Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment\textsuperscript{1,2}

Achim Schwenk, Alexander Beisenherz, Katja Römer, Gisela Kremer, Bernd Salzberger, and Marinos Elia

ABSTRACT

Background: Highly active antiretroviral treatment (HAART) reduces the risk of wasting in HIV infection and may alter the prognostic weight of wasting. The phase angle from bioelectrical impedance analysis (BIA) can be interpreted as a surrogate marker for the catabolic reaction to chronic HIV infection and opportunistic disease.

Objective: Our objective was to assess the prognostic ability of the phase angle in HIV-infected patients in the era of HAART.

Design: Two cross-sectional observation studies were conducted in 1996 and 1997 at a German university outpatient HIV clinic. In the 1996 and 1997 cohorts, HAART was prescribed to 17 of 212 and 168 of 257 patients at baseline and to 179 of 212 and 234 of 257 patients during observation, respectively. Whole-body BIA was assessed at 50 kHz. Time to clinical progression and survival were calculated by using Cox proportional hazard models with time-dependent covariates. Median observation times were 1000 and 515 d for the 1996 and 1997 cohorts, respectively.

Results: Higher phase angle was associated with a lower relative mortality risk, adjusted for viral load and CD\textsuperscript{4} cell count, of 0.49 (95% CI: 0.30, 0.81) per degree in 1996 and of 0.33 (95% CI: 0.18, 0.61) in 1997. The influence of phase angle on time to clinical progression, adjusted for viral load and CD\textsuperscript{4} cell count, was not significant in 1996 but the relative risk was 0.58 (0.36, 0.83) in 1997.


KEY WORDS Acquired immunodeficiency syndrome, AIDS, biological markers, body fluid compartments, body composition, bioelectrical impedance, HIV infection, survival analysis

INTRODUCTION

Loss of body weight and wasting of lean body mass are leading symptoms of the advanced stages of HIV infection. Early in the epidemic it was proposed that malnutrition may be an important cofactor of disease progression (1). Several studies undertaken before the era of highly active antiretroviral treatment (HAART) showed that weight loss was associated with more rapid disease progression and shorter survival after CD\textsuperscript{4} cell count was controlled for (2, 3). Body-composition studies done with bioelectrical impedance analysis (BIA) suggested that low body cell mass was an adverse prognostic marker (4). The correlation of BIA and prognosis was found to be particularly strong when a measured BIA parameter, phase angle, was used instead of the derived body-composition estimates (5). However, changes in weight and fat-free mass (FFM) had no significant influence on disease progression of asymptomatic HIV-infected patients in a study that measured body composition with another method (6). Since these studies were conducted, the prognosis of HIV-infected patients in industrialized countries has changed considerably. HAART has reduced morbidity and mortality (7, 8), including the incidence of malnutrition (9). Additionally, viral load has been found to be a much more powerful predictor of risk than is CD\textsuperscript{4} cell count (10).

The current study was undertaken to determine whether a low phase angle with BIA is still associated with a poor prognosis if considered together with other state-of-the-art prognostic markers and their changes during antiretroviral treatment. The phase angle is defined as the relation between the 2 vector components of impedance: resistance and reactance. It may be interpreted as an indicator of water distribution between the extra- and intra-cellular spaces. However, the relation of impedance to body composition is indirect and incompletely understood (11). Therefore, the phase angle, rather than derived body-composition estimates, was examined for its prognostic weight in the current study.

This study was part of a series of cross-sectional and longitudinal BIA measurements in a defined population of HIV-infected outpatients in the era of rapid improvements in antiretroviral therapy. Data on the effect of protease inhibitors on weight and BIA data have been published elsewhere (9, 12). In this article, we report the prognostic weight of phase angle for survival and progression-free survival in the same population, before and after the introduction of HAART.

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TABLE 1
Baseline characteristics and outcomes

<table>
<thead>
<tr>
<th></th>
<th>1996 Cohort</th>
<th>1997 Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 181 M, 31 F)</td>
<td>(n = 220 M, 37 F)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>40.4 ± 10.6</td>
<td>39.7 ± 10.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 3.1</td>
<td>23.1 ± 3.3</td>
</tr>
<tr>
<td>Total weight change</td>
<td>-3.1 ± 10.3</td>
<td>0.9 ± 9.8</td>
</tr>
<tr>
<td>(% of usual body weight)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4⁺ cell count (10⁶ cells/L)</td>
<td>203 ± 209</td>
<td>306 ± 212</td>
</tr>
<tr>
<td>HIV RNA (log₁₀ copies/L)</td>
<td>7.3 ± 1.1</td>
<td>6.3 ± 1.1</td>
</tr>
<tr>
<td>HAART at baseline¹</td>
<td>17 (8)</td>
<td>168 (65)</td>
</tr>
<tr>
<td>HAART during observation time</td>
<td>179 (84)</td>
<td>234 (91)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No progression</td>
<td>153 (72)</td>
<td>233 (91)</td>
</tr>
<tr>
<td>Progression, survived</td>
<td>32 (15)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Death, no other progression</td>
<td>13 (6)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Death after progression</td>
<td>14 (7)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Observation time (d)</td>
<td>1000 (28–1203)²</td>
<td>515 (28–704)²</td>
</tr>
</tbody>
</table>

¹132 of 1997 cohort were also in the 1996 cohort.
²± SD.
³Significantly different from 1996 cohort: *P < 0.05, **P < 0.001.
⁴HAART, highly active antiretroviral treatment.
⁵Median; range in parentheses.
⁶n; percentage in parentheses.
⁷Total weight change ± (percent of usual body weight).

SUBJECTS AND METHODS

The study was conducted at the outpatient clinic for infectious diseases of a large university hospital in western Germany. All HIV antibody–positive outpatients attending the department during 2 periods of 6 wk each were asked to participate. The 2 periods in March–April 1996 and July–August 1997 were spaced 500 d apart. Patients were excluded from the analysis if they were receiving enteral or parenteral nutrition or any drug treatment for wasting, lacked documentation of HIV viremia or CD4⁺ cell count, or had had follow-up of < 2 wk, unless progression or death occurred during this period.

During the period in 1996, 250 of 254 clinic patients consented to BIA measurement. The current analysis was restricted to 212 patients because 3 patients received parenteral nutrition, 20 had an insufficient length of follow-up, and 15 had missing data. During the period in 1997, 266 of 276 patients participated but 9 patients were excluded because their follow-up periods were too short. Baseline characteristics of the remaining 212 and 257 patients are given in Table 1. Likewise, BIA results suggested healthier body compositions in the 1997 cohort than in the 1996 cohort, as reported previously (9). In both cohorts, a lower phase angle with BIA was significantly associated with shorter survival and time to clinical progression, as shown in Figure 1. Survival after 1996 was significantly shorter for patients in the lowest quartile of the phase angle (< 5.3°): 878 d (95% CI: 758, 998) compared with 1013 d (985, 1041) in the 3 higher quartiles together (P < 0.001). When the same thresholds were applied to a similar analysis in the 1997 cohort, patients with a phase angle < 5.3° again had a shorter estimated survival of 463 d (397, 528) compared with 697 d (690, 705) for patients with a higher phase angle (P < 0.001). All deaths in both cohorts were either directly attributable to opportunistic infections or tumors or occurred in advanced AIDS cases without other apparent reasons. The influence of phase angle on time to next clinical progression was not significant in the 1996 cohort. In the 1997 cohort, patients with a phase angle < 5.3° had a clinical progression after 406 d (330, 483) compared with 670 d (652, 688) in patients with a higher phase angle (P < 0.001).

In multivariate Cox models with survival as the endpoint, the relative risk (RR) reduction associated with an increase of the
phase angle by 1° was 0.33 (95% CI: 0.21, 0.52) in the 1996 cohort and 0.29 (0.16, 0.53) in the 1997 cohort. In comparison, a log_{10} increase of CD4+ cells was associated with an RR of 0.19 (0.12, 0.32) in 1996 and 0.11 (0.06, 0.22) in 1997. A log_{10} increase of viral load was associated with an RR of 2.64 (1.76, 3.97) in 1996, but in 1997, this association was less pronounced with an RR of 1.84 (1.14, 2.67). Patients with prior AIDS had a 7.56 (2.61, 21.9) times higher mortality risk in 1996, but this association was only marginally significant in 1997 (RR: 3.82; 0.99, 14.8). Age, sex, and body mass index had no significant influence on the relative mortality risk. Clinical progression, rather than death, was the endpoint in another set of similar monovariate models. Again, significant associations with RR were seen with the same independent variables, and body mass index was not associated with the risk of progression.

In multivariate Cox models, survival time after 1996 was predicted only by the CD4+ cell count, HIV viral load, and the phase angle (Table 2). Survival after 1997 was predicted only by phase angle and CD4+ cell count, not by viral load. Time to clinical progression was predicted by the CD4+ cell count in both cohorts, together with a prior AIDS diagnosis in 1996, and together with the phase angle in 1997 (Table 2). Viral load did not contribute significantly to the prediction of clinical progression in either cohort.

Significant correlations between CD4+ cell count, viral load, prior AIDS, and the phase angle were observed. They were further explored in general linear models (Table 3). Together with age, sex, and body mass index, these variables explained 33.8% and 25.6% of the variance in phase angle in 1996 and 1997, respectively. However, the contribution of CD4+ cell count, viral load, and prior AIDS to this model decreased from 17.5% in 1996 to 5.6% in 1997. The roles of these 3 variables also differed between the cohorts. In 1996, prior AIDS was the most powerful predictor of a low phase angle, and high viral load had a moderate influence. In 1997, neither of these variables was significantly associated with the phase angle, whereas a lower CD4+ cell count was associated with a lower phase angle (Table 3).
As expected from theory, phase angle was strongly correlated with the BIA estimate of the ECW-ICW ratio \( r = 0.82 \) in men, \( r = 0.65 \) in women, \( P < 0.001 \). An increase of phase angle by 1º corresponded to a decrease of the ratio by the factor 0.901 (0.897, 0.906).

**DISCUSSION**

The results of this study show a strong ability of the phase angle to predict survival and clinical progression in HIV-infected patients, independent of the degree of immunodeficiency and viremia. The introduction of HAART to this population has not eliminated the prognostic role of the phase angle shown earlier in the HIV epidemic (5). However, the percentage of patients eliminating the prognostic role of the phase angle shown earlier in the HIV epidemic (5).

Others surrogate markers for these pathogenic events are more widely known to predict survival than is the phase angle. Loss of intracellular potassium and extracellular accumulation of sodium result in an increased whole-body exchangeable Na\(^+\)-K\(^+\) ratio, which is a strong predictor of mortality in surgical patients (26). Hypoalbuminemia results largely from protein leakage (23) and is an adverse prognostic marker in systemic illness, such as bacteremia (27), HIV infection (28), and tuberculosis (29). Like the Na\(^+\)-K\(^+\) ratio and serum albumin, phase angle can be interpreted as a global marker of the systemic reaction that forms an integral part of the host defense to systemic infection but may eventually result in malnutrition (30). Further studies comparing the phase angle with more direct assessment of metabolic distress will be needed to test this hypothesis.

If one accepts this interpretation of the phase angle, our findings indicate that the systemic response that predisposes patients to malnutrition (30).

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**TABLE 2**

Multivariate Cox proportional hazard models\(^2\)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Unit of increase</th>
<th>1996 Cohort (n = 212)</th>
<th>1997 Cohort (n = 257)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR(^3) 95% CI</td>
<td>RR (6) 95% CI</td>
<td>RR (6) 95% CI</td>
</tr>
<tr>
<td><strong>Endpoint: death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase angle</td>
<td>1º</td>
<td>0.49(^4) (0.30, 0.81)</td>
<td>0.33(^4) (0.18, 0.61)</td>
</tr>
<tr>
<td>CD4(^+) cell count</td>
<td>1 log10</td>
<td>0.40(^3) (0.21, 0.74)</td>
<td>0.10(^4) (0.04, 0.26)</td>
</tr>
<tr>
<td>HIV viremia</td>
<td>1 log10</td>
<td>1.82(^3) (1.16, 2.84)</td>
<td>1.31(^3) (0.85, 2.02)</td>
</tr>
<tr>
<td><strong>Endpoint: clinical progression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase angle</td>
<td>1º</td>
<td>(0.99)(^6) (0.71, 1.41)</td>
<td>0.58(^1) (0.36, 0.83)</td>
</tr>
<tr>
<td>CD4(^+) cell count</td>
<td>1 log10</td>
<td>0.31(^4) (0.21, 0.46)</td>
<td>0.15(^4) (0.08, 0.26)</td>
</tr>
<tr>
<td>Prior AIDS</td>
<td></td>
<td>4.20(^4) (2.05, 8.61)</td>
<td>1.24(^4) (0.52, 2.98)</td>
</tr>
</tbody>
</table>

\(^1\)For observation times, see Table 1.
\(^2\)Relative risk (Cox proportional hazard).
\(^3\)\(P < 0.05\).
\(^4\)\(P < 0.01\).
\(^6\)CD4\(^+\) cell count and HIV viral load were treated as time-dependent covariates.

\(^4\)For variables without significant contribution to the final model, RRs in parentheses are derived from the forced addition of this variable to the final model.

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**TABLE 3**

Determinants of the phase angle\(^7\)

<table>
<thead>
<tr>
<th>Determinant</th>
<th>1996 Cohort parameter estimates (95% CI)</th>
<th>1997 Cohort parameter estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior AIDS</td>
<td>0.69(^1) (0.84, 0.56) 0.88 (1.08, 0.72)</td>
<td>0.88 (1.08, 0.72)</td>
</tr>
<tr>
<td>Baseline CD4(^+) count (log10)</td>
<td>1.06 (0.91, 1.24) 1.31(^1) (1.02, 1.69)</td>
<td>1.31(^1) (1.02, 1.69)</td>
</tr>
<tr>
<td>Baseline HIV RNA (log10)</td>
<td>0.92(^1) (0.84, 1.00) 1.00 (0.92, 1.09)</td>
<td>1.00 (0.92, 1.09)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.44(^1) (1.1, 1.87) 1.91(^1) (1.46, 2.49)</td>
<td>1.91(^1) (1.46, 2.49)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.97(^1) (0.96, 0.98) 0.97(^1) (0.96, 0.98)</td>
<td>0.97(^1) (0.96, 0.98)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>1.09(^2) (1.05, 1.12) 1.09(^2) (1.06, 1.12)</td>
<td>1.09(^2) (1.06, 1.12)</td>
</tr>
</tbody>
</table>

\(^1\)Parameter estimates in general linear models predicting the phase angle. For example, for 2 patients who differed in baseline HIV RNA in 1996 by 1 log10 but were identical in all other variables, the patient with higher HIV RNA would be expected to have a 0.92 times lower phase angle.

\(^2\)\(P < 0.001\).

\(^3\)\(P < 0.05\).
to malnutrition and wasting is an independent risk factor in HIV infection together with viral load and immunodeficiency. Malnutrition, when more strictly defined by a low body mass index, was not significantly associated with prognosis in the current study. Effective antiretroviral treatment reduces the risk of wasting, controls viremia, and restores immune competence. Although statistically independent, these 3 effects are inseparable in patients. Different associations between phase angle and other measures of disease severity were found between 1996 and 1997. In the 1996 cohort, the patients’ nutritional status was largely determined by their history of opportunistic infections, reflecting the episodic nature of malnutrition in HIV infection (31, 32). Effective antiretroviral treatment not only led to a lower incidence of opportunistic infections before 1997 but may also have reduced the severity of episodes and their metabolic consequences. This may have unmasked the metabolic effect of chronic HIV infection, as reflected in the CD4+ cell count.

Metabolic adverse effects of HAART may have confounded our data. Because this prospective study was designed before the first description of the fat redistribution syndrome, or lipodystrophy (33, 34), incidence of this syndrome could be determined only retrospectively in a subset (n = 111) of this population. As described elsewhere (9), the fat redistribution syndrome was associated with a greater increase of the phase angle between 1996 and 1997. Diagnosis of the fat redistribution syndrome did not have a detectable influence on prognosis in this subset (data not shown), but the statistical power of this finding is small. A protective effect of the syndrome is unlikely, apart from its association with low viral load (34, 35); hence, it could either have no effect or lead to underestimation of the prognostic power of phase angle.

Because of the close association between metabolic status and other manifestations of HIV infection, our data do not provide a causal link between reversal of catabolism and improved prognosis. However, they do underline the importance of monitoring the patient’s metabolic status alongside viral load and CD4+ cell count in assessing prognosis. Phase angle with BIA may become a useful surrogate marker for the systemic response to chronic HIV infection, as reflected in the CD4+ cell count.

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REFERENCES


