

## Original Research

# Weight Loss and Body Mass Index as Predictors of HIV Disease Progression to AIDS in Adults. Aquitaine Cohort, France, 1985–1997

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**Key words:** acquired immunodeficiency syndrome, body mass index, disease progression, HIV infection, weight loss

**Objective:** To assess the performance of weight related nutritional markers (reported involuntary weight loss greater than 10%, measured weight loss and body mass index-BMI-) in predicting HIV disease progression.

**Design:** Multirisk cohort of HIV-1 infected patients.

**Method:** The three nutritional variables were studied in Cox proportional hazard models as time dependant variables.

**Results:** The sample included 2376 subjects (median follow up: 43.1 months), of those 675 experienced an AIDS defining event. After adjustment for well known prognostic factors, the reported weight loss greater than 10% tripled the risk of progression to clinical AIDS (Hazard ratio [HR] 3.0, 95% confidence interval [CI] 2.5–3.7). For measured weight loss under 5%, between 5% and 10% and greater than 10% of baseline weight compared with no weight loss, hazard ratios were respectively 1.8 (CI 1.5–2.2), 2.6 (CI 2.1–3.2) and 5.1 (CI 4.1–6.4). The relative risks of AIDS were 1.7 (CI 1.3–2.2) for BMI between 17 kg/m<sup>2</sup> and 18.5 kg/m<sup>2</sup>, 2.6 (CI 1.7–4.0) for BMI between 16 kg/m<sup>2</sup> and 17 kg/m<sup>2</sup> and 4.7 (CI 3.0–7.4) for BMI under 16 kg/m<sup>2</sup>.

**Comments:** Even a limited weight loss measured at a given time during follow up increases the risk of HIV progression; moreover, a simple cross-sectionnal measure of BMI has a good predictive value for subsequent development of clinical disease.

## INTRODUCTION

Malnutrition is a frequent but heterogenous phenomenon during the course of Human Immunodeficiency Virus (HIV) infection and remains among major causes of morbidity in this context. Etiological factors, still only partially understood, are dietary reduction, nutrient malabsorption, metabolic disturbances and endocrine dysfunction [1–4]. Studies of nutritional status of HIV-infected patients have shown a substantial weight loss during the course of infection, and this phenomenon has often been considered as an unfavorable prognostic factor of survival [5, 6]. Few studies have been conducted however on the relation between malnutrition and disease progression, and most of them dealt with targeted populations [7–10]. While biological markers are now being used in clinical practice, the performance of clinical indicators of nutritional status in

predicting HIV disease progression still needs further study as they are more often and more easily available.

The objective of this study was to evaluate in a large cohort of HIV infected individuals of both genders and all HIV transmission categories the performance of three weight-related nutritional markers in predicting HIV disease progression: a reported unintentional weight loss greater than 10% of usual weight without any underlying disease, a measured weight loss during follow-up and the body mass index (BMI) value.

## MATERIALS AND METHODS

### Study Population and Study Sample

The Groupe d'Epidémiologie Clinique du Sida en Aquitaine (GECSA) implemented in 1987 a hospital-based surveillance

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system of HIV infection in the Bordeaux University Hospital and four other public hospitals in Aquitaine, southwestern France [11]. All HIV-1 positive in- or out-patients of the participating clinic wards, aged over 13 and giving informed consent, are thus reported. A standardized questionnaire with epidemiological, clinical, biological and therapeutic data is completed by physicians at each hospital contact. Thus, the Aquitaine Cohort is constituted of patients with longitudinal data available (i.e., at least one follow-up hospital visit after enrollment or a known date of death after initial reporting).

The study sample consisted of the Aquitaine Cohort subjects who were aged over 18, enrolled between 1985 and December 31, 1996 and having at least two available documented weights including the baseline measure. Patients presenting clinical AIDS or an involuntary weight loss greater than 10% of usual weight at enrollment; pregnant women were not included.

### Statistical Analysis

The primary prognostic variable of interest was weight, documented in three ways:

1) Information about involuntary weight loss greater than 10% of usual weight in the absence of an underlying condition reported by a physician was considered a binary variable extracted from the clinical records.

2) Weight loss was calculated at each time of follow-up when weight was available. These variations of weight were compared to the baseline value. Three categorial variables were then calculated: weight loss less than 5%, between 5 and 10% and greater than 10%. Each of these was compared to no weight loss or weight gain used as the reference category.

3) BMI or Quetelet's index was then calculated, as weight divided by height squared, when both height and weight measures were available. The BMI was divided into four categories according to World Health Organisation (WHO) threshold values: BMI <16 kg/m<sup>2</sup>, 16–16.9 kg/m<sup>2</sup>, 17–18.4 kg/m<sup>2</sup> and ≥18.5 kg/m<sup>2</sup> (considered as the reference). The primary outcome was the occurrence of the AIDS stage, using the clinical definition of the Centers for Disease Control adopted in France [12] with the exception of the CD4 cell count criteria [13].

The anthropometric indices were treated as time-dependent variables. The baseline adjustment variables used in this study were gender, age, HIV transmission group (reference: men who have sex with men), period of enrollment, clinical stage and CD4 cell count. The model, including measured weight loss, was also adjusted on baseline weight. Other variables were documented during follow-up and used as time dependent variables: first CD4 cell count under 200/mm<sup>3</sup>, first prescription of antiretroviral therapy and first prescription of prophylaxis against opportunistic infections. Four periods of enrollment were considered according to the evolution of treatment practices in France: <1987, 1987–1990, 1991–1994, 1995–1996, the latter being used as the reference.

Comparisons between groups were conducted using the chi-square test for categorical data and Student's *t* test for continuous data. Univariate and multivariate statistical analyses of the predictors of the progression to AIDS were conducted using Cox proportional hazard models (SAS® software version 6.12, PHREG procedure). Patients without AIDS on December 31, 1997 were censored at the date of their last assessment. Patients whose last follow-up had occurred more than 12 months prior to that date were considered lost to follow-up. The proportional hazards assumption was verified using graphical methods by examining log [-log(survival probability)] versus log(time) plots for each variable not taken into account as a time dependent variable. Hazard ratios (HR) with their 95 percent confidence intervals (CI) estimated the strength of the epidemiological associations and thus the risk associated with a given value of the prognostic indicator.

### RESULTS

During the study period, 2376 patients were included in this analysis and 675 of them reached AIDS stage, with one AIDS defining event for 81%, two for 14% and three or more for 5%. The description of those events is presented in Table 1.

The median length of follow-up was 43.1 months (range: 0.7–148 months). Sixteen percent (n = 387) of patients were lost to follow-up according to the study criteria. They were more likely female (31.5% vs. 25.9%, *p* < 0.02), intravenous drug users (40.8% vs. 28.0%, *p* < 0.001) and younger than other patients (29.9 vs. 34.3 years, *p* < 0.0001). Moreover, they had a greater CD4 cell count at baseline (482 vs. 398 CD4/mm<sup>3</sup>, *p* < 0.0001). However, baseline weight did not differ between the two groups (*p* = 0.32).

Baseline and follow-up characteristics of the study sample are presented in Table 2. Among the 2376 patients studied, 231 (9.7%) had indication of "involuntary weight loss greater than

**Table 1.** Most Frequent AIDS Defining Events Initially Diagnosed among Patients Who Developed AIDS during Follow-up (675 Patients, 772 Events)—Aquitaine Cohort, France, 1985–1997

AIDS Defining Event	Number of Events
Invasive Candidiasis	103
Pneumocystis carinii pneumonia	96
Wasting syndrome	92
Toxoplasmosis	88
Kaposi's sarcoma	82
Mycobacteriosis	65
Tuberculosis	60
Neurologic diseases	54
Cytomegalovirus disease	38
Lymphoma	26
Other diagnoses	68
Total events	772

**Table 2.** Description of Baseline and Follow-up Characteristics of the Study Sample (2376 Subjects, 675 Who Experienced an AIDS Event)—Aquitaine Cohort, France, 1985–1997

Variable	All Patients		Patients Who Experienced an AIDS Event	
	N/Median	%/Range	N/Median	%/Range
Gender: Male	1738	73.1	517	29.8
Age (years)	31	18–78	33	18–74
HIV transmission category				
Homosexuals	860	36.2	285	33.1
Intravenous Drug Users	714	30.0	209	29.3
Blood recipients	163	6.9	67	41.1
Heterosexuals	547	23.0	103	18.8
Indeterminate	92	3.9	11	12.0
Period of enrollment				
1985–1986	64	2.7	31	48.4
1987–1990	867	36.5	368	42.5
1991–1994	1031	43.4	260	25.2
1995–1997	414	17.4	16	3.8
Baseline clinical stage <sup>a</sup>				
A	1992	83.8	520	26.1
B	384	16.2	155	40.4
Baseline weight	64	34–120	63	34–116
CD4 cell count at enrollment	367	1–2530	275	1–1248
Drop under 200 CD4/mm <sup>3</sup>	1344	56.6	636	47.3
Any antiretroviral treatment	1840	77.4	538	29.2
Primary prophylaxis	1090	45.9	443	40.6

<sup>a</sup> CDC clinical stage (Centers for Disease Control, 1992).

10%” during follow-up. When calculating weight loss, 1579 (66.5%) experienced weight loss (median of maximum loss: 6% of baseline weight, range: 0.4%–42%). Categorizing the weightloss, 1334 (56.1%) experienced a loss less than 5%, 814 (34.3%) between 5% and 10% and 417 (17.6%) more than 10% of baseline weight. In these three categories of increasing severity, 419 (31.4%), 277 (34.0%) and 160 (38.4%) patients experienced AIDS, respectively.

The subsample allowing BMI calculation represented 1570 subjects (66.1%), of whom 493 reached the AIDS stage during follow-up. The comparison of the two groups with or without BMI information showed the following differences: patients with BMI values were more frequently women (28.8% vs. 23.1%,  $p = 0.003$ ) and had longer follow-up (47.7 vs. 34.9 months,  $p < 0.0001$ ). Both groups were comparable for age, HIV transmission category, clinical stage, CD4 cell count, antiretroviral treatment and probability of AIDS occurrence (logrank test,  $p < 0.06$ ). Median BMI at baseline was 21.5 kg/m<sup>2</sup> (range 14.0–37.9). The tenth percentile was 18.5 kg/m<sup>2</sup> corresponding to the WHO threshold for malnutrition. During follow up, 47 of these 1570 patients had at least one BMI value under 16 kg/m<sup>2</sup>, 112 between 16 kg/m<sup>2</sup> and 16.9 kg/m<sup>2</sup> and 342 between 17 kg/m<sup>2</sup> and 18.5 kg/m<sup>2</sup>. Among them, 57.5%, 44.6% and 38.01% experienced an AIDS event, respectively.

### Univariate Analysis

All adjustment variables were significant univariate predictors of disease progression (Table 3). The most predictive

negative factor was the drop under the threshold of 200 CD4/mm<sup>3</sup> (HR 13.3, CI = 10.6–16.8). Female gender and CD4 cell count at baseline were both protective. Thus, an increase of 100/mm<sup>3</sup> of CD4 cell count at baseline decreased the risk of AIDS occurrence by 30%.

Univariate analysis of nutritional variables is reported in Table 4. The three weight indicators were significantly predictive for the risk of AIDS occurrence. The relative hazard increased with the magnitude of the measured weight loss or the lower BMI categories. The same trend remained when the analysis was conducted excluding the 92 cases who reached an AIDS diagnosis event based on the occurrence of wasting syndrome (reported weight loss >10%, HR = 3.2; CI = 2.4–3.8; measured weight loss >10%, HR = 4.1; CI = 2.9–5.2).

### Multivariate Analysis

After adjustment for the variables presented in Table 2, the three weight indicators analyzed in three different models (Table 4) remained independent predictors of the progression to AIDS. A reported weight loss greater than 10% of the usual weight tripled the risk of disease progression (HR = 3.0, CI = 2.5–3.7). HR of disease increased with measured weight loss as with severity of malnutrition, represented by the WHO categories of BMI. Even among patients having lost less than 5% of their baseline weight or patients having a BMI between 17 and 18.5 kg/m<sup>2</sup>, the adjusted risk of progression to AIDS still

**Table 3.** Univariate Analysis (Cox Model) of Adjustment Variables (2376 Subjects, 675 Who Experienced an AIDS Event)—Aquitaine Cohort, France, 1985–1997

Variables	Categories	HR	(95% CI)	<i>p</i>
Gender	Male	Ref		
	Female	0.73	(0.61–0.87)	<0.0001
Age		1.31 <sup>a</sup>	(1.22–1.40)	<0.0001
HIV transmission category	Homosexuals	Ref		
	Intravenous drug users	0.78	(0.65–0.93)	<0.001
	Blood recipients	1.00	(0.77–1.31)	0.99
	Heterosexuals	0.57	(0.45–0.71)	<0.0001
Period of enrollment	Indeterminate	0.41	(0.23–0.75)	<0.01
	1995–1997	Ref		
	1991–1994	2.22	(1.33–3.71)	<0.01
	1987–1990	2.41	(1.44–4.04)	<0.001
Baseline clinical stage <sup>b</sup>	1985–1986	1.84	(0.99–3.43)	0.06
	A	Ref		
Baseline weight	B	2.24	(1.87–2.68)	<0.0001
		0.99	(0.98–1.00)	0.04
CD4 cell count at enrollment		0.69 <sup>c</sup>	(0.66–0.73)	<0.0001
Drop under 200 CD4/mm <sup>3</sup>	No	Ref		
	Yes	13.3 <sup>d</sup>	(10.56–16.84)	<0.0001
Antiretroviral treatment	No	Ref		
	Yes	4.39 <sup>d</sup>	(3.63–5.30)	<0.0001
Primary prophylaxis	No	Ref		
	Yes	4.94 <sup>d</sup>	(4.21–5.81)	<0.0001

<sup>a</sup> For increase of 10 years (continuous variable).

<sup>b</sup> CDC clinical stage (Centers for Disease Control, 1992).

<sup>c</sup> For increase of 100 CD4/mm<sup>3</sup> (continuous variable).

<sup>d</sup> Time dependent variable.

HR = Hazard Ratio, 95% CI = 95 percent confidence interval.

increased by 1.7 compared with patients with no weight loss or normal BMI value. Finally, both severe thinness (BMI <16 kg/m<sup>2</sup>) and measured loss of weight greater than 10% of baseline weight increased the risk of disease progression by fivefold.

## DISCUSSION

Within a large multirisk population of HIV-positive patients, a history of involuntary weight loss greater than 10%, measured weight loss and BMI were identified as predictors of HIV disease progression independently of the usual prognostic indicators.

Our cohort has a large number of participants enrolled at all stages of HIV infection; a long follow-up period and the progression of disease is prospectively documented. Moreover, the Aquitaine Cohort is considered highly representative of the HIV-infected population of Aquitaine patients since it includes 85% of HIV-positive patients of the area and 90% of reported AIDS cases [11]. In such a cohort study, recruitment is subject to potential sources of bias [14,15], but it reflects usual clinical management of HIV-infected people in the study setting. Moreover, adjustment for clinical stage, CD4 cell count and treatment was performed and allowed us to conclude what the contribution of nutritional markers to HIV disease progression is.

Well known prognostic factors were used to fit the multivariate models such as age [16,17], gender [18], use of antiretroviral treatment and primary prophylaxis [19] and baseline CD4 cell count [7,20]. We also used a drop below 200 cells/mm<sup>3</sup> during follow-up as an adjustment variable because this threshold was included in the 1993 revised CDC AIDS classification [13], but was not used to define AIDS in our study. The negative role of primary prophylaxis and antiretroviral treatment observed in the univariate analysis was probably explained by initial recruitment of subjects who tended to be more advanced in the disease when they began a treatment, as already reported [21]. Indeed, the first prescription of antiretroviral treatment did not reach statistical significance in multivariate analyses. Contrary to the findings of other investigators [18,22,23], men had a higher risk of disease progression in univariate analysis, but this effect disappeared in multivariate analyses, possibly due to bias as discussed in the literature.

The prognostic role of involuntary weight loss greater than 10% is not surprising, insofar as this variable constitutes one of the criteria used to define wasting syndrome as an AIDS defining event since 1987 [24]. However, the same statistical significance for the independent impact of the event was found when the 92 cases of a defining AIDS diagnosis based on the wasting syndrome were excluded, allowing the conclusion that weight loss was a specific predictor of wasting-syndrome based

**Table 4.** Risk of Progression to AIDS according to Three Weight Indicators in Univariate and Multivariate Analysis (2376 Patients, 675 Who Experienced an AIDS Event in the First and Second Model; 1570 Patients, 493 experienced an AIDS event in the Third Model)—Aquitaine Cohort, France, 1985–1997

Time Dependant Variables	Univariate Analysis			Multivariate Analysis <sup>a</sup>		
	HR	(95% CI)	<i>p</i>	HR	(95% CI)	<i>p</i>
Model #1						
Reported weight loss >10%						
No	Ref			Ref		
Yes	4.58	(3.74–5.60)	<0.0001	3.03	(2.46–3.72)	<0.0001
Model #2						
Measured weight loss						
No weight loss or weight gain	Ref			Ref		
<5%	2.31	(1.89–2.82)	<0.0001	1.81	(1.48–2.21)	<0.0001
Between 5% and 10%	3.16	(2.54–3.93)	<0.0001	2.59	(2.08–3.23)	<0.0001
>10%	6.53	(5.27–8.08)	<0.0001	5.10	(4.07–6.37)	<0.0001
Model #3						
BMI thresholds						
≥18.5	Ref			Ref		
17–18.4	1.74	(1.33–2.27)	<0.0001	1.69	(1.28–2.25)	<0.001
16–16.9	3.22	(2.08–4.98)	<0.0001	2.57	(1.65–4.02)	<0.0001
<16	6.82	(4.41–10.60)	<0.0001	4.73	(3.00–7.45)	<0.0001

<sup>a</sup> Cox models adjusted for gender, age, HIV transmission group, period of enrollment, clinical stage at enrollment, baseline CD4 cell count, drop under 200 CD4/mm<sup>3</sup>, antiretroviral treatment and primary prophylaxis of opportunistic infection.

HR = Hazard Ratio, 95% CI = 95 percent confidence interval.

AIDS. Moreover, the role of this variable can be misevaluated in the absence of effective measurement.

When measuring the loss of body weight by comparing subsequent weights to a reference weight, this reference can be the usual weight reported by the patient [25] or the weight at enrollment [8,18], and the two values can be different. The patient’s usual weight was not available in our database, so we considered the baseline weight measure as the reference weight. The patient may indeed have lost weight prior to enrollment. To avoid this potential bias, those patients self-reporting weight loss at enrollment have been excluded from the analysis.

A measured weight loss greater than 10% increased the risk of progression to AIDS as well as reported involuntary weight loss greater than 10%. Clark *et al.* [8] did not find a significant prognostic role of weight loss greater than 10% in a 12-month follow-up, but their small sample may have lacked statistical power. The only significant variable in their model was also the most contributive prognostic variable of our study, i.e., the drop under 200 CD4/mm<sup>3</sup>.

According to the literature [25–27], a weight loss ranging between 5% and 10% of usual body weight corresponds to moderate malnutrition while a loss greater than 10% represents an intermediate malnutrition stage. It is thus not surprising to observe a higher risk of disease progression in the second category. Moreover, in our study, a weight loss less than 5% was significantly and negatively predictive of disease progression. Suttman *et al.* [1] reported that disease progression was similar in both groups: “weight loss >5%” and “weight loss <5% of body weight.” In other studies, subjects have been considered controls when a weight loss under 5% of the usual

weight occurred [18,25,28]. However, some modification of body composition appears with limited weight loss [29], and a recent study has reported the predictive impact on disease progression of both mild (0%–5%) and moderate (5%–10%) weight loss [10].

The evaluation of a measured weight loss requires follow-up data whereas the BMI can be measured at any consultation or within a cross-sectional survey. It is recognised as an indicator of chronic energy deficiency [30] and is often lower for HIV-positive subjects than for HIV-negative comparables ones [29,31]. According to thresholds established by WHO [32], our study population corresponded at enrollment to a population with mild prevalence of malnutrition, since 10% of patients had a BMI lower than 18.5. It should be noted that, in the study by Hogg *et al.* [31], HIV-positive subjects were more frequently smokers than seronegative subjects, and tobacco is known to be associated with both weight loss and faster progression to AIDS [33]. We acknowledge that smoking habits are not available in the Aquitaine Cohort database. Only two-thirds of our study population had a BMI documented, but the progression to AIDS between these patients and those without measured BMI did not differ. This supports the assumption that patients with documented BMI were not more advanced in HIV disease than the others. The predictive role of BMI was already highlighted in other studies using different methodological approaches [21,34,35]. In our study, we fitted BMI as a dummy variable according to WHO thresholds and found that BMI was as informative as weight loss for predicting progression of HIV disease. Moreover, the increase in relative risk with the severity of thinness defined by WHO thresholds favors the validity of these thresholds in HIV infected subjects.

## CONCLUSIONS

This study confirms the predictive role of weight loss in disease progression to AIDS independently of powerful indicators such as low CD4 cell count. Moreover, only one measurement of BMI can predict the risk of disease progression as well as weight loss measured during follow-up. Therefore, as biological factors now take the forefront in patient management, it is important to be aware that such simple nutritional markers still should be mandatory in HIV patient management.

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