

The changing face of AIDS: translators needed^{1,2}

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Changes in body composition have been a central feature of HIV infection and AIDS since the beginning of the epidemic (1–3). Wasting, characterized by loss of both lean tissue and fat, has been the most common clinical alteration and was once nearly universal in advanced AIDS.

However, the face of HIV-related disease has undergone a dramatic change in recent years, as clinicians and patients in the field know all too well. A syndrome characterized by loss of fat in the extremities (lipodystrophy), accumulation of visceral and abdominal fat (paunch), breast hypertrophy, and, less commonly, emergence of the interscapular fat pad (buffalo hump) has become increasingly prevalent in patients receiving potent antiretroviral regimens (4, 5). Most often, these regimens have included protease inhibitor (PI) antiretroviral agents. Metabolic disturbances, including striking hypertriglyceridemia and insulin resistance, are also often present (5). Understanding and managing this syndrome has become one of the highest priorities in contemporary HIV and AIDS research and clinical care.

In this issue, Schwenk et al (6) report an intriguing result concerning body-composition changes in patients following PI-containing regimens. They concluded, based on bioelectrical impedance analysis (BIA) of a large number of patients studied cross-sectionally and longitudinally, that body weight and fat-free mass (FFM) increased after PI treatment but total body fat did not. Moreover, this FFM gain represented intracellular water (ICW), thus, true tissue mass—not extracellular water (ECW). They concluded that nutritional status improved with PI-containing regimens, ie, the changes in body composition were beneficial.

The study has several strong points, particularly the large number of subjects studied and the inclusion of a longitudinal component. For these reasons, the surprising result is important and deserves publication. However, there is a major concern: the real meaning of the findings is uncertain. Interpretation of these findings is uncertain for 2 reasons.

The first reason concerns the validity of BIA results when body fat distribution has been altered. The key findings of Schwenk et al are that whole-body electrical resistance decreases in these patients (and therefore FFM increases) and that phase angle (and therefore ICW:ECW) increases. An understanding of these results and their potential limitations warrants a brief review of the theory behind BIA for body-composition assessment. Phase angle and impedance (or resistance) are whole-body electrical parameters. Phase angle reflects the electrical capacitance of the body, ie, the ability of tissues to store a charge temporarily and thereby create a lag between voltage and current. Impedance reflects the ability of tissues to transmit a current,

which, as Foster and Lukaski (7) pointed out, depends on 3 factors: geometry, the scale (size) of tissues, and the intrinsic electrical properties of tissues (specific conductivity). Because we are only interested in scale, or the mass of tissue present, in body-composition assessments with BIA, the other factors are assumed to be constant. The body is assumed to be a cylinder and the specific conductivity of tissues is assumed to be invariant.

It is essential to recognize, however, that the relations between impedance and FFM or between phase angle and ICW:ECW are not fundamental, but merely empirical. The assumptions do not apply equally in all settings and human populations. Each clinical population requires its own validation (8).

As such, the syndrome of lipodystrophy with abdominal paunch represents BIA's worst nightmare. Geometry (shape) is by definition different in people with this syndrome; the body is surely neither a cylinder nor invariant in shape. Specific conductance and capacitance of tissues may also be strongly affected, eg, by altered infiltration of muscle by fat. Indeed, the fact that >60% of impedance in BIA measurements is attributable to the forearms and lower legs (7), which represent <2% of total FFM (7), and that the trunk contributes <10% of total resistance but >50% of FFM, makes BIA uniquely susceptible to artifacts if there are changes in the distribution of tissue between the extremities and the trunk. The dependence of electrical capacitance on interfaces between conducting tissue and lipids also means that validation (by use of dilution techniques) is required to understand the meaning of phase angle in this clinical setting. Moreover, Schwenk et al did not use the optimal method (multifrequency analysis) for assessing phase angle, but used only a single frequency at a value (50 kHz) that is not well suited for differentiating ICW from ECW (7). Even if they had used multifrequency BIA, however, interpretation would be uncertain without empirical validation in this specific patient population.

Schwenk et al emphasize the previously reported utility of BIA in predicting the survival of AIDS patients (8). However, because all of these previous correlations were observed before the use of PIs, BIA parameters may not have the same clinical meaning in Schwenk et al's study. This is not to say that BIA is

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the only body-composition technique that would have had limitations in their study. All body-composition-measurement techniques have major limitations. However, if BIA does have an "Achilles' heel," it would be the addition of abdominal fat (9) with concurrent alteration of interfaces between lean tissue and body lipids. The syndrome of lipodystrophy with abdominal paunch is therefore almost uniquely problematic for the BIA technique.

Second, the results of Schwenk et al's longitudinal study are inconsistent with the clinical observations of Silva et al (10), who reported a 1.5-kg increase in weight without any significant increase in FFM on the basis of BIA after 12 mo of PI treatment. Silva et al concluded that mostly body fat was gained with PI therapy. Nor is it easy to accept that 3 kg appendicular muscle could have accrued, as Schwenk et al concluded, and not be obvious visually to clinicians or patients or apparent via anthropometry or subjectively improved strength.

We are therefore left with a basic ambiguity, which the authors themselves note. The results might mean that PI treatment increases lean tissue mass rather than body fat and improves nutritional status (contrary to the prevalent clinical impression) or that BIA is unreliable if body shape or fat distribution change after PI treatment. Although both interpretations are interesting, the implications of each are rather different.

How, then, did we find ourselves in such a muddled state, with an intriguing result that we cannot interpret definitively? The answer, of course, relates to deficiencies in current *in vivo* measurement methods used in humans. Phase angle and impedance are, unfortunately, not direct surrogate biological markers of disease. BIA is a black-box (or, more accurately, a black-cylinder) method. Extrapolation from physics (electrical conductance and capacitance of the body) to clinical function and even prognosis spans so many levels of biological organization and explanation—including biochemistry, physiology, and pathophysiology—that it can never be a direct, proximate indicator of disease events. Correlations are at best empirical rather than mechanistic; if any confounding variables arise, such as a change in fat distribution, interpretation becomes ambiguous. The absence of a gold standard method of body-composition assessment or *in vivo* metabolic measures of biochemical events of interest (eg, the rate of visceral fat deposition, extremity fat mobilization, or muscle deposition) further constrains the field. Even empirical validation of BIA becomes uncertain and strictly correlative in the absence of a true gold standard.

These factors remind us, regrettably, how inadequate our current techniques are for studying living people and, therefore, how little we really know about the pathophysiology of human disease. The notion of translational research—translating advances in basic biology to human disease—has received lip service but little systematic effort. The problem of changes in body composition during PI therapy exemplifies this inadequacy. At every level, there remain more questions than answers. What is the biology of local fat depots in humans? Are there unambiguous metabolic markers of visceral or peripheral fat anabolism or catabolism that could make clearer the biochemical and metabolic mechanisms at work during PI treatment? How can antiretroviral agents change macronutrient metabolism and body composition? Once again, translators are needed. 

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