Obesity Affects the Association of Bioelectrical Impedance Phase Angle With Mortality in People Living With HIV

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Abstract

Bioelectrical impedance analysis phase angle (BIA-PA) is a valid indicator of mortality risk in people living with HIV; however, it is not known whether BIA-PA is valid for people living with HIV who are overweight or obese. We assessed whether BIA-PA differentially predicted mortality by body mass index category in participants receiving clinical care at a single site between 2000 and 2012. Change in BIA-PA from the highest versus last available phase angle was assessed using multivariate logistic regression models. Eight hundred ninety participants were included in the final analyses, with 102 deaths recorded during the study period. Decline in BIA-PA was associated with mortality in underweight and normal weight participants but not in overweight or obese participants. Additional investigation is warranted to determine the appropriate clinical BIA-PA equations and parameters to identify overweight and obese patients with increased mortality risk.

Key words: HIV, bioelectrical impedance, phase angle, mortality, obesity

The introduction of combination antiretroviral therapy (cART) for people living with HIV (PLWH) was accompanied by a shift from wide spread undernutrition and wasting to overnutrition and obesity (Crum-Cianflone, Tejidor, Medina, Barahona, & Ganesan, 2008; Guehi et al., 2016; Kim et al., 2012; McCormick et al., 2014; Smit et al., 2002; Tate et al., 2012). In the pre-cART era, loss of body weight and wasting of lean body mass were considered symptoms of advanced stages of HIV infection and an independent factor contributing to disease progression and mortality (Schwenk et al., 2000). Biomarkers of health status were needed to track wasting and related health outcomes; thus, bioelectrical impedance analysis was used to assess changes in nutritional status and body composition before and after cART initiation.

Bioelectrical impedance analysis phase angle (BIA-PA) is a noninvasive technique that measures electrical resistance and reactance to calculate a person's phase angle and estimate total body fat. The results reflect not only the body cell mass but also the cell membrane function related to water distribution between the extracellular and intracellular spaces (Barbosa-Silva & Barros, 2005; Kyle, Bosaeus, De Lorenzo, Deurenberg, Elia, Gomez, et al., 2004). There is a strong association between cellular health and BIA-PA such that a high BIA-PA indicates intact cell membranes and body cell mass, whereas low BIA-PA suggests poor selective permeability of the cell membrane and poor cellular energy storage (Kyle, Genton, Slosman, & Pichard, 2001; Ott et al., 1995). Before the availability of cART, BIA-PA decline was a validated, recognized prognostic marker for mortality in the setting of untreated HIV infection; low values were associated with a rapid clinical progression and shorter survival time, regardless of the degree of immunodeficiency and viremia (Ott et al., 1995). The correlation between declines in BIA-PA and mortality has similarly been observed in other diseases, including frailty (Mullie et al., 2018), cancer (lung, colorectal, and pancreatic; Gupta, Lammersfeld, et al., 2004; Gupta et al., 2009; Gupta, Lis, et al., 2004; Norman et al., 2010), cirrhosis (Selberg & Selberg, 2002), and hemodialysis for end stage renal disease (Di Iorio, Scalfi, Terracciano, & Bellizzi, 2004). In the cART

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era, the prognostic ability of BIA-PA has been confirmed, suggesting that the decrease in BIA-PA is not only a consequence of body cell mass and wasting syndrome but also a reflection of systemic reaction to infection (Schwenk et al., 1999, 2000).

Bioelectrical impedance analysis phase angle is currently used by health care professionals to monitor health status and mortality risk of PLWH; however, BIA measures are inaccurate at extremely low or high body weights (Kyle, Bosaeus, De Lorenzo, Deurenberg, Elia, Gomez, et al., 2004; Kyle, Bosaeus, De Lorenzo, Deurenberg, Elia, Manuel Gomez, et al., 2004), and the increasing obesity (body mass index [BMI] $\geq$ 30 kg/m^2) prevalence among PLWH could alter the prognostic capabilities of PA change. Moreover, cART has radically changed from the beginning of the HIV epidemic. Current cART regimens have less toxicity on metabolic parameters, yet most studies on the relationship between PA and cART include only early cART regimens (Schwenk et al., 1999, 2000). Analysis of the utility of BIA-PA in current clinical practice is necessary to inform the 21st century clinical care of PLWH. The aim of this study is to evaluate the association of change in PA with mortality in a recent cohort of PLWH who experience greater prevalence of overweight and obesity compared with cohorts in previous investigations.

Methods

Data were obtained from the University of Alabama at Birmingham (UAB) 1917 HIV/AIDS Clinic Cohort Observational Database Project (UAB 1917 Clinic Cohort). This cohort forms an ongoing prospective clinical study that has collected detailed sociodemographic, psychosocial, and clinical data from individuals diagnosed with HIV since 1988. For this study of BIA-PA, we conducted a retrospective analysis of Centers for AIDS Research Network of Integrated Clinical Systems data collected at the 1917 Clinic between 2000 and 2012. During the study period, the Clinic used a locally programmed electronic medical record (EMR) containing detailed provider encounter notes, imported all laboratory values from the central UAB laboratory, and required electronic prescriptions for all medications. The EMR and database were quality controlled, with all provider notes reviewed to ensure appropriate data capture regarding diagnoses and medications (including start and stop dates for prescriptions). New and ongoing diagnoses are recorded in patients' active problem lists, whereas resolved diagnoses discontinued by the provider remain part of the patients' EMR after removal from the active problem list. The UAB Institutional Review Board approved this retrospective study nested in the UAB 1917 Clinic Cohort.

Participants

All patients seen at the UAB 1917 HIV Clinic between January 1, 2000, and June 30, 2012, were eligible. Inclusion criteria were the following: (a) $\geq$ 19 years of age, (b) diagnosis of HIV, (c) at least two primary care visits at the UAB 1917 Clinic at which BIA-PA was performed, and (d) height, weight, plasma HIV RNA, and CD4 count measured within the study period. All data were acquired through electronic queries (MS SQL) of the UAB 1917 Clinic database.

Study Variables

Body composition. Height to the nearest 0.1 cm and weight to the nearest 0.1kg were obtained from the EMR and used to calculate BMI (weight [kg]/height [m^2]). The following categories were used to classify patients by BMI: underweight $<$ 18.5 kg/m^2, normal weight = 18.5–24.9 kg/m^2, overweight = 25–29.9 kg/m^2, and obese $\geq$ 30 kg/m^2. All BIA measurements were performed or confirmed by the same registered dietitian at the time of the patient's regularly scheduled clinic appointment. Tetrapolar BIA was completed with a bioelectrical impedance analyzer (RJL Systems Inc.; Clinton Township, MI) while participants lay supine on an examination table with legs and arms apart. Electrodes were placed on the right side of the body near the wrist and ankle joints of the hand and foot. A 50 kHz excitation current was initiated and used to compute resistance (R; sum of geometrical in-phase vectors) and reactance (X; capacitance or sum of out-phase vectors). Resistance and reactance were used to estimate body fat mass, fat-free mass, and total body water. Phase angle (BIA-PA) was computed using the following equation: BIA-PA = (resistance/reactance) $\times$ (180/3.14159153).

Covariates. We extracted demographic and laboratory information from the EMR including age, gender, self-reported race/ethnicity, CD4$^+$ T-cell count, plasma HIV RNA, antiretroviral regimen (use of protease inhibitors), insurance status (none, private, public), history of substance abuse (yes/no), and the year the patient started care at the 1917 Clinic. Because patients with advanced-stage infection would be expected to have greater mortality risk, the history of opportunistic infections was also abstracted to identify those staged as Centers for Disease Control (CDC) Class C (Centers for Disease Control, 1992).

Mortality. Patients were classified according to mortality (yes/no) during the study period. The year of death

was abstracted from the EMR, and the BIA-PA value at the closest date before death was recorded. For patients who were not deceased at the end of the study period, the last available BIA-PA value was recorded.

Statistical Analysis

Chi-square, Kruskal–Wallis, and one-way analyses of variance tests were used to analyze differences between BMI categories related to descriptive characteristics and BIA parameters (resistance, reactance, phase angle, fat mass percent, fat-free mass percent).

Change in BIA-PA was computed as highest BIA-PA—last BIA-PA. Reconstitution of health and immune function is associated with the initiation of cART and an increase in BIA-PA; thus, we used the highest BIA-PA reported for a patient as a more accurate indicator of cellular status following reconstitution of health. Univariate logistic regression models were run for the total sample and by BMI category to evaluate the association of BIA-PA decline with mortality. Univariate modeling of covariates was also conducted to identify factors associated with mortality in the total sample. Multivariate logistic regression was used to model the impact of change in BIA-PA on mortality risk in the total sample and by BMI category after controlling for highest BIA-PA measurement, insurance type, CDC "C" classification, history of protease inhibitor use, and $CD4^+$ T-cell count. All data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC) with a significance level of $p < .05$.

Results

Characteristics of the study population by BMI category are presented in Table 1. There were 1,149 patients who met the criteria of age, height, and weight. Of those, 213 patients were excluded for having less than two BIA-PA measurements, and 46 deceased patients were excluded who did not have a BIA measurement within the year before death, leaving a final sample size of 890 participants. At the time of highest BIA-PA measurement, participants were aged 41.9 ± 9.6 years, with no difference among the groups. Approximately 73% of participants were men and 51% self-reported as racial/ethnic minorities. All but five non-White participants self-identified as Black, with the remaining five self-reporting as Hispanic ethnicity with multiracial or Black race; therefore, we were not powered to analyze these five individuals separately and included them in the "minority" racial group. A greater percentage of women and minorities were observed in both the underweight and obese groups ($p < .01$). Obese participants were more likely to have private health insurance and higher $CD4^+$ T-cell count compared with other groups (all at $p < .01$). There were no group differences in viral load, the history of substance abuse, the year of initiating care at the clinic, or disease staging of CDC "C" classification. By 2012, 102 (11.5%) deaths had been recorded, with significantly more deaths occurring in the underweight ($n = 13$; 26%) group compared with normal weight ($n = 62$; 15.2%), overweight ($n = 18$; 6.9%), and obese ($n = 9$; 5.3%) groups ($p = .01$).

Bioelectrical Impedance Analysis

The results of bioelectrical impedance analysis were significantly different by BMI category at the time of highest and last BIA-PA measurement (Table 2). At the time of highest BIA-PA, underweight participants had significantly greater resistance and reactance measures and a lower BIA-PA compared with all other groups ($p < .01$). Obese participants had a lower measure of resistance compared with normal weight/overweight participants and a higher percentage of body fat mass (33.2%), and a lower percent lean mass (66.8%) compared with all other groups (all at $p < .01$). There were no significant group differences in change between the highest and last BIA; however, underweight participants were the only group to experience a median decline in resistance (−15.5).

Mortality Risk

In univariate models, a decline in BIA-PA was associated with increased mortality risk in the total sample (odds ratio [OR] 1.8; 95% confidence interval [CI] 1.5–2.2) and in underweight (OR 5.8, 95% CI 1.8–19.0) and normal weight (OR 2.2, 95% CI 1.6–3.1) participants (all at $p < .01$; Table 3). BIA-PA decline was not associated with mortality risk in overweight or obese participants.

In multivariable regression models (Table 3), BIA-PA decline remained significantly associated with increased mortality in the total sample (OR 2.2, 95% CI 1.6–2.9; $p < .01$) and among underweight (OR 6.6, 95% CI 1.2–34.8; $p = .02$) and normal weight (OR 2.2, 95% CI 1.5–3.4; $p < .01$) groups. There was no association of BIA-PA decline with mortality among overweight or obese participants. A higher initial BIA-PA was associated with decreased mortality risk in the total sample (OR 0.6, 95% CI 0.4–0.7; $p < .01$) and normal weight (OR 0.6, 95% CI 0.4–0.8; $p < .01$) and overweight (OR 0.6, 95% CI 0.3–0.9; $p = .04$) groups, but not among underweight or obese participants.

Table 1. Participant Characteristics (*M* ± *SD* or *n* [%]) Stratified by Body Mass Index (BMI) Category at the Time of Highest Bioelectrical Impedance Analysis Measurement

Variable	Total[a] *N* = 890	Underweight (BMI < 18.5 kg/m^2) *n* = 50	Normal Weight (BMI 18.5–24.9 kg/m^2) *n* = 409	Overweight (BMI 25-29.9 kg/m^2) *n* = 261	Obesity (BMI ≥ 30 kg/m^2) *n* = 170	*p*-Value[b]
Age	41.9 ± 9.6	41.2 ± 11.3	41.3 ± 9.6	42.4 ± 9.5	42.5 ± 9.0	.33
Gender						
Male	706 (79.3%)	35 (5.0%)	345 (48.7%)	213 (30.2%)	113 (16.0%)	<.01
Female	184 (20.7%)	15 (8.2%)	64 (34.8%)	48 (26.1%)	57 (30.9%)	
Race						
White	430 (48.7%)	17 (3.9%)	225 (52.3%)	131 (30.5%)	57 (13.3%)	<.01
Minority[c]	453 (51.3%)	32 (7.1%)	183 (40.4%)	128 (28.2%)	110 (24.3%)	
Health insurance						
Uninsured	245 (28.2%)	12 (4.9%)	114 (46.5%)	76 (31.0%)	43 (17.6%)	<.01
Public	320 (36.8%)	29 (9.0%)	151 (47.2%)	86 (26.9%)	54 (16.9%)	
Private	304 (35.0%)	7 (2.3%)	133 (43.8%)	95 (31.3%)	69 (22.7%)	
Sexual risk factor						
Heterosexual	345 (38.8%)	23 (6.7%)	139 (40.3%)	95 (27.5%)	88 (25.5%)	<.01
MSM	510 (57.3%)	23 (4.5%)	252 (49.4%)	159 (31.2%)	76 (14.9%)	
Other/unknown	35 (3.9%)	4 (11.4%)	18 (51.4%)	7 (20.0%)	6 (17.1%)	
Substance abuse (ever)	256 (28.8%)	14 (28.0%)	130 (31.8%)	73 (27.9%)	39 (22.9%)	.19
CD4$^+$ count (cells/μl)						
0–199/μl	288 (33.6%)	27 (9.4%)	137 (47.6%)	78 (27.1%)	46 (15.9%)	<.01
200–350/μl	186 (21.7%)	7 (3.8%)	88 (47.3%)	62 (33.3%)	29 (15.6%)	
>350/μl	383 (44.7%)	15 (3.9%)	166 (43.3%)	117 (30.6%)	85 (22.2%)	
$\log_{10}$ plasma HIV RNA (copies/ml)	2.9 ± 1.4	3.4 ± 1.7	3.0 ± 1.4	2.7 ± 1.3	2.9 ± 1.4	.08
Viral load < 200 (copies/ml)	424 (49.3%)	22 (44.9%)	182 (46.1%)	141 (54.7%)	79 (50.0%)	.17
CDC "C" diagnosis	355 (39.9%)	26 (52.0%)	171 (41.8%)	98 (37.6%)	60 (35.3%)	.12
Year starting care						
2000–2004	331 (37.2%)	23 (6.9%)	168 (50.8%)	91 (27.5%)	49 (14.8%)	.10
2005–2008	308 (34.6%)	15 (4.8%)	132 (42.9%)	97 (31.5%)	64 (20.8%)	
2009–2012	251 (28.2%)	12 (4.8%)	109 (43.4%)	73 (29.1%)	57 (22.7%)	
Use of PI regimen (yes)	546 (61.4%)	24 (48.0%)	255 (62.4%)	166 (63.6%)	101 (59.4%)	.19
Deaths at the last observation period	102 (11.5%)	13 (26.0%)	62 (15.2%)	18 (6.9%)	9 (5.3%)	.01

Note: MSM = men who have sex with men; PI = protease inhibitor; RNA = ribonucleic acid.
[a] Missing values: race = 7; insurance = 21; CD4$^+$ = 33; Viral load = 30.
[b] *p*-Value based on Kruskal–Wallis or chi-square test.
[c] Five Minority participants identified as Hispanic ethnicity with multiracial or Black race; the remaining participants identified as Black.

Table 2. Measurements Associated With Bioelectrical Impedance Analysis (BIA) Phase Angle Measurement, Stratified by Body Mass Index (BMI) Category

Variable	Total	Underweight (BMI < 18.5)	Normal Weight (BMI 18.5–24.9)	Overweight (BMI 25–29.9)	Obesity (BMI ≥ 30)
At the time of highest BIA[c]	*N* = 890	*n* = 50	*n* = 409	*n* = 261	*n* = 170
Height (cm)	175.3 (170.2, 182.9)	175.3 (165.1, 180.3)	177.8 (170.2, 182.9)	176.5 (170.2, 182.9)	174.6 (166.4, 182.9)[a]
Weight (kg)	76.8 (67.3, 89.5)	52.0 (46.4, 56.8)	69.5 (63.6, 74.5)	84.1 (78.2, 90.5)	102.3 (94.5, 112.7[b]
Body mass index	24.7 (21.8, 28.6)	17.1 (16.2, 17.9)	22.1 (21.0, 23.4)	26.9 (25.8, 28.2)	33.2 (31.6, 35.8)[b]
Resistance	488.5 (440.0, 548.0)	644.0 (604.0, 695.0)	510.0 (473.0, 562.0)	463.0 (423.0, 506.0)	423.5 (390.0, 482.0)[b]
Reactance	57.0 (51.0, 63.0)	63.5 (52.0, 70.0)	59.0 (54.0, 65.0)	56.0 (51.0, 61.0)	52.0 (47.0, 57.0)[b]
Phase angle	6.7 (6.0, 7.3)	5.5 (4.6, 6.2)	6.5 (5.9, 7.1)	6.9 (6.3, 7.5)	6.9 (6.3, 7.6)[b]
Fat mass %	23.9 (18.1, 30.1)	15.7 (12.5, 19.4)	20.3 (16.0, 24.8)	25.6 (22.0, 31.3)	33.2 (27.9, 42.4)[b]
Fat-free mass %	76.1 (69.9, 81.9)	84.3 (80.6, 87.5)	79.7 (75.2, 84.0)	74.4 (68.7, 78.0)	66.8 (57.6, 72.1)[b]
At the time of last BIA[d]	*N* = 890	*n* = 65	*n* = 382	*n* = 266	*n* = 177
Height (cm)	175.3 (170.2, 182.9)	175.3 (166.4, 180.3)	176.5 (170.2, 182.9)	177.8 (170.2, 182.9)	175.3 (165.1, 180.3)[b]
Weight (kg)	77.3 (66.8, 90.9)	51.4 (45.0, 55.9)	68.6 (62.7, 74.1)	84.5 (79.1, 90.9)	106.1 (95.5, 117.3[b]
Body mass index	25.0 (21.6, 28.8)	17.1 (15.8, 17.9)	22.0 (20.8, 23.5)	27.0 (26.0, 28.2)	33.5 (31.5, 38.2)[b]
Resistance	487.5 (436.0, 547.0)	646.0 (556.0, 709.0)	511.0 (475.0, 566.0)	465.5 (429.0, 518.0)	425.0 (388.0, 459.0)[b]
Reactance	53.0 (47.0, 59.0)	52.0 (44.0, 59.0)	55.0 (49.0, 60.0)	53.0 (48.0, 59.0)	49.0 (44.0, 54.0)[b]
Phase angle	6.2 (5.5, 6.9)	4.7 (3.7, 5.6)	6.1 (5.4, 6.7)	6.4 (5.9, 7.1)	6.5 (5.8, 7.3)[b]
Fat mass %	24.3 (18.6, 30.7)	12.8 (9.3, 19.1)	20.1 (15.9, 25.2)	26.8 (22.1, 31.6)	33.4 (28.3, 42.7)[b]
Fat-free mass %	75.7 (69.3, 81.4)	87.2 (80.9, 90.7)	80.0 (74.8, 84.1)	73.2 (68.4, 77.9)	66.6 (57.3, 71.7)[b]

[a]Kruskal–Wallis test $p < .05$.
[b]Kruskal–Wallis test $p < .01$.
[c] BMI categories for the "At time of highest BIA" values are based on the BMI at the time of highest BIA.
[d] BMI categories for the "At time of last BIA" values are based on the BMI at the time of last BIA.

Additional covariates were associated with mortality risk in the total sample and normal weight participants. Increased mortality was observed with public versus private insurance, with a CDC "C" disease classification and with a $CD4^+$ T-cell count < 200 cells/μL at time of highest BIA-PA. Greater change in $CD4^+$ T-cell count was associated with decreased mortality among the total sample and normal weight and overweight participants.

Discussion

This is one of the first studies to investigate the association of BIA-PA with mortality in HIV in a population that includes significant numbers of overweight/obese individuals. Our results reveal that in the current era of cART, BIA-PA remains a valuable prognostic indicator of mortality risk in underweight and normal weight PLWH; however, BIA-PA is not predictive of mortality in overweight or obese PLWH. These findings are in contrast to previous studies of PLWH in the pre-cART or early cART eras, which identified an inverse association between mortality and BIA-PA, regardless of body weight (Ott et al., 1995; Schwenk et al., 1999, 2000). Those data were collected before 2000 and typically included participants with a mean BMI in the normal weight range and mean $CD4^+$ values < 350 cells/μL.

Table 3. Demographic and Clinical Characteristics Associated With Mortality by BMI Category in Separate Logistic Regression Models

	Total Sample $N = 890$ (102 Deaths)	Underweight (BMI < 18.5) $n = 50$ (13 Deaths)	Normal Weight (BMI 18.5–24.9) $n = 409$ (62 Deaths)	Overweight (BMI 25–29.8) $n = 261$ (18 Deaths)	Obesity (BMI ≥ 30) $n = 170$ (9 Deaths)
Univariate models					
BIA-PA change (per 1 unit decrease)	1.8 (1.5, 2.2)[b]	5.8 (1.8, 19.0)[b]	2.2 (1.6, 3.1)[b]	1.3 (0.9, 2.0)	0.9 (0.4, 2.2)
Multivariate models					
BIA-PA change (per 1 unit decrease)	2.2 (1.6, 2.9)[b]	6.6 (1.2, 34.8)[a]	2.2 (1.5, 3.4)[b]	1.7 (0.9, 3.2)	0.9 (0.3, 3.0)
BIA-PA (highest)	0.6 (0.4, 0.7)[b]	0.5 (0.1, 1.5)	0.6 (0.4, 0.8)[b]	0.6 (0.3, 0.9)[b]	0.9 (0.4, 1.8)
Insurance type					
Private	referent	referent	referent	referent	referent
Public	2.7 (1.5, 5.1)[b]	1.2 (0.1, 30.3)	2.8 (1.2, 6.4)[a]	2.2 (0.5, 9.5)	6.3 (0.8, 52.5)
None	1.2 (0.5, 2.6)	1.3 (0.1, 60.3)	0.8 (0.3, 2.3)	2.1 (0.4, 9.9)	0.1 (0.1, 100.0)
CDC "C" diagnosis	1.9 (1.1, 3.2)[a]	3.8 (0.3, 46.3)	2.4 (1.1, 5.2)[a]	0.9 (0.3, 2.7)	1.9 (0.3, 12.0)
Protease inhibitor (ever)	1.7 (0.9, 3.1)	1.0 (0.2, 8.1)	1.3 (0.6, 3.1)	1.8 (0.5, 6.4)	2.3 (0.2, 24.1)
$CD4^+$ (at highest BIA)					
>350	referent	referent	referent	referent	referent
200–350	1.5 (0.7, 3.4)	5.2 (0.2, 176.0)	1.4 (0.5, 4.1)	1.9 (0.3, 10.9)	0.1 (0.1, 100.0)
<200	4.3 (2.2, 8.3)[b]	1.9 (0.1, 29.8)	4.5 (1.8, 10.9)[b]	5.8 (1.3, 26.5)[a]	7.8 (1.0, 71.6)[a]
$CD4^+$ change (per 50 cell increase)[c]	0.9 (0.8, 0.9)[b]	1.0 (0.7, 1.3)	0.8 (0.7, 0.9)[b]	0.9 (0.8, 1.0)	0.8 (0.6, 1.0)

Note: BIA-PA = bioelectrical impedance analysis phase angle; BMI = body mass index; CDC = Centers for Disease Control and Prevention.
[a] $p < .05$.
[b] $p < .01$.
[c] Change between highest and last BIA-PA measurements.

The present investigation measured BIA-PA over a decade later than the previous studies, in a population where almost half of the participants (48%) were classified as overweight/obese and had $CD4^+$ values > 350 cells/μL. Thus, the present study may more accurately reflect the prognostic capability of BIA-PA for present-day HIV treatment.

Currently, BIA-PA is assessed in PLWH when an individual is new to HIV care, is underweight, experiences unplanned weight loss, or has a low $CD4^+$ percent. BIA-PA measurements are determined primarily by biological factors, such as age and gender; however, obesity is associated with increased fat mass and variations in hydration status that can alter the accuracy of bioelectrical impedance assessment (Bosy-Westphal et al., 2006; Dittmar, 2003). BIA-PA is a less reliable measure of body compartment mass once BMI surpasses 34 kg/m^2, at which point errors in prediction are greater (Kyle, Bosaeus, De Lorenzo, Deurenberg, Elia, Gomez, et al., 2004; Kyle, Bosaeus, De Lorenzo, Deurenberg, Elia, Manuel Gomez, et al., 2004). In addition, BIA-PA increases with BMI until a BMI of 40 kg/m^2 is reached, at which lower BIA-PA is observed (Bosy-Westphal et al., 2006); however, our sample size was underpowered to analyze separate categories within obesity (BMI ≥ 30 kg/m^2). Despite the use of an HIV-specific equation for BIA-PA measurement, additional work may be required to develop equations that consider the impact of both HIV and obesity on tissue hydration status and cellular mass. Bioelectrical impedance measures are more accurate in overweight individuals; however, we did not detect an association of BIA-PA with mortality in this study sample. Of interest, we previously observed higher than expected levels of adiposity in overweight PLWH (Willig

et al., 2017; Willig, Heath, Muhammad, & Overton, 2015); PLWH who are overweight per BMI but have very high levels of body fat may experience similar measurement error issues observed with extreme obesity. It is also possible that overweight and obese individuals with HIV maintain adequate cellular mass for survival even when general cellular degradation results in a declining BIA-PA. The factors contributing to a lower mortality risk with declining BIA-PA in this group require additional investigation.

Although phase angle was not associated with mortality in overweight/obese PLWH, BIA-PA remained an important indicator of mortality risk in underweight and normal weight individuals. A decline in phase angle represents a breakdown of cellular membranes that may be detrimental to overall health. Generally, a phase angle $>$ 5.0 degrees in women and $>$ 6.0 degrees in men is considered healthy (Kyle et al., 2001). Most (79%) of our study participants were men, with a median BIA-PA $>$ 6.0; however, median BIA-PA ranged from only 5.5–6.9 across BMI categories. Overall, these values are significantly lower than those reported in HIV-uninfected groups. Barbosa-Silva et al. reported that although BIA-PA did decline with age, the median score for men was 6.2–8.0 and 5.6–7.0 for women (Barbosa-Silva, Barros, Wang, Heymsfield, & Pierson, 2005). They observed a median BIA-PA $<$ 7.0 only in men older than 60 years, whereas the median age in our study sample was only 42 years. In another sample of HIV-uninfected participants, Kumar et al. likewise reported a mean BIA-PA of 7.4 in men and 7.1 in women (Kumar, Dutt, Hemraj, Bhat, & Manipadybhima, 2012). Collectively, this suggests that the BIA-PA of PLWH at all body sizes remains lower than that observed in healthy, HIV-uninfected groups. Further investigations of factors that contribute to degradation of cellular membranes in the current era of HIV treatment are warranted.

Bioelectrical impedance analysis phase angle can be used clinically to identify and monitor PLWH who have controlled viremia yet are experiencing decreased cellular integrity (i.e., nutritional decline) and mortality risk. Those individuals who present with a low BIA-PA can receive more intensive medical nutrition therapy with a focus on food and nutritional supplementation to improve body protein stores and decrease mortality risk ("Erratum," 2018; Viertel, Bock, Reich, Loser, & Plauth, 2018; Willig, Wright, & Galvin, 2018). The results of the current study affirm that BIA-PA assessed in the clinical setting to identify patients in need of focused medical nutrition therapy remains valid for underweight and normal weight PLWH; however, alternative approaches may be needed to identify overweight and obese individuals with declining health who are in need of more intensive interventions focused on maintaining body protein stores. The development of these tools will be necessary because the prevalence of obesity among PLWH in low-, middle-, and high-income countries continues to increase (Crum-Cianflone et al., 2008; Hidalgo et al., 2018; Semu et al., 2016; Tate et al., 2012).

These findings should be placed in the context of certain limitations. Although participants received an annual BIA-PA screen during the study period, those who were at high risk for malnutrition (CD4% $<$ 15%, previously documented low BIA-PA) were more likely to complete additional BIA-PA assessments. Thus, the study sample may include a greater proportion of participants with medical complications compared with studies of healthy populations. Consideration of diagnosed infections and comorbidities in this cohort did not alter the association of BIA-PA with mortality; however, the overall number of patients with diagnoses such as cirrhosis, cancer, and acute infections was low, limiting our ability to explicate the contributions of these individual diagnoses to BIA-PA levels. The evaluations were conducted as part of routine clinical visits; thus, some participants may not have adhered to guidelines for avoiding moderate/vigorous exercise or excessive fluid consumption several hours before measurement. Significantly, less mortality was observed in overweight/obese groups compared with underweight/normal weight participants; however, the study was powered to detect the association of BIA-PA with mortality in all groups. In addition, this investigation focused on mortality and does not exclude the prognostic value of BIA-PA in risk for other metabolic diseases, including cardiovascular, renal, and cancer diagnoses.

In conclusion, BIA-PA remains an independent predictor of mortality among underweight/normal weight PLWH. It is less clear whether BIA-PA has prognostic value for mortality risk among overweight/obese PLWH, which is concerning given the rapid increase in body weight among HIV-infected groups. Besides evaluating underweight PLWH, current triggers for BIA-PA assessment (new to care, low $CD4^+$%, unplanned weight loss) do not consider the impact of being overweight or obese on the interpretation of BIA-PA results. Adjusted BIA-PA equations that simultaneously consider HIV infection and excess adiposity are needed. Additional study of appropriate prognostic indicators for cellular membrane degradation and mortality risk in this increasing subset of PLWH is greatly needed to improve clinical care in HIV treatment.

Key Considerations

- ❍ BIA-PA is a validated predictor of cellular health and mortality risk in normal weight PLWH on early cART regimens.
- ❍ In the current era of cART, BIA-PA remains a valuable prognostic indicator of mortality risk in underweight and normal weight adults with HIV, and it can be used to identify patients who need more intensive medical nutrition therapy.
- ❍ BIA-PA does not predict mortality risk in overweight or obese adults with HIV.
- ❍ Because the prevalence of overweight and obesity continues to increase globally among adults with HIV, new approaches for estimating cellular integrity and mortality risk in the context of controlled virema are needed.

Disclosures

The authors report no real or perceived vested interests that relate to this article that could be construed as a conflict of interest.

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