n* = 266), were conducted in HIV-infected outpatients. Among patients who participated in both studies, 111 patients started a new antiretroviral treatment including a PI between t96 and t97 and were studied longitudinally. Total body water (TBW), intracellular water (ICW), extracellular water (ECW), and fat mass were estimated by monofrequency bioelectrical impedance analysis (BIA).

Results: Prevalence of malnutrition was reduced by 30–50% from t96 to t97, depending on the definition used. In the longitudinal study, TBW and the ratio between ICW and ECW increased and fat mass decreased (*P* < 0.001). BIA indicated a greater increase in ICW in 23 (21%) patients with clinically apparent fat redistribution than in patients without this syndrome, but estimates of fat mass changes were not significantly different.

Conclusions: Triple antiretroviral treatment may protect HIV-infected patients against the development of malnutrition. Whole-body BIA data suggest an increase in appendicular body cell mass associated with improved antiretroviral treatment. However, the method is unreliable in detecting fat redistribution, and current prediction equations will need to be recalibrated for HIV-infected patients receiving highly active antiretroviral treatment. *Am J Clin Nutr* 1999;70:867–73.

KEY WORDS AIDS, anti-HIV agents, body weight, body composition, bioelectrical impedance analysis, BIA, fat redistribution, protease inhibitors, lipodystrophy, malnutrition, wasting syndrome, weight loss, triple antiretroviral treatment, humans

INTRODUCTION

The introduction of triple antiretroviral treatment including protease inhibitors (PIs) has changed the natural history of HIV infection in industrialized countries in an unprecedented way. Viremia (1, 2), incidence of opportunistic infections (3, 4), and mortality (5) have been reduced efficiently. However, weight data have not been included in most reports of controlled trials of PI treatment (1, 4, 6) and little is known about the effect of such treatment on constitutional symptoms of HIV infection, such as weight loss.

The aim of this study was to assess the effect of triple antiretroviral treatment on nutritional status and body composition in a representative sample of HIV-infected patients. A cross-sectional study of the prognostic effect of body composition was conducted in 1996 before the widespread use of triple antiretroviral treatment. The study was repeated in 1997 after the treatment policy changed to include triple antiretroviral treatment. Patients who participated in both studies were followed longitudinally. Nutritional status was assessed by monofrequency bioelectrical impedance analysis (BIA), a noninvasive technique validated in HIV-infected patients (7) and shown previously to predict clinical outcome (8). Weight trends before and after the introduction of PIs in a malnourished subset of this population were published elsewhere (9).

After the conclusion of this study, characteristic changes in body shape with PI treatment were described by others. Redistribution of body fat stores from subcutaneous to visceral fat was observed in HIV-infected subjects, which is frequently referred to as lipodystrophy syndrome (10–12) or fat redistribution syndrome (13). In light of such observations, the focus of the present study was extended to address whether changes in BIA data reflect clinical evidence of fat redistribution.

SUBJECTS AND METHODS

Patients

The study was conducted in outpatients at the Department of Infectious Diseases, Department of Internal Medicine, University of Cologne, Germany, in accordance with the Helsinki

TABLE 1
Patient characteristics during the 2 cross-sectional studies conducted in 1996 (t96) and 1997 (t97) and the longitudinal study[1]

	Cross-sectional study		Longitudinal study subgroup at t96 (n = 97 M, 14 F)
	t96 (n = 210 M, 37 F)	t97 (n = 229 M, 37 F)	
Age (y)	39.7 ± 10.6	39.7 ± 10.5	41.0 ± 9.9[2]
CD4+ cell count (× 10^6/L)	212 ± 211	325 ± 221[3]	165 ± 157
$\log_{10}$ HIV RNA (× 10^3 copies/L)	4.3 ± 1.1	2.9 ± 1.4[3]	4.3 ± 1.0
Height (cm)	174 ± 8	175 ± 8	175 ± 8
AIDS diagnosis before the study	142 (57.5)	167 (62.8)	57 (51.3)
Opportunistic infection in the year preceding the study	60 (24.3)	51(19.2)	28 (25.2)
Infection mode[4]			
Homosexual or bisexual	161 (65.2)	159 (59.8)	75 (67.6)
Endemic areas	18 (7.3)	17 (6.4)	8 (7.2)
Intravenous drug user	19 (7.7)	15 (5.6)	8 (7.2)
Other or unknown	49 (19.8)	75 (28.2)	20 (18)

[1] x ± SD; percentages in parentheses.
[2] Significantly different from nonparticipants from the 1996 cross-sectional study, $P = 0.05$.
[3] Significantly different from t96, $P < 0.001$ (unpaired Mann-Whitney U or chi-square test).
[4] $P < 0.02$ for distribution among infection modes between t96 and t97 (chi-square test).

Declaration. All HIV-antibody-positive outpatients attending the department over two 6-wk periods were asked to participate. Three patients were excluded from the analysis because they received parenteral nutrition for >2 wk. Enteral tube feeding, human growth hormone, and progesterone or androgen derivatives were not prescribed to any patient during the study.

The first period was from March to April 1996 (t96) and the second period was from July to August 1997 (t97). Only data from the patient's first visit during each period were considered for further analysis. For t96, 247 of 254 (97.3%) patients attending the outpatient clinic gave their consent and were eligible to participate in the study; 266 of 276 patients (96.4%) participated in t97.

Of 135 patients who participated in both studies, 111 received a prescription for a new PI between their t96 and t97 assessments. These 111 patients were followed longitudinally for 497 ± 17 d (range: 445–539 d) via monthly body measurements. Body-composition trends before and after the first PI treatment were compared in a subgroup of 53 (48%) of the 111 patients in whom the first PI treatment was given ≥60 d after t96 and for whom BIA data were available within 1 wk from this starting date.

Baseline characteristics, CD4+ cell counts, and viral loads of patients in the cross-sectional and longitudinal studies are given in **Table 1**. The participants in the longitudinal study subgroup were significantly older than the patients assessed only at t96, but no other baseline characteristics were significantly different. Previous antiretroviral treatment was highly heterogeneous. In the longitudinal study, 98 (88.3%) patients had received prior treatment (median: 2 regimens; range: 1–7 regimens) for a total duration of 21 mo (range: 1–94 mo).

Study methods

Whole-body bioelectrical impedance was measured at 50 KHz with a BIA 2000-1 bioimpedance meter (Data Input, Frankfurt, Germany). All measurements were done by the same investigator (AB), using standard electrode positions (14). The relation of the 2 impedance components, reactance (Xc) and resistance (R), was expressed as phase angle $\alpha = (Xc \times 180°)/(R \times \pi)$ (8).

Total body water (TBW), fat-free mass (FFM), and intracellular water (ICW) were estimated from BIA data. We used predic-

tion equations that had been developed in HIV-infected and healthy subjects, with total body potassium, dual-energy X-ray absorptiometry, and ^3H_2O dilution as reference methods (7), assuming a constant potassium concentration in the ICW of 150 mmol/L (15). Extracellular water (ECW) was calculated as TBW minus ICW, and body fat was calculated as body weight minus FFM. Results are presented as water compartments (TBW, ICW, and ECW) rather than as the corresponding mass compartments (FFM, body cell mass, and extracellular mass) to reduce any bias resulting from abnormal hydration. Results were not significantly different from those presented below when they were calculated by using Segal et al's prediction of FFM (16), Paton et al's prediction of TBW and ICW in HIV-positive men (17), or the manufacturer's unpublished prediction equation, which calculates ICW as TBW $\times$ phase angle $\times$ constant (18) (data not shown).

Weight, in patients wearing light clothes but no shoes, was measured at every visit with an electronic scale and was recorded to the nearest 0.1 kg. The HIV load was assessed at the Institute of Virology, University of Cologne, by using quantitative polymerase chain reaction with a detection limit of 300 000 copies/L (Roche Amplicor; Hoffmann-La Roche Inc, Grenzach-Wyhlen, Germany). Routine methods were used for all other laboratory tests.

Statistics were calculated by using SPSS 7.5 (19). Comparisons were tested with nonparametric methods: Pearson's chi-square was used for dichotomous variables and the Mann-Whitney U test was used for intraindividual and intergroup comparisons of continuous variables. The effect of fat redistribution on the relation between changes in body weight, fat mass, ICW, and ECW was determined with a general linear model.

Because there is no generally accepted definition of malnutrition (20, 21), several definitions were arbitrarily chosen to compare the prevalence of malnutrition in the 2 cross-sectional studies:
1) the wasting syndrome as defined in the 1993 AIDS case definition (22): weight loss of >10% of body weight in a 3-mo period, together with fever, diarrhea, or both, of unknown origin;
2) actual body weight <90% of usual weight, as self-reported, preceding the first disease symptoms (23);
3) current weight loss >5% in a 1-mo period;
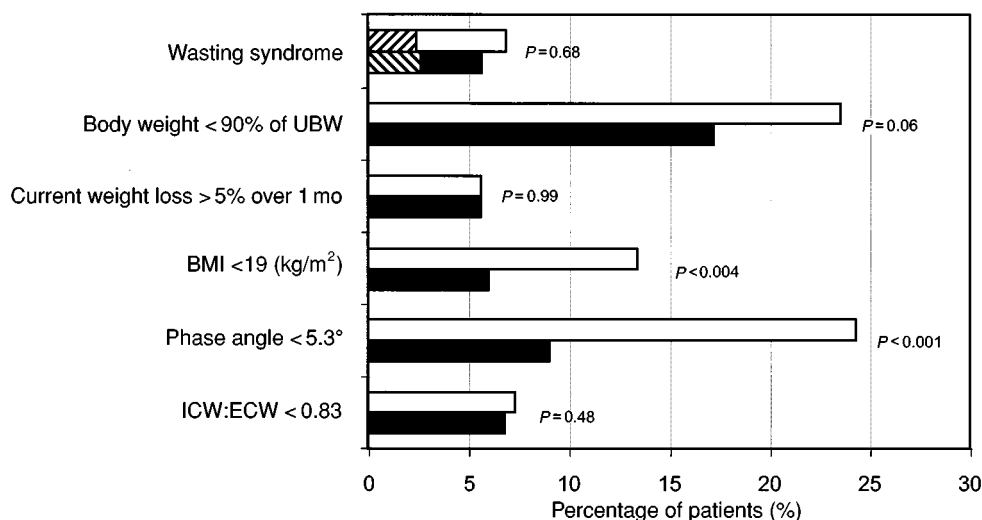*4*) actual body mass index (BMI; in kg/m²) <19 (24);

FIGURE 1. Prevalence of malnutrition in HIV-infected outpatients in 2 time periods: April to May 1996 (white bars; $n = 247$) and July to August 1997 (black bars; $n = 266$). For wasting syndrome, the black and striped bars indicate a diagnosis ≤ and >1 y before the assessment, respectively. Significance was determined by chi-square test. UBW, usual body weight; ICW, intracellular water; ECW, extracellular water.

5) phase angle α $<5.3°$ by BIA (which is the lower quartile of the t96 sample, *see* Discussion); and

6) ICW:ECW <0.83, analogous to the proposed ratio of extracellular and body cell mass of >1.2 (25).

Cases with fat redistribution between t96 and t97 were identified retrospectively by a dietitian (GK) and 2 physicians (BS and GF) from the outpatient department, who were blinded to the BIA data but had been continuously involved in the clinical care of the patients throughout the study period. Fat redistribution was defined as either a disproportionate increase in abdominal girth in a patient who was weight stable or lost weight, or a visible reduction in subcutaneous fat in the extremities or face irrespective of weight changes during the time period between t96 and t97. Objective measurement of fat mass distribution was not available in this study, which was planned before recognition of the fat redistribution syndrome.

RESULTS

During the time between the 2 cross-sectional studies, the antiretroviral treatment policy in the department changed considerably. At t96, only 17 patients (7%) had been treated with a PI, all having received saquinavir (Invirase; Hoffmann-La Roche Ltd, Basel, Switzerland) for a mean (±SD) of 155 ± 163 d. By t97, 171 patients (64%) were receiving treatment including a PI, with a mean (±SD) treatment duration of 187 ± 126 d. The PIs used at t97 were indinavir (Crixivan; Merck & Co, Inc, Whitehouse Station, NJ), ritonavir (Norvir; Abbott Laboratories, Chicago), saquinavir, and nelfinavir (Viracept; Agouron Pharmaceuticals, Inc, La Jolla, CA) in 75, 48, 25, and 23 patients, respectively. Eight additional patients had taken a PI for 38 ± 73 d but had discontinued treatment before t97. Other components of antiretroviral treatment changed as well. For example, the number of patients taking the nucleoside analogue lamivudine (Epivir; Glaxo Wellcome Inc, Research Triangle Park, NC) increased from 26 (10%) at t96 to 197 (74%) at t97.

The prevalence of malnutrition was lower at t97 than at t96 according to most of the definitions of malnutrition (**Figure 1**). Differences in prevalence between t96 and t97 were largest for definitions based on the percentage loss from usual body weight and on BIA data (definitions *2*, *5*, and *6*). Nonsignificant trends toward a lower prevalence of wasting syndrome and of current weight loss in t97 were observed (definitions *1* and *3*). The distribution of BIA results and BMI at t96 and t97 is shown in **Table 2**. Patients participating in the t97 study had a higher BMI, lower resistance and reactance, and higher phase angle than did patients participating in the t96 study. These data resulted in significantly higher estimates of TBW, ICW, and ECW; lower estimates of body fat; and a higher ECW:ICW ratio in t97 than in t96 patients.

These changes were partly explained by demographic shifts in the population studied. Those patients in the t96 study who also participated in the t97 study ($n = 135$) entered the t96 study with a higher BMI and phase angle than did patients who died ($n = 36$) or who were lost to follow-up ($n = 76$) between t96 and t97 ($P < 0.02$). This was explained by the association between the lowest quartile of phase angle ($<5.3°$) at t96 and higher mortality (A Schwenk et al, unpublished data, 1999). Furthermore, CD4+ cell counts in patients who participated in t97 only were $255 ± 224 ×10^6/L$ during 1996 and $320 ± 273 × 10^6/L$ during 1997 ($P < 0.01$), possibly because antiretroviral treatment tends to be started earlier now in the course of infection (26). Other clinical data with potential effects on the prevalence of malnutrition are given in Table 1. Patients in the t97 study had a lower viral load and higher CD4+ cell counts than did those in the t96 study ($P < 0.001$), but the incidence of opportunistic infections in the preceding year was not significantly different.

In the longitudinal study of patients commencing PI treatment, marked changes in bioelectrical impedance were observed. Both resistance and reactance decreased and the phase angle increased (resistance: from 572 ± 78 to 502 ± 70 Ω; reactance: from 59 ± 9 to 55 ± 9 Ω; and phase angle: from 5.9 ± 0.7 to 6.3 ± 0.8°; $P < 0.001$ for all). BIA estimates of body composition showed a significant

TABLE 2
Differences in weight and body-composition values between the 1996 (t96) and 1997 (t97) cross-sectional studies[1]

	t96 ($n = 247$)	t97 ($n = 266$)
Body mass index (kg/m^2)	22.3 ± 3.2	23.1 ± 3.3[2]
Reactance (Ω)	58.5 ± 10.2	55.1 ± 9.2[3]
Resistance (Ω)	579.9 ± 89.0	506.5 ± 74.7[3]
Phase angle α (°)	5.8 ± 0.9	6.2 ± 0.8[3]
Total body water (L)	39.5 ± 6.2	42.6 ± 6.8[3]
Intracellular water (L)	20.7 ± 3.9	22.7 ± 4.3[3]
Extracellular water (L)	18.8 ± 2.8	19.9 ± 3.1[3]
Fat-free mass (kg)	54.5 ± 7.9	57.8 ± 8.3[3]
Body fat (kg)	13.5 ± 5.5	13.0 ± 5.9
ICW:ECW	1.10 ± 0.16	1.15 ± 0.17[3]

[1] $\overline{x}$ ± SD. ICW, intracellular water; ECW, extracellular water.
[2,3] Significantly different from t96 (unpaired Mann-Whitney U test): [2] $P = 0.007$, [3] $P < 0.001$.

gain in TBW and a loss of body fat mass (**Figure 2**). ICW:ECW increased from 1.12 ± 0.15 to 1.16 ± 0.16 ($P < 0.001$).

However, these changes seem to have begun before PI treatment began. Changes in body weight and BIA before and after the first PI treatment in the 53 patients evaluable in this analysis are given in **Table 3**. Although these patients lost weight before and gained weight after the first PI dose, the phase angle increased likewise before and after this date. On the basis of BIA data, weight loss before PI treatment began was mainly due to a loss in fat mass, whereas weight gain after the first PI dose occurred mainly in the

water compartments. Similar results were obtained when changes were calculated as trends (kg/d or °/d, data not shown). The subset of 53 patients analyzed for these changes was not representative of the 111 patients studied longitudinally. This subset of 53 patients tended to have lost more weight before their first PI dose and gained more weight afterward (before PI: −0.1 ± 4.0 compared with 1.0 ± 3.7 kg, $P = 0.17$; after PI: 1.9 ± 5.3 compared with −1.0 ± 2.6 kg, $P < 0.001$) than did the other patients and were also more likely to receive nutritional counseling [27 of 53 (51%) compared with 19 of 58 (33%) patients, $P < 0.05$].

Fat redistribution syndrome was identified by retrospective clinical observation of 23 of the 111 patients (20.7%) in the longitudinal study. It was associated with an increased phase angle and increased estimates of ICW but not of body fat or ECW (**Table 4**). In a general linear model with weight change and fat redistribution as independent variables and change in ICW as the dependent variable, patients with fat redistribution syndrome had a significantly higher ICW at every level of weight gain than patients without the syndrome. In contrast, similar models with ECW change or fat mass change as dependent variables showed no influence of fat redistribution on the regression between changes in the compartment and in weight ($P = 0.49$ and $P = 0.18$ for ECW and body fat, respectively).

Virologic and immunologic outcome criteria of antiretroviral treatment were not significantly associated with changes in TBW or ICW:ECW between t96 and t97. Criteria tested for this were the extent and duration of reduction in HIV viremia, an increase in CD4$^+$ cells, and the duration of time that CD4$^+$cell counts were >50 × 10^6/L. Patients who began taking 1 or 2 other new
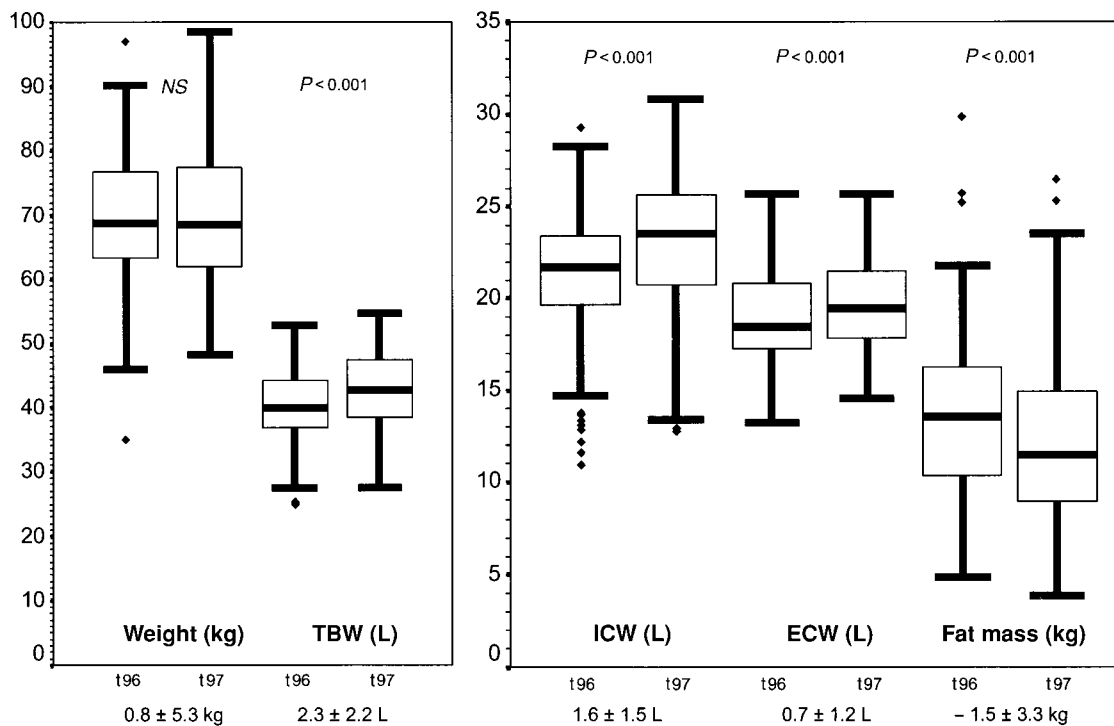

FIGURE 2. Changes in body-composition estimates in HIV-infected patients ($n = 111$) from 1996 (t96) to 1997 (t97) before and during treatment with protease inhibitors. The box and whisker plot show the median (horizontal line), interquartile range (box: contains 50% of all values), outlier (whiskers: contain values outside of the interquartile range, excluding extreme values), and extreme (diamonds: > 3.5 interquartile ranges different from the median) values. Mean (±SD) changes from t96 to t97 are indicated below the panels. Significance was determined by using paired Mann-Whitney U tests. TBW, total body water; ICW, intracellular water; ECW, extracellular water.

TABLE 3
Changes in bioelectrical impedance analysis (BIA) data before and after the first treatment with a protease inhibitor (PI)[1]

	Before (from t96 to first PI treatment)	After (from first PI treatment to t97)
Phase angle (°)	0.21 ± 0.51	0.21 ± 0.65
TBW (kg)	0.7 ± 1.7	2.0 ± 2.5[2]
ICW (kg)	0.6 ± 1.2	1.2 ± 1.7
ECW (kg)	0.0 ± 1.0	0.8 ± 1.2[3]
Fat (kg)	−1.0 ± 2.2	0.1 ± 3.3
Weight (kg)	−0.4 ± 3.5	2.2 ± 5.5[2]

[1] $\bar{x}$ ± SD. Data were from a subset of 53 of 111 patients with a baseline period >60 d between t96 and the first PI treatment and in whom BIA was performed within 1 wk of the first PI treatment (*see* text). TBW, total body water; ICW, intracellular water; ECW, extracellular water; t96, 1996 study; t97, 1997 study.

[2,3] Significantly different from before PI treatment (paired Mann-Whitney *U* test): [2] $P < 0.02$, [3] $P < 0.01$.

antiviral medications at the same time as beginning PI treatment had a greater increase in ICW:ECW than did patients who began taking a PI as part of an existing regimen (0.05 ± 0.08 compared with 0.02 ± 0.06, $P = 0.03$). Otherwise, no influence on changes in TBW or ICW:ECW was identified on the basis of the antiretroviral drug combination, the duration of PI treatment between t96 and t97, the number of previous treatment regimens, or the time since antiretroviral treatment began.

DISCUSSION

In the 2 cross-sectional studies, a marked reduction in the prevalence of malnutrition in HIV-infected outpatients was observed between spring 1996 and autumn 1997 (Figure 1). About 33% fewer patients were found to be underweight when compared with their usual body weight or with BMI standards, and the prevalence of malnutrition on the basis of BIA criteria decreased by >50% between t96 and t97.

In the patients followed longitudinally, BIA data suggest a mean increase in TBW of 2.3 L and a loss in body fat of 1.5 kg (Figure 2). Moreover, the increase in TBW appeared to consist predominantly of ICW. This observation contrasts with the findings of longitudinal studies in HIV-infected patients before the era of highly active antiretroviral treatment, in which decreases in ICW:ECW and body cell mass were observed consistent with a chronic catabolic illness (27, 28).

How much of such an improvement in body composition can be attributed to the new antiretroviral therapies? Although it has been proposed that the HIV viral load itself contributes to the pathogenesis of wasting (29, 30), improvements in viral load and immune function with the new therapies were not correlated with changes determined by BIA in our study. Weight gain was documented previously in patients receiving PI treatment (31, 32; A Teixeira, JC Leu, P Honderlick, A Trylesinski, D Zucman, unpublished observations, 1997). Two smaller studies of body composition during PI treatment had conflicting results, one showing increased body cell mass (D Berger, G Bucher, P Cimoch, et al, unpublished observations, 1997) and the other showing predominantly fat gain (33). In our study, BIA indexes showed an improving trend even before the first PI dose. In a malnourished subset of the same population, we showed previously that

weight trends were similar 100 d before and 200 d after the first PI treatment (9). An explanation for this finding is that the loss in body fat may have balanced the gain in FFM. Alternatively, previous changes in antiretroviral treatment may have improved body composition by reducing morbidity (5).

A new pattern of body fat redistribution was observed recently in HIV-infected patients: an increase in visceral fat and a decrease in subcutaneous fat (10, 12). Hyperlipoproteinemia and insulin resistance are regular features of the syndrome (12, 34). There is controversy about whether it represents a side effect of PI treatment on lipid metabolism (35) or whether it is related to improved antiretroviral control irrespective of the drugs used (13, 36, 37). In the present study, BIA showed a similar pattern of improvement in body composition in patients with and without a clinical diagnosis of fat redistribution (Table 4). Moreover, fat redistribution was associated with an increase in ICW adjusted for weight changes. In contrast, changes in body fat estimates from BIA were independent of fat redistribution.

Two contrasting interpretations of these data are as follows. First, fat redistribution may introduce a systematic bias into BIA estimates of TBW and its components. Alternatively, the results of BIA may represent a true increase in TBW and ICW:ECW, which might result from a gain in appendicular muscle mass because of improved antiretroviral control and reduced catabolic drive.

The first interpretation is based on limitations of the BIA method that are not always appreciated. Measured whole-body impedance is determined predominantly (>90%) by the impedance of the limbs, even though the limbs contain <50% of TBW (38). An apparent increase in TBW may therefore be due to redistribution of TBW from the trunk to the extremities. BIA is unreliable for estimating total body fat (39) because the electrical current mainly passes through FFM, and fat mass is calculated by subtraction. Whole-body BIA does not assess regional body

TABLE 4
Comparison of changes from t96 to t97 in bioelectrical impedance analysis results, body weight, and serum lipids between patients with and without fat redistribution syndrome[1]

	Fat redistribution[2]	
	No ($n = 88$)	Yes ($n = 23$)
ΔPhase angle (°)	0.28 ± 0.53	0.64 ± 0.68[3]
ΔResistance (Ω)	−65.2 ± 40.6	−86.1 ± 39.8[4]
ΔReactance (Ω)	−4.3 ± 6.66	−3.17 ± 6.49
ΔTBW (L)	2.1 ± 2.0	3.1 ± 2.8
ΔFFM (kg)	2.1 ± 2.4	3.0 ± 3.4
ΔICW (L)	1.4 ± 1.3	2.3 ± 1.9[5]
ΔECW (L)	0.7 ± 1.2	0.7 ± 1.4
ΔICW:ECW	0.031 ± 0.075	0.073 ± 0.084[4]
ΔFat mass (kg)	−1.5 ± 3.1	−1.3 ± 4.2
ΔWeight (kg)	0.6 ± 4.8	1.7 ± 7.1
ΔTriacylgerol (mmol/L)	1.2 ± 3.1	3.1 ± 5.6[6]
ΔCholesterol (mmol/L)	0.71 ± 1.3	1.5 ± 2.2

[1] $\bar{x}$ ± SD. TBW, total body water; ICW, intracellular water; ECW, extracellular water; FFM, fat-free mass; t96, the 1996 study; t97, the 1997 study.

[2] Cases of fat redistribution were identified retrospectively on the basis of a disproportionate increase in abdominal girth in a patient who was weight stable or lost weight or who had a visible reduction in subcutaneous fat in the extremities or face, irrespective of weight changes during the time period between t96 and t97.

[3–6] Significantly different from no fat redistribution (unpaired Mann-Whitney *U* test): [3] $P = 0.03$, [4] $P = 0.04$, [5] $P = 0.02$, [6] $P = 0.05$.

composition, in contrast with dual-energy X-ray absorptiometry (40) and, perhaps, segmental BIA (41, 42). Finally, loss of intramuscular fat could potentially alter the dispersion of the electrical current within the muscle and thus the phase angle. For all these reasons, empirical prediction equations for body composition from BIA may no longer be valid in populations of HIV-infected patients with a high incidence of fat redistribution. Because BIA is often used in this setting for clinical monitoring and research, new validation studies are warranted.

The second interpretation relied on the finding that an improved phase angle was already observed before PI treatment began. Because fat redistribution was not observed in any patient before the first PI dose, it is unlikely that the changes detected with BIA were entirely attributable to fat redistribution. As discussed above, BIA mostly detects changes in appendicular body mass. Increased TBW estimates and an increased ICW:ECW may therefore be best interpreted as a gain in appendicular muscle mass. BIA estimates of body cell mass are well correlated with muscular performance (43, 44). Suppression of the catabolic effects of viremia, decreased incidence of opportunistic infections, or increased physical activity of patients are plausible explanations for a gain in appendicular muscle mass in patients receiving successful antiretroviral treatment.

Even though the biological correlate of impedance is incompletely understood, a decreased phase angle has predicted mortality in HIV-infected subjects not receiving PI treatment, independent of $CD4^+$ cell count (8, 45). A similar prognostic effect of phase angle was found in our study population (A Schwenk et al, unpublished data, 1999). Apart from its correlation with the ICW:ECW, the phase angle may be interpreted as a global marker for cell membrane integrity (8, 46).

Some limitations of the study should be considered. Cases of fat redistribution syndrome were identified retrospectively by clinical judgement, not by anthropometric assessment. Although clinical judgement correlates well with objective criteria (47), the study could not provide valid data about the prevalence of the syndrome. The longitudinal study excluded patients who died or were lost to follow-up between t96 and t97 or who did not start PI treatment between these 2 time points. Therefore, malnourished patients from the t96 sample were underrepresented and PI-unrelated effects could be detected. Comparison of trends before and after the first PI dose must consider a bias in the evaluable subgroup toward patients undergoing nutritional counseling.

This study may have important implications for clinical research and care. Researchers planning controlled trials of antiretroviral treatment in HIV-infected patients are encouraged to incorporate weight and body composition as secondary endpoints. In HIV-infected patients, whole-body BIA should not be used to quantify body fat redistribution. Even for TBW and ICW assessment, this method will need recalibration by reference methods in populations receiving highly active antiretroviral treatment. In more general terms, our study provides evidence that, despite its adverse effects, highly active antiretroviral treatment may protect HIV-infected patients against malnutrition.

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