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Cytokine-Driven Inflammatory Response Is Associated with the Hypermetabolism of AIDS Patients with Opportunistic Infections

Pilar García-Lorda, MD*; Pilar Serrano, MD†; María Jesús Jiménez-Expósito, MD*‡; Julia Fraile, RN†; Mónica Bulló, BSc*; Carlos Alonso, MD PhD‡; Anna Bonada, MD*‡; Pompeyo Viciana, MD†; Pedro P. García Luna, MD, PhD†; and Jordi Salas-Salvadó, MD, PhD*‡

*From the *Human Nutrition Unit, Faculty of Medicine and Health Sciences, Rovira i Virgili University, Reus; ‡Service of Internal Medicine, University Hospital of Sant Joan, Reus; and †Nutrition Unit, Virgen del Rocío Hospital, Sevilla, Spain*

ABSTRACT. *Background:* To assess a possible role of systemic inflammation in the resting metabolic response in AIDS patients with active secondary infections. *Methods:* Fifty-two patients with AIDS-defined criteria and concomitant active infections and 19 healthy subjects were studied. Measurements were as follows: body composition assessed by bioelectrical impedance; resting energy expenditure (REE) by 30-minute indirect calorimetry; cytokine concentrations (IL-6, IFNα, TNFα, sTNF-R1) by ELISA; C-reactive protein (CRP), erythrocyte sedimentation rate, fibrinogen, and nutritional parameters by standard techniques. *Results:* REE adjusted for fat-free mass (REE_{FFM}) was significantly increased in AIDS patients despite 39% of them not being hypermetabolic. The patients were undernourished and were found to have increased levels of acute-phase proteins and increased concentrations of IL-6 and sTNF-R1 relative to controls. REE parameters were positively related to CRP, ESR, ferritin, IL-6, and sTNF-R1 and negatively related to albumin, prealbumin, and transferrin. CRP was an independent predictor of REE_{FFM} in AIDS patients and explained 25% of its variability. Patients with severe inflammation (CRP ≥ 37 mg/dL) were significantly hypermetabolic with respect to patients without inflammation (CRP < 6 mg/dL) and had higher levels of IL-6 and sTNF-R1 and lower levels of albumin and prealbumin. Although no significant differences were observed with respect to the infection type, patients with tuberculosis and *Pneumocystis carinii* infections had higher resting metabolic and inflammatory responses, whereas patients with recurrent bacterial pneumonia were normometabolic and had lower levels of inflammatory markers. *Conclusions:* Resting hypermetabolism observed in AIDS patients with concurrent active infections is related to the presence and severity of systemic cytokine-driven inflammatory response, which could reflect the type of secondary infection. (*Journal of Parenteral and Enteral Nutrition* **24**:317–322, 2000)

Weight loss is a common feature in the natural history of acquired immunodeficiency syndrome (AIDS). With new treatments the clinical course of the disease has changed, and survival has improved significantly.[1] Despite this, however, even modest weight losses have been shown to have deleterious health effects.[2] Several variables affecting energy balance, such as a reduced energy intake, malabsorption, and hypermetabolism, have been implicated in this phenomenon[3,4] but, to date, without consensus. Although some studies have shown an increase in resting energy expenditure (REE) in the early stages of the disease,[5–7] others have failed to demonstrate it.[8] Resting hypermetabolism appears somewhat more consistent when advanced phases of the disease are investigated and when intercurrent, secondary infections are present. However, in patients with signs or symptoms of active secondary infections, a high variability in the hypermetabolic resting response is observed between individuals and between studies. Increases ranging from 11% in REE adjusted for lean body mass[9] to 58% in REE:fat free mass (FFM)[10] relative to control subjects have been reported.

Variability in REE response to secondary infections may have a variety of causes. First, differences between patients with respect to body composition need to be taken into account. Also, depending on the type of the opportunistic infection involved, different metabolic responses, ranging from hypometabolism to hypermetabolism, have been observed.[11] Furthermore, intestinal loss of calories because of malabsorption (a common feature in advanced stages of AIDS) is known to produce a decrease in REE as an adaptive response to energy restriction.[12] Finally, it has been suggested that the rate of viral turnover could be related to the hypermetabolism seen in HIV-infected patients.[13]

Infection could cause a cytokine-mediated host response such as a systemic acute-phase response leading to metabolic derangements, including hypermetabolism.[14] The contribution of cytokine-driven inflammation to hypermetabolism has been investigated in different clinical conditions.[15,16] Recently, the involvement of inflammatory mediators, such as TNF in resting hypermetabolism accompanying HIV infection, has

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Correspondence and reprint requests: Jordi Salas-Salvadó, MD, PhD, Unitat de Nutricio Humana, Universitat Rovira i Virgili, C/ Sant Llorenc 21, 43201 Reus, Spain. Electronic mail may be sent to jss@fmcs.urv.es.

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been widely debated but without clear conclusions.[17] Hence, we undertook to explore the systemic inflammatory response and the energy expenditure response in HIV-infected patients with active secondary opportunistic infections.

MATERIALS AND METHODS

Subjects and Study Design

Fifty-two AIDS patients who presented with active opportunistic infections related to the AIDS were included in the study (42 men, 10 women, age range, 24 to 56 years). Seventeen of these patients were being cared for in the Internal Medicine wards of Hospital Sant Joan de Reus and the rest in the Nutrition Unit wards of Hospital Virgen del Rocío. All were seropositive for HIV infection by enzyme-linked immunosorbent assay (ELISA), confirmed by Western blot analysis, and met criteria for AIDS classification according to the Centers for Disease Control and Prevention.[18] Criteria for inclusion into the study were the existence of signs or symptoms of active opportunistic infections at the time of study, and those patients who presented with Kaposi's sarcoma, lymphoma, or any other neoplastic disease were excluded. Other exclusion criteria were the presence of diabetes, kidney failure, nephrotic syndrome, active hepatitis, or cirrhosis; a body temperature >38°C at the time of the metabolic measurements; or the use of corticoids, hormone replacement, or any other drug known to affect energy expenditure.

Nineteen clinically healthy and weight stable volunteers at low risk of HIV infection were recruited from among the hospital staff to serve as a control group (14 men, 5 women; age range, 27 to 44 years).

At 8 AM, after an overnight 12-hour fast, blood samples were drawn for laboratory analyses, and body composition and energy expenditure measurements were performed.

The study was approved by the Medical Ethics Committees of both hospitals on the understanding that inclusion into the study would not modify the antiretroviral treatment received by the patients in accordance with the protocols of both hospitals. All participants provided fully informed consent.

Body Composition Measurements

Height and weight were recorded on admission and body mass index (BMI) was then calculated. Body composition was assessed by tetrapolar bioelectrical impedance analysis[19] as we have described elsewhere,[20] and FFM was estimated using the specific equations of Segal et al.[21]

Blood Analyses

The blood samples were processed immediately on receipt in the laboratory. Plasma was frozen and stored at −70°C for batched determination of cytokines.

Serum albumin, prealbumin, total iron-binding capacity, ferritin, and erythrocyte sedimentation rate (ESR) were measured using standard in-house methods. Serum concentration of C-reactive protein (CRP) was measured using an immunoturbidimetric assay (Analizador ILab 900; Instrumentation Laboratories, Milano, Italy). Fibrinogen was determined by spectrophotometry (ACL 1000; Instrumentation Laboratories). IL-6, IFNα, and TNFα plasma concentrations were determined using ELISA (Amersham, Buckinghamshire, United Kingdom), and the levels of sensitivity of the assays were 1, 3, and 5 pg/mL, respectively. sTNF-R1 plasma concentrations were determined using ELISA (BioSource Europa, Nivelles, Belgium), the level of sensitivity of which was 0.05 ng/mL. All cytokine measurements were performed in duplicate. Peripheral blood CD4 and CD8 lymphocyte subset counts were by flow cytometry (FacScan; Becton-Dickinson, San Jose, CA). Viral load was quantified by reverse transcriptase-polymerase chain reaction (RT-PCR) using commercial kits (Amplicor HIV-1 Monitor; Roche Diagnostic Systems, Branchburg, NJ). β_2-microglobulin (B_2M) was determined using quantitative enzyme immunoassay (Ilab 7200; Biokitt, Barcelona, Spain).

Energy Expenditure Measurements

Vo_2 and Vco_2 were measured under basal conditions by 30-minute open-circuit indirect calorimetry (Deltatrac; Datex Instrumentation; Helsinki, Finland) as previously described.[22]

The within-individual coefficient of variation for day-to-day replicate measurements of REE was 2.3% and 2.1% in the two hospitals. Twenty-four-hour urinary nitrogen excretion was determined by the Kjeldahl technique. From these measurements, the observed REE (REEo) was calculated using the equation of Weir.[23] The modified Weir's equation was used when urinary nitrogen elimination was not available (7 patients and 1 control subject). Fasting respiratory quotient (RQ) was calculated as Vo_2/Vco_2. The predicted REE (REEp) was calculated from the Harris and Benedict equations[24] and the ratio REEo/REEp was expressed as a percentage. Resting energy expenditure values are expressed as kJ/d.

Statistical Analyses

Data are presented as means ± SD unless otherwise indicated. Prevalences were compared using the contingency table χ^2 test. Differences in mean values between control subjects and HIV-infected groups were assessed by the Mann–Whitney nonparametric test. Groups of patients were compared using the Kruskal–Wallis test. When group comparisons were significant, pairs of populations were compared using the Mann–Whitney test. Regression analyses were conducted for quantitative variables and regression coefficients (r) were derived. Probability values of $p < .05$ were considered significant.

To allow for comparisons among subjects with different body composition, the unexplained residual of REE values in each subject was calculated by the general linear model procedure, introducing FFM as a covariate. The adjusted REE (REE_{FFM}) values for each individual were calculated by adding the individual's residual REE value to the mean REE value of the whole study population or to the mean REE value of the AIDS

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TABLE I
Energy metabolism parameters in control subjects and AIDS patients

	Control subjects (n = 19)	AIDS patients (n = 52)
$REE_{observed}$ (kJ/d)	6884.1 ± 863.3	6762.04 ± 1190.8
REE_{FFM} (kJ/d)	6290.3 ± 432.8	6978 ± 846.8*
REE_{Weight} (kJ/d)	6213.1 ± 526.3	7007.2 ± 966.5*
REEo/REEp (%)	99.9 ± 6.7	115.0 ± 15.3†
RQ	0.84 ± 0.003	0.83 ± 0.007

Values are presented as means ± SD. REE_{FFM}, REE adjusted for fat-free mass; REE_{Weight}, REE adjusted for body weight; REEo/REEp, REE as a percentage of predicted; RQ, respiratory quotient.
*$p < .005$; †$p < .001$.

patients when this group was analyzed separately. The same procedure was used to adjust REE for differences in body weight (REE_{Weight}).

To identify the factors affecting REE, a multiple stepwise regression analysis was conducted in which age, gender, BMI, previous weight losses, albumin, prealbumin, CRP, TNFα, sTNF-R1, IFNα, IL-6, B_2M, CD4, and viral load were entered as independent variables.

RESULTS

AIDS patients were undernourished, as reflected in the anthropometric measurements and nutritional parameters (BMI, 18.5 ± 2.4 [kg/m^2]; percentage body fat; 11.1% ± 7.5%; albumin 27.4 ± 7.8 g/L; prealbumin 0.15 ± 0.11 g/L). All AIDS patients were below what they reported as having been their customary pre-HIV–infection weight; losses in weight ranged from 1.6% to 43% of the reported body weight. About 96% of the patients had lost >5% of their customary weight, 78% >10%, 39% >20%, and only 7.8% had lost >30% of their usual body weight. Mean weight lost in the previous month was 5.14 ± 3.2 kg.

Compared with controls, AIDS patients presented higher levels of inflammation markers: CRP (33.0 ± 57.2 *vs* <6 mg/L; $p < .001$), ESR (73.5 ± 38.4 *vs* 5.05 ± 4.01; $p < .001$), and ferritin (879.6 ± 769.8 *vs* 81.5 ± 76.6 μg/L; $p < .001$). IL-6 concentrations were significantly higher in AIDS patients than in control subjects (8.32 ± 13.5 *vs* 1.34 ± 3.0 pg/mL; $p < .005$). IL-6 was undetectable in 14% of the AIDS patients. No significant differences in plasma concentrations of TNFα and IFNα were observed between groups. Plasma concentrations of sTNF-R1 were significantly increased in HIV-infected patients compared with healthy controls (4.06 ± 1.8 *vs* 1.72 ± 0.3 ng/mL; $p < .001$).

In relation to energy expenditure parameters, no significant differences were found in the REEo but, when adjusted for FFM or for weight, the patients showed a significantly higher REE compared with controls (Table I). The REEo/REEp was significantly increased in AIDS patients relative to controls. Only 2% of the AIDS patients (n = 1) were hypometabolic (REEo/REEp < 90%), 36.5% (n = 19) were normometabolic (REEo/REEp 90% to 110%), and 61.5% (n = 32) were hypermetabolic (REEo/REEp ≥ 110%). Energy expenditure parameters were positively correlated with CRP, ESR, IL-6, sTNF-R1, and ferritin and negatively with albumin, prealbumin, and total iron-binding capacity (Fig. 1). A significant relationship between plasma IL-6 concentrations and plasma sTNF-R1 concentrations was observed ($r = .63$; $p < .01$). Serum CRP concentrations were significantly related to IL-6 concentrations ($r = .66$, $p < .01$) and to sTNF-R1 concentrations ($r = .54$; $p < .01$) in the overall study population.

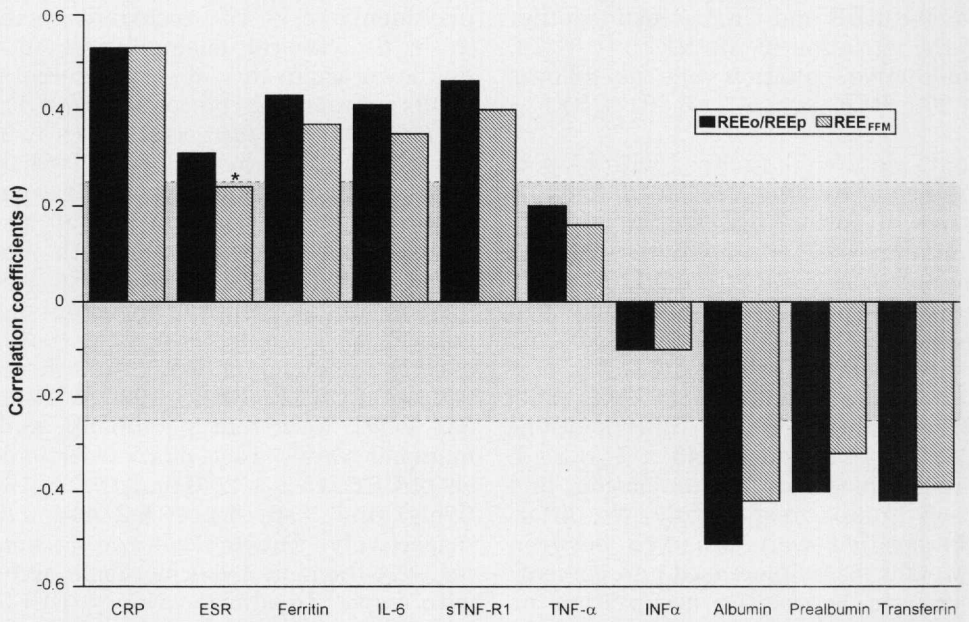

FIG. 1. Correlation coefficients of energy expenditure parameters and inflammation markers in the whole study population (n = 71). REE_{FFM}, resting energy expenditure adjusted by fat-free mass; REEo/REEp, observed resting energy expenditure as a percentage of predicted. Bars beyond the horizontal dotted lines correspond to $p < .01$; *$p < .05$.

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TABLE II
Comparisons between the inflammation categories in AIDS patients

	No inflammation (CRP < 6 mg/L) (n = 23)	Moderate inflammation (CRP 6–37 mg/L) (n = 13)	Severe inflammation (CRP ≥ 37 mg/L) (n = 13)
REE (kJ/d)	6313 ± 1199	6760 ± 1008	7543 ± 1009*
REE_{FFM} (kJ/d)	6554 ± 676	6610 ± 975	7181 ± 806†
REEo/REEp (%)	109 ± 15	114 ± 15	124 ± 14*
RQ	0.86 ± 0.08	0.81 ± 0.05	0.78 ± 0.03‡
IL-6 (pg/mL)	4.03 ± 9.6	5.1 ± 6.9	20.57 ± 18.4‡¶
TNFα (pg/mL)	2.1 ± 5.0	6.2 ± 11.8	1.3 ± 4.2
sTNF-R1 (ng/mL)	3.38 ± 1.04	3.77 ± 1.05	5.41 ± 2.6*††
IFNα (pg/mL)	9.0 ± 12.6	4.9 ± 4.7	3.8 ± 4.8
Fibrinogen (mg/dL)‖	344.6 ± 76.4	466.3 ± 166.4	471.8 ± 174.3§
Erythrocyte sedimentation rate	65.23 ± 37.2	72.27 ± 38.7	83.5 ± 36.0
Ferritin (μg/L)	667.4 ± 511.6	597.3 ± 385.0	1604.6 ± 1004.3§¶
Albumin (g/L)	32.0 ± 6.9	25.4 ± 6.3†	21.5 ± 5.4‡
Pre-albumin (g/L)	0.22 ± 0.13	0.12 ± 0.06*	0.06 ± 0.05‡¶
Transferrin (g/L)	2.3 ± 0.6	1.8 ± 0.3*	1.4 ± 0.3‡#
CD4	86.1 ± 111.3	116.6 ± 119.3	89.3 ± 145.8
Log viral load	5.42 ± 0.69	4.87 ± 1.05	4.82 ± 0.86
β_2 microglobulin (mg/dL)	4.04 ± 1.7	3.4 ± 1.0	3.0 ± 0.8†

Values are presented as mean ±SD. Only 49 patients are presented as no C-reactive protein data were available in 3 patients. IFN, interferon.
‖Fibrinogen determinations were only available in 14, 8, and 9 patients classified as having none, moderate, and severe inflammation, respectively.
*$p < .005$; †$p < .05$; ‡$p < .001$; §$p < .01$ *versus* group without inflammation.
#$p < .05$; ¶$p < .01$ *versus* patients with moderate inflammation.
‡‡$p = .05$ *versus* patients with moderate inflammation.

FFM was the main determinant of REE for the whole study population (control subjects and AIDS patients) and explained 46% of the variation observed. When AIDS patients were assessed separately, REE remained dependent on FFM ($r = .73$; $p < .01$), and CRP was an independent predictor of REE_{FFM} ($r = .50$; $p < .001$). No significant relationship between previous weight losses and REE, CRP production, or cytokine levels was observed in the group of HIV-infected patients. A weak, but significant, correlation between the REEo and the REEp was found in the AIDS group ($r = .59$; $p < .01$). In a multiple stepwise regression analysis, the predicted REE and CRP values together explained 55% of the variation in the REEo ($r = .74$; $p < .01$). The predictive equation was as follows: $REE_{observed} = (1.273\ REE_{predicted} + 6.891\ CRP) - 959.178$.

The AIDS patients' data were grouped with respect to presence or absence of inflammation as defined by the laboratory range of normal distribution of CRP: those with inflammation (CRP ≥ 6 mg/L, n = 26) and those without inflammation (CRP < 6 mg/L, n = 23). The group with inflammation was further subdivided on the 50th percentile into two groups: those patients having moderate inflammation (CRP <37 mg/L; n = 13) and those with severe inflammation (CRP ≥ 37 mg/L; n = 13). Mean values for CRP concentrations were 5.0 ± 1.2, 19.95 ± 11.6, and 104.45 ± 71.8 mg/L for no inflammation, moderate inflammation and severe inflammation groups, respectively. No differences in body composition were observed between groups. Previous weight losses increased and percentage fat mass decreased across the group from no inflammation to moderate inflammation to severe inflammation categories, albeit not statistically significantly. As shown in Table II, REE variables increased progressively across categories of inflammation. Compared with control subjects, REEo/REEp was 24% higher in the patients with severe inflammation but only 9% higher in those without inflammation. Fibrinogen, sTNF-R1, and IL-6 values were significantly increased across the groups from those without to moderate to severe inflammation, whereas the acute-phase negative proteins (albumin, prealbumin, transferrin) decreased from the low to the high category of inflammation.

The secondary infections were subsequently diagnosed as: tuberculosis (n = 15), *Pneumocystis carinii* pneumonia (n = 12), recurrent bacterial pneumonia (n = 6), visceral leishmaniasis (n = 6), fever of unknown origin (n = 6), cryptococcal meningitis (n = 2), disseminated cryptococcosis (n = 1), systemic *Mycobacterium avium intracellulare* (n = 2), cytomegalovirus (CMV) colitis (n = 1), and giardiasis (n = 1).

No significant differences in REE parameters nor in anthropometrical or nutritional parameters were observed between the groups with opportunistic infections. REE_{FFM} and REEo/REEp were significantly increased in all groups of opportunistic infections compared with controls, except for those with recurrent bacterial pneumonia, which was the only normometabolic group (REEo/REEp, 102% ± 9%; REE_{FFM}, 6392 ± 521 kJ/d). Recurrent pneumonia and visceral leishmaniasis were the secondary infections with lower levels of CRP (15.2 ± 25.6 and 10.6 ± 16.8 mg/L, respectively) and IL-6 (3.1 ± 5.2 and 0.8 ± 1.3 pg/mL, respectively). Tuberculosis and *Pneumocystis* pneumonia were the more hypermetabolic secondary infections with respect to adjusted values (REE_{FFM}, 6763 ± 969 and 6968 ± 963 kJ/d, respectively) or as percentages of predicted values (REEo/REEp, 115% ± 16% and 118% ± 18%, respectively). Patients with tuberculosis and *P.*

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carinii pneumonia had with higher levels of CRP (48.45 ± 58.9 and 50.21 ± 90.5 mg/L, respectively), IL-6 (9.15 ± 13.4 and 9.05 ± 15.7 pg/mL, respectively), and sTNF-RI (3.70 ± 1.5 and 4.36 ± 1.9 ng/mL, respectively).

DISCUSSION

The present study shows that resting hypermetabolism in AIDS-infected patients with active secondary infections is related to the presence and severity of a cytokine-driven systemic inflammatory response. This is borne-out by the relationship between REE and acute-phase proteins and inflammation mediators. Moreover, CRP was observed to be an independent predictor of REE_{FFM} in our AIDS population.

Studies conducted in a variety of clinical situations such as infectious,[14,25] inflammatory[15] or neoplastic conditions[16] support the widely accepted concept that inflammation could lead to hypermetabolism. Roles for inflammatory mediators in the hypermetabolism and the wasting associated with HIV infection often have been postulated,[17,26] but their relative contributions remain controversial. Cytokines such as TNFα and IL-1 have been involved in AIDS wasting,[17] but, except for IFNα in lipid abnormalities,[27] no consistent relationships between circulating cytokine levels and metabolic disturbances in AIDS have been established. Also, studies of medications capable of lowering TNFα levels show conflicting results in the reversal of the metabolic syndrome.[28–30] Experimental studies have shown that IL-6 is involved in the increased production of acute-phase proteins, the decreased production of albumin, and the cachexia induced by cancer or severe inflammation.[31] Our study demonstrated that plasma IL-6 levels, and to a lesser extent sTNF-R1 concentrations, were correlated with REE parameters in AIDS patients with concomitant active infections. In the present study, no relationship between circulating TNFα concentrations and metabolic alterations related to AIDS wasting, such as hypermetabolism, could be observed. Methodological difficulties linked to the short half-life of TNFα and circumstances of the autocrine and paracrine action of cytokines could account for this result. Indeed, the finding of increased sTNF-R1 levels in our AIDS patients would indicate that the TNF system was activated and related to the hypermetabolic response. In our study, a significant positive correlation found between plasma IL-6 concentrations and CRP levels is consistent with the view that the synthesis of CRP may be induced by IL-6.[17] In addition, circulating sTNF-R1 concentrations were clearly linked with the acute-phase response.

Serum measurements of circulating cytokine concentrations are, because of the sites of action (mainly autocrine and paracrine), limited in their value as predictor parameters in standard clinical practice. On the other hand, CRP is a widely used plasma marker of acute stress. Hence, CRP can be viewed as an easily available parameter to estimate the degree of hypermetabolism associated with secondary infections in AIDS patients, which, in turn, could influence energy requirements. However, our data also indicate that increased REE is not a constant feature of active opportunistic infections secondary to HIV infection because almost 39% of the patients were not hypermetabolic. As has been previously suggested,[32] this variability in REE response could be explained, partially, by factors related to low energy availability, such as malabsorption[8,12] or reduced energy intake.[9] In a previous report,[33] we demonstrated that the prevalence and severity of malabsorption is higher in those HIV patients with acute opportunistic infections and that, even in the presence of active secondary infections, a significant relationship exists between the degree of malabsorption and REE in HIV infection. Furthermore, although no quantitative data are available with respect to food intake for the current patient population, 77% of them had reported a considerable loss of appetite.

Finally, some authors have suggested that a variable metabolic response may depend on the type of concurrent infection. In a study comparing opportunistic infections, Sharpstone et al[11] reported that *P. carinii* and *M. avium intracellulare* elicited a hypermetabolic response, whereas protozoan diarrhea was accompanied by a hypometabolic response. In the study cited above, circumstances other than the digestive-tract infection might be involved in this metabolic response because no modification in REE had been observed in the patients with CMV enteritis. It could be hypothesized that differences in the degree of the systemic inflammatory response could be partially responsible for the variation in resting metabolic response among the different opportunistic infections. Although we failed to demonstrate significant differences (because of small sample size, perhaps) in energy expenditure or inflammatory response between the different opportunistic infections, our data does lend support to this hypothesis. For example, bacterial pneumonia presented with lower levels of CRP and IL-6 and was the only infection group with a normometabolic response. In contrast, tuberculosis and *P. carinii* pneumonia infections presented with a higher degree of hypermetabolism (from 15% to 18%) and the highest levels of inflammatory markers (up to a two- or threefold increase).

Hence, we concluded that the type of concurrent active infections in patients with AIDS is associated with a variable systemic inflammatory response, which may, in part, explain the resting hypermetabolism observed in this patient population.

Further studies comparing larger samples of different HIV-related infections would be required to identify those secondary infections that are associated with the more severe cytokine-driven inflammatory response and, as a consequence, to a higher degree of hypermetabolism.

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