Weight gain at 3 months of antiretroviral therapy is strongly associated with survival: evidence from two developing countries

Weight gain at 3 months of antiretroviral therapy is strongly associated with survival: evidence from two developing countries

Yoann Madec[a], Elisabeth Szumilin[b], Christine Genevier[b,c], Laurent Ferradini[b,d], Suna Balkan[b], Mar Pujades[e] and Arnaud Fontanet[a]

Background: In developing countries, access to laboratory tests remains limited, and the use of simple tools such as weight to monitor HIV-infected patients treated with antiretroviral therapy should be evaluated.

Methods: Cohort study of 2451 Cambodian and 2618 Kenyan adults who initiated antiretroviral therapy between 2001 and 2007. The prognostic value of weight gain at 3 months of antiretroviral therapy on 3–6 months mortality, and at 6 months on 6–12 months mortality, was investigated using Poisson regression.

Results: Mortality rates [95% confidence interval (CI)] between 3 and 6 months of antiretroviral therapy were 9.9 (7.6–12.7) and 13.5 (11.0–16.7) per 100 person-years in Cambodia and Kenya, respectively. At 3 months, among patients with initial body mass index less than or equal to 18.5 kg/m^2 (43% of the study population), mortality rate ratios (95% CI) were 6.3 (3.0–13.1) and 3.4 (1.4–8.3) for those with weight gain less than or equal to 5 and 5–10%, respectively, compared with those with weight gain of more than 10%. At 6 months, weight gain was also predictive of subsequent mortality: mortality rate ratio (95% CI) was 7.3 (4.0–13.3) for those with weight gain less than or equal to 5% compared with those with weight gain of more than 10%.

Conclusion: Weight gain at 3 months is strongly associated with survival. Poor compliance or undiagnosed opportunistic infections should be investigated in patients with initial body mass index less than or equal to 18.5 and achieving weight gain less than or equal to 10%.

AIDS 2009, **23**:853–861

Keywords: developing countries, HIV, monitoring tool, mortality, weight

Introduction

In 2007, over 22 million people were estimated to be HIV-infected in sub-Saharan Africa, and approximately 4 million in South-east Asia [1]. Following the World Health Organisation (WHO) '3 by 5' initiative aimed at providing antiretroviral therapy (ART) to 3 million individuals by 2005 [2], tremendous efforts have been made to increase ART access in resource-limited countries [3,4], and programmes providing ART in such settings have proved their efficiency [5–9].

Scaling up ART resulted in the rapid increase of the number of patients entering and requiring long-term HIV care. Decentralization of HIV care through nurses and clinical officers is one of the key elements for wider access to ART to overcome physician shortages [3,10,11]. Experience from several resource-limited countries

[a]Unité d'Epidémiologie des Maladies Emergentes, Institut Pasteur, 25-28 rue du Docteur Roux, [b]Médecins Sans Frontières, 8 rue Saint Sabin, Paris, France, [c]Médecins Sans Frontières, Nairobi, Kenya, [d]Infectious Diseases Department, Khmero-Soviet Friendship Hospital, St. 134 Sangkat Vealvong Khan 7 Makara, Phnom Penh, Cambodia, and [e]Epicentre, 42 bis boulevard Richard Lenoir, Paris, France.

Correspondence to Yoann Madec, Unité d'Epidémiologie des Maladies Emergentes, Institut Pasteur, 25-28 rue du Docteur Roux, 75015 Paris, France.

E-mail: yoann.madec@pasteur.fr
Received: 11 September 2008; revised: 18 December 2008; accepted: 23 December 2008.

DOI:10.1097/QAD.0b013e32832913ee

where HIV care is provided by nurses and/or clinical officers has been successful [3,4], but requires simplified and standardized follow-up of HIV-infected patients [12]. In such settings, in which access to laboratory tests remains limited, identifying simple tools to monitor disease progression is important [13–16]. Weight gain/loss is one potential tool, as it is easily measurable and costs little. Indeed, body mass index (BMI) at ART initiation is a strong predictor of disease progression [7,17,18], and the proportion of patients achieving weight gain of at least 10% 6 months after ART initiation is one of the indicators proposed by WHO to evaluate HIV programmes [19].

In developed countries, little attention has been paid to the evolution of weight under ART, and studies have reported only moderate increases [20,21]. However, weight loss was found to be associated with increased mortality [22,23]. In resource-limited settings, in which patients initiate treatment at a more advanced stage of disease [6,7], weight gain under ART might be greater. Researchers from India reported a mean weight increase of 2.5 kg after 6 months under nevirapine-based therapy [24] but did not investigate its prognostic value on disease progression.

Our goals were to describe weight gain in patients on ART enrolled in Médecins Sans Frontières (MSF) programmes in two resource-limited countries (Cambodia and Kenya), and to evaluate the prognostic value of weight gain on mortality to determine whether it could be used as a monitoring tool for patients on ART.

Methods

Study population

Study participants were patients treated with ART (ART was defined as three or more antiretroviral drugs, irrespective of their class) in two MSF programmes based at the Khmero-Soviet Friendship Hospital of Phnom Penh, Cambodia, and the district hospital of Homa Bay, Kenya. In both programmes, following WHO recommendations, ART initiation criteria were a WHO stage 4 condition, WHO stage 3 condition with CD4 cell count less than 350 cells/μl, or a CD4 cell count less than 200 cells/μl. Patients were seen monthly the first 6 months following ART initiation, then every 2 months if stable. At each visit, patients underwent an interview and clinical examination, with the corresponding data routinely entered into the FUCHIA database (Epicentre, Paris, France).

Patients included in this analysis were ART-naive adults (≥18 years), in whom weight was recorded at ART initiation and at least once during follow-up, and with a minimum follow-up of 3 months on ART. Thus, 344 Cambodians and 277 Kenyans were not considered because of a follow-up less than 3 months (in Cambodia: 135 deaths, 28 lost to follow-up, and 181 ART initiation within 3 months from cut-off date 12 July 2007; in Kenya: 149 deaths, 119 lost to follow-up, nine ART initiation within 3 months from cut-off date 26 January 2007). Only patients who initiated ART before 1 January 2006 in Kenya were included, as no nutritional supplementation was provided before this date. We excluded women enrolled in mother-to-child prevention programmes, as well as 13 patients from Kenya who interrupted their follow-up for ≥18 months. A total of 2451 patients from Phnom Penh and 2618 patients from Homa Bay were considered for the analysis.

Weight measurements

Eligible patients contributed a total number of 58 654 visits in Cambodia and 50 703 visits in Kenya during the entire follow-up; median follow-up were 45 and 32 months in Cambodia and Kenya, respectively. In 190 (0.3%) and 683 (1.3%) visits in Cambodia and Kenya, respectively, weight was not recorded.

We validated and eliminated inconsistencies in weight measurements first by identifying 49 patients with low (<25 kg) weight measurements. In 33 of these patients, these weights were inconsistent (>10 kg difference with other weight measurements) and were then considered as missing; in the remaining 16 patients, weight was consistent with other measurements. Secondly, we identified 23 patients with a weight difference of at least 10 kg between two consecutive visits separated by less than 1 week; these weight measurements were considered as missing. Finally, in 99 patients, a weight difference of at least 15 kg within 3 months was observed. Of these patients, 70 presented a weight difference of 15 kg or more with both the previous and the next visit, but the differences being in opposite directions; the middle weight measurement was thus considered missing. In the remaining 29 patients, weight was consistent with the other measurements. After exclusion of inconsistent weight values, missing weight measurements [243 (0.4%) and 702 (1.4%) in Cambodia and Kenya, respectively] were estimated through linear extrapolation using adjacent weight measurements.

Weight gain at 3 or 6 months was expressed as the percentage gained with respect to the weight measured at ART initiation, using the closest measurement to 3 or 6 months.

Sensitivity analyses were performed defining weight gain with respect to the mean of the two weight measurements obtained within 1 month after ART initiation, which was available for 94 and 68% of patients in Cambodia and Kenya, respectively. The second weight measurement was larger than the first in 40 and 50% of the patients, respectively. Similarly, alternative weight gain at 3 or 6 months was estimated using the mean weight of all

Table 1. Patient characteristics at ART initiation by programme.

		Cambodia ($N=2451$)	Kenya ($n=2618$)	*P*-value
Sex	Men (%)	1324 (54.0)	969 (37.0)	<0.001
Age (years)	Median (IQR)	34 (30–40)	35 (30–42)	<0.001
WHO clinical stage	1–2 (%)	236 (9.6)	89 (3.4)	<0.001
	3 (%)	1063 (43.4)	1276 (48.7)	
	4 (%)	1152 (47.0)	1253 (47.9)	
CD4 cell count (cells/μl)	*N* (%)	2304 (94.0)	1663 (63.5)	
	Median (IQR)	33 (8–115)	114 (57–170)	<0.001
BMI (kg/m^2)	*N* (%)	2122 (86.6)	2606 (99.5)	
	Median (IQR)	18.8 (16.9–20.8)	19.4 (17.6–21.2)	<0.001
	≤17[a]	569 (26.8)	500 (19.2)	
	17–18.5[b]	408 (19.2)	514 (19.7)	
	18.5–20	426 (20.1)	530 (20.3)	
	>20	719 (33.9)	1062 (40.8)	
ART regimen	3TC-d4T-NVP (%)	1249 (51.0)	2239 (85.5)	<0.001
	3TC-d4T-EFV (%)	1139 (46.5)	226 (8.6)	
	Other (%)	63 (2.5)	153 (5.9)	

ART, antiretroviral therapy; BMI, body mass index; d4T, stavudine; EFV, efavirenz; IQR, interquartile range; NVP, nevirapine; WHO, World Health Organisation; 3TC, lamivudine.
[a]Severe-to-moderate malnutrition.
[b]Mild malnutrition.

measurements recorded within the 2-month interval around the third or sixth month.

Laboratory tests

At ART initiation, and then every 6 months, whole blood samples were collected for total lymphocyte and CD4 cell counts. In Cambodia, CD4 measurements were performed until 2005 at the Institut Pasteur in Phnom Penh and then at the national Public Health Institute of Phnom Penh using FACSCalibur flow cytometry technology (BD Biosciences, Immunocytometry Systems, San Jose, California, USA). In Kenya, CD4 measurements were performed at the Homa Bay district hospital using FACSCount (Becton Dickinson Immunocytometry Systems, San Jose, California, USA).

Statistical analysis

Median weight gains at different time points were calculated by BMI level at ART initiation defined in four categories (≤17, >17 and ≤18.5, >18.5 and ≤20, and >20 kg/m^2), the first two categories representing severe-to-moderate and mild malnutrition, respectively [25,26]. To describe the weight gain evolution, we used a nonparametric method: locally weighted smoothed spline (LOWESS) curves which draw a representative smooth curve through data using robust local regression [27].

The prognostic value of weight gain at 3 and at 6 months of ART on short-term mortality (within the following 3 and 6 months, respectively) was investigated using Poisson regression models. These time points were chosen as they represent important visits in the follow-up of patients. Weight gains achieved were categorized as less than or equal to 5%, more than 5 and less than or equal to 10%, and more than 10%. We first investigated the prognostic value of weight gain, by programme and by BMI level at ART initiation. Interaction effects between weight gain and programme, and between weight gain and BMI level at ART initiation, were assessed. The prognostic value of weight gain was then evaluated in a multivariate Poisson model adjusting for confounding factors.

Finally, we described the time to reach weight gain more than 10% using Kaplan–Meier estimates. In patients who achieved weight gain more than 10%, we described the time until a weight measurement was lower or equal to the weight at ART initiation using Kaplan–Meier estimates, and estimated the prognostic value of this weight loss on mortality using a Cox model.

Statistical analyses were performed using Stata 8 (Stata Corp., College Station, Texas, USA). All significance tests were two-sided and *P* values less than 0.05 were considered significant.

Results

In this analysis, 2451 patients from Cambodia and 2618 patients from Kenya were included. The proportion of men was significantly higher in Cambodia than in Kenya (54 and 37%, respectively, $P<0.001$). In both programmes, nearly all patients were in WHO stage 3 or 4 at ART initiation (Table 1), but Cambodian patients had lower median CD4 cell counts than Kenyans (33 vs. 114 cells/μl, respectively, $P<0.001$). Median BMI was also lower in Cambodians than in Kenyans (18.8 vs. 19.4, respectively, $P<0.001$), and the proportions of patients with severe-to-moderate and mild malnutrition at ART initiation were 27 and 19%, respectively, in Cambodia, and 19 and 20%, respectively, in Kenya.

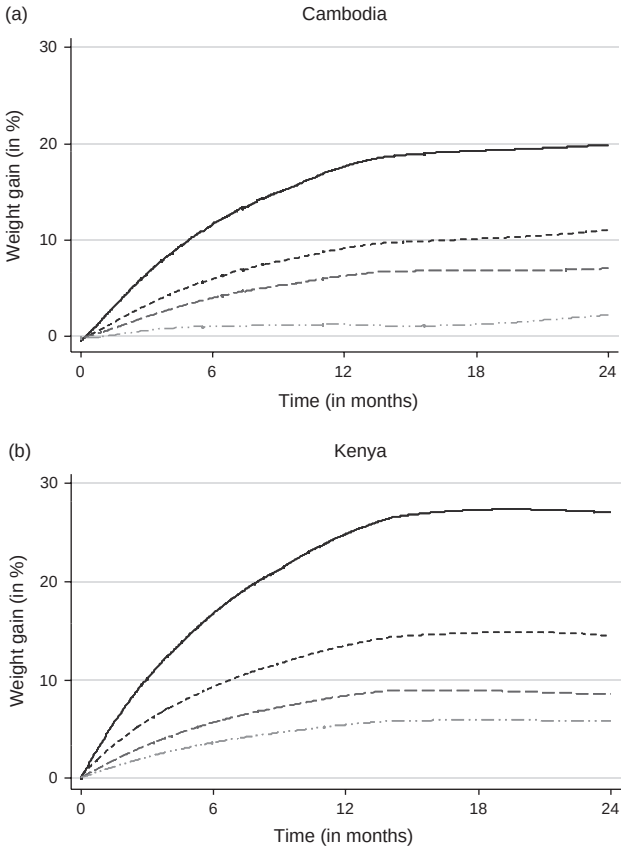

Fig. 1. Evolution of weight gain under ART in Cambodia (a) and Kenya (b) programmes, by BMI at ART initiation. Plain line: BMI less than or equal to 17 kg/m^2 (severe-to-moderate malnutrition). Dotted line: BMI more than 17 and less than or equal to 18.5 kg/m^2 (mild malnutrition). Dashed line: BMI more than 18.5 and less than or equal to 20 kg/m^2. Dashed-dotted line: BMI more than 20 kg/m^2. ART, antiretroviral therapy.

In both programmes, ART consisted in a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and one nonnucleoside reverse transcriptase inhibitor (NNRTI). The most frequently prescribed first-line ART regimens were lamivudine (3TC)-stavudine (d4T)-nevirapine (NVP) (50.5% in Cambodia and 85.5% in Kenya) and 3TC-d4T-efavirenz (EFV) (46.8% in Cambodia and 8.6% in Kenya).

Weight gain under antiretroviral therapy

Body mass index level at ART initiation was associated with the magnitude of subsequent weight gain, such that patients with lower BMI had larger weight gains (Fig. 1). Within each BMI category, observed weight gain was larger in Kenyans than in Cambodians. Nevertheless, LOWESS curves showed similar patterns of weight gain in the two programmes and across BMI categories. Hence, weight gain increased during the first year of ART and then remained stable or moderately increased afterward.

At 3 months of ART, in the four BMI categories at ART initiation – less than or equal to 17, more than 17 and less than or equal to 18.5, more than 18.5 and less than or equal to 20, and more than 20 – median [interquartile range (IQR)] weight gains (in %) were 5.4 (0.0;13.3), 2.5 (0.0;8.0), 1.8 (−1.8;5.4), and 0.0 (−1.8;3.4) in Cambodia; and 10.5 (2.2;19.6), 6.7 (1.9;12.3), 3.7 (0.0;7.7), and 1.8 (−1.6;6.2) in Kenya. Similarly, in the four BMI categories, median (IQR) weight gains at 6 months of ART (in %) were 12.5 (4.4;22.5), 6.5 (2.0;13.3), 4.0 (0.0;9.1), and 1.8 (−1.9;6.1) in Cambodia; and 18.8 (8.0;30.8), 11.9 (5.3;20.9), 8.0 (1.6;15.4), and 3.7 (−0.7;8.7) in Kenya.

Prognostic value of weight gain at 3 months

Of the patients alive 3 months after ART initiation, 59 in Cambodia and 86 in Kenya died within the following 3 months corresponding to an overall mortality rate [95% confidence interval (CI)] of 9.9 (7.6–12.7) per 100 person-years in Cambodia and 13.5 (11.0–16.7) per 100 person-years in Kenya. During this period, 62 (2.1%) and 46 (1.8%) patients were lost to follow-up in Cambodia and Kenya, respectively.

The prognostic value of weight gain at 3 months differed according to BMI level at ART initiation, such that in patients with BMI less than or equal to 18.5, those achieving weight gain less than or equal to 5%, and those achieving weight gain more than 5% and less than or equal to 10% had an increased risk of death compared with those with weight gain more than 10% [mortality rate ratio (MRR) 4.8 (95% CI 2.3–10.1) and 2.6 (95% CI 1.1–6.4), respectively]. In patients with BMI more than 18.5, weight gain was not associated with mortality ($P = 0.11$) (Table 2). Testing for interaction, no significant differences were found in the prognostic value of weight gain between men and women ($P = 0.85$), between Kenya and Cambodia ($P = 0.68$), between patients with WHO clinical stage 4 at ART initiation and other patients ($P = 0.57$), between CD4 categories at ART initiation ($P = 0.57$), or between patients who initiated a NVP-based or EFV-based combination ($P = 0.78$).

After adjusting for other factors, weight gain at 3 months remained strongly associated with mortality (Table 3). Other baseline factors associated with higher mortality were WHO stage 4 (compared with stage 3) and BMI. Interestingly, CD4 cell count at ART initiation was no longer associated with mortality.

Sensitivity analyses using the mean of the first two weight measurements recorded within the first month of ART and/or defining weight at 3 months as the mean of all measurements recorded within the 2-month period around the third month after ART initiation gave similar results (data not shown).

Table 2. Prognostic value of weight gain at 3 months of ART (M3) on mortality during the 3–6-month period, and at 6 months of ART (M6) on mortality during the 6–12-month period, by BMI level at ART initiation.

BMI (kg/m^2)	Weight gain	*N*	Death	PY	Mortality rate (95% CI)	MRR (95% CI)	*N*	Death	PY	Mortality rate (95% CI)	MRR (95% CI)
M3											
≤17[a]	≤5%	432	34	101.4	33.5 (24.0–46.9)	4.4 (2.0–9.5)					
	>5 and ≤10%	168	9	40.5	22.2 (11.6–42.7)	2.9 (1.1–7.6)					
	>10%	431	8	105.4	7.6 (3.8–15.2)	1	898	51	214.3	23.8 (18.1–31.3)	4.8 (2.3–10.1)
>17 and ≤18.5[b]	≤5%	466	17	112.9	15.1 (9.4–24.2)	2.6 (0.8–9.0)	381	12	92.8	12.9 (7.3–22.8)	2.6 (1.1–6.4)
	>5 and ≤10%	213	3	52.3	5.7 (1.8–17.8)	1	654	8	161.1	5.0 (2.4–9.9)	1
	>10%	223	0	55.7	0.0 (0.0–6.6)	–					
>18.5 and ≤20	≤5%	619	11	151.3	7.2 (4.0–13.1)	–					
	>5 and ≤10%	199	0	49.1	0.0 (0.0–7.5)	–					
	>10%	128	0	32.0	0.0 (0.0–11.5)	–	1952	31	478.0	6.5 (4.6–9.2)	2.1 (0.5–8.9)
>20	≤5%	1333	20	326.7	6.1 (3.9–9.5)	1.0 (0.2–4.4)	490	2	121.0	1.7 (0.4–6.6)	0.5 (0.1–3.8)
	>5 and ≤10%	291	2	71.9	2.8 (0.7–11.1)	0.5 (0.1–3.3)	264	2	65.6	3.0 (0.8–12.2)	1
	>10%	136	2	33.6	5.9 (1.5–23.8)	1					
M6											
≤17[a]	≤5%	230	28	100.0	28.0 (19.3–40.6)	8.5 (4.2–17.9)					
	>5 and ≤10%	119	4	56.4	7.1 (2.7–18.9)	2.1 (0.6–7.0)	546	46	246.6	18.7 (14.0–24.9)	6.0 (3.3–10.7)
	>10%	609	10	295.4	3.4 (1.8–6.3)	1	289	4	138.5	2.9 (1.1–7.7)	0.9 (0.3–2.8)
>17 and ≤18.5[b]	≤5%	316	18	146.6	12.3 (7.7–19.5)	5.6 (2.1–15.0)	988	15	479.5	3.1 (1.9–5.2)	1
	>5 and ≤10%	170	0	82.1	0.0 (0.0–4.5)	–					
	>10%	379	5	184.1	2.7 (1.1–6.5)	1					
>18.5 and ≤20	≤5%	467	9	222.2	4.1 (2.1–7.8)	1.1 (0.4–3.2)					
	>5 and ≤10%	188	3	91.2	3.3 (1.1–10.2)	0.8 (0.2–3.5)					
	>10%	252	5	123.3	4.1 (1.7–9.7)	1	1526	38	729.5	5.2 (3.8–7.2)	1.7 (0.8–3.7)
>20	≤5%	1059	29	507.3	5.7 (4.0–8.2)	2.5 (0.7–8.5)	537	7	259.7	2.7 (1.2–5.7)	0.9 (0.3–2.5)
	>5 and ≤10%	349	4	168.5	2.4 (0.9–6.3)	1.1 (0.3–4.8)	544	8	265.2	3.0 (1.5–6.0)	1
	>10%	292	3	141.9	2.1 (0.7–6.6)	1					

ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; MRR, mortality rate ratio; PY, person-years.
[a]Severe-to-moderate malnutrition.
[b]Mild malnutrition.

Prognostic value of weight gain at 6 months

At 6 months, 2340 (95%) Cambodian and 2486 (95%) Kenyan patients were still alive and followed up. Of these, 60 in Cambodia [mortality rate: 5.4 per 100 person-years (95% CI 4.2–6.9)] and 82 in Kenya [6.8 (95% CI 5.5–8.5)] died within the following 6 months. During this period, 47 (2.0%) and 163 (6.6%) patients were also lost to follow-up in Cambodia and Kenya, respectively.

Weight gain at 6 months was predictive of mortality over the 6–12-month period. However, as previously, the prognostic value differed by BMI level at ART initiation, such that in patients with severe-to-moderate and mild malnutrition (BMI ≤18.5), a six-fold increase in mortality was observed in those with weight gain less than or equal to 5% (compared with those with weight gain >10%), whereas no increased risk was observed in patients with BMI more than 18.5 ($P = 0.14$) (Table 2). As before, testing for interaction, no significant differences were found in the prognostic value of weight gain at 6 months between sex ($P = 0.09$), between Kenya and Cambodia ($P = 0.98$), between patients who initiated ART in WHO clinical stage 4 and other patients ($P = 0.35$), between CD4 categories at ART initiation ($P = 0.41$), and between patients who initiated a NVP-based or EFV-based combination ($P = 0.65$).

In patients with severe-to-moderate and mild malnutrition at ART initiation, weight gain remained significantly associated with mortality in a multivariate model (Table 3). Other factors associated with mortality were WHO stage 4 (compared with stage 3), severe-to-moderate malnutrition (compared with mild malnutrition), and CD4 cell count at 6 months less than or equal to 100 cells/μl (compared with CD4 101–200 cells/μl).

Mortality after at least 10% weight gain

Median duration of follow-up on ART was 45 months in Cambodia and 32 months in Kenya, and 3085 (60.9%) patients experienced weight gain at least 10% on ART (1369 and 1716 in Cambodia and Kenya, respectively). Of these patients, 196 (6.4%) subsequently died.

Median delay (IQR) to reach a weight gain of at least 10% was shorter in Kenya than in Cambodia: 8.5 (3.1–41.9) vs. 14.7 (4.6–63.4) months, respectively ($P < 0.001$). This delay in weight gain increased as BMI at ART initiation increased; median delays in the four BMI categories (≤17, >17 and ≤18.5, >18.5, and ≤20, and >20) were 3.8, 6.0, 13.1, and 35.4 months, respectively ($P < 0.001$).

Of the 3085 patients on ART with weight gain at least 10% during follow-up, 548 (17.8%) subsequently lost

Table 3. Prognostic factors of mortality during 3–6 and 6–12-month periods after ART initiation, in patients with BMI≤18.5 at ART initiation.

	M3 to M6 mortality		M6 to M12 mortality	
	Adjusted MRR (95% CI)		Adjusted MRR (95% CI)	
	Full model	Reduced model	Full model	Reduced model
Weight gain[a]				
≤5%	6.5 (3.1–13.7)	6.3 (3.0–13.1)	7.6 (4.0–14.2)	7.3 (4.0 – 13.3)
>5 and ≤10%	3.4 (1.3–8.4)	3.4 (1.4–8.3)	1.1 (0.3–3.6)	1.1 (0.4 – 3.5)
>10%	1	1	1	1
Programme				
Cambodia	1		1	
Kenya	1.9 (0.9–3.7)		1.9 (0.9–4.0)	
Sex				
Men	1		1	
Women	0.7 (0.4–1.2)		0.6 (0.3–1.0)	
Age (years)[b]				
<30	1		1	
30–39	1.4 (0.8–2.5)		0.8 (0.4–1.5)	
40–49	0.8 (0.4–1.9)		0.9 (0.4–1.8)	
≥50	2.1 (0.9–5.1)		0.7 (0.2–2.2)	
WHO clinical stage[b]				
3	1	1	1	1
4	4.1 (1.9–9.0)	4.9 (2.2–10.9)	2.0 (1.1–3.8)	2.3 (1.2–4.1)
BMI (kg/m^2)[b]				
≤17[d]	2.4 (1.4–4.0)	2.4 (1.4–4.0)	2.2 (1.3–3.7)	2.1 (1.2–3.5)
>17 and ≤18.5[e]	1	1	1	1
TB diagnosed[c]				
No	1		1	
Yes	1.3 (0.7–2.3)		1.5 (0.9–2.6)	
Diarrhoea[c]				
No	1		1	
Yes	1.9 (1.0–3.5)		1.5 (0.6–3.6)	
CD4 cell count (cells/μl)[b]				
≤50	0.9 (0.4–1.9)			
51–100	1			
>100	0.4 (0.1–1.3)			
Missing	0.7 (0.3–1.8)			
CD4 cell count at M6 (cells/μl)				
≤100			2.7 (1.0–7.0)	3.0 (1.2–7.6)
101–200			1	1
>200			1.7 (0.5–5.1)	1.7 (0.6–4.7)
Missing			3.1 (1.1–8.8)	3.7 (1.5–8.8)

ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; MRR, mortality rate ratio; TB, tuberculosis; WHO, World Health Organisation. Bold: significant covariate ($P < 0.05$).
[a]Measured at M3 in the analysis of mortality between M3 and M6, and M6 in the analysis of mortality between M6 and M12.
[b]Measured at ART initiation.
[c]Between ART initiation and M3, or between M3 and M6, depending on the analysis.
[d]Severe-to-moderate malnutrition.
[e]Mild malnutrition.

weight down to or below the weight recorded at ART initiation. This delay in weight loss did not differ between the two programmes (log rank, $P = 0.43$). In univariate Cox regression, weight loss was associated with higher mortality (Table 4). After adjustment for baseline characteristics at ART start (WHO stage, CD4 count, and BMI), weight loss remained significantly associated with higher mortality [hazard ratio 6.6 (95% CI 4.7–9.3)].

Discussion

This study is of major importance for the management of HIV-infected patients under ART in developing countries as it shows that weight gain is strongly associated with survival. At 3 months, among patients with severe-to-moderate or mild malnutrition at ART initiation (43% of study population), those with weight gain of less than or equal to 5% or more than 5 and less than or equal to 10% were, respectively, six-fold and three-fold more likely to die within the next 3 months compared with those with weight gain of more than 10%. At 6 months, in patients with severe-to-moderate or mild malnutrition at ART initiation, the prognostic value of weight gain was still high (MRR of 8), but only for those not achieving at least 5% weight gain.

Because greater weight gain can be expected at 6 months than at 3 months of ART, it seems paradoxical that weight gain of more than 5 and less than or equal to 10% would be considered sufficient at 6 months but not at 3 months.

Table 4. Prognostic factors of mortality after weight gain ≥10% under ART (*N* = 3085).

	Crude HR (95% CI)	Adjusted HR (95% CI)
Programme		
Cambodia	1	
Kenya	1.1 (0.8–1.6)	
Sex		
Men	1	1
Women	0.6 (0.5–0.9)	0.6 (0.4–0.8)
Age at ART initiation (years)		
<30	1	
30–39	1.2 (0.8–1.8)	
40–49	1.0 (0.6–1.6)	
≥50	1.3 (0.7–2.5)	
WHO clinical stage at ART initiation		
1–2	0.4 (0.1–2.8)	0.4 (0.1–3.1)
3	1	1
4	2.9 (2.0–4.2)	2.3 (1.6–3.4)
Delay to weight gain ≥10% (months)		
≤6	1	
>6	0.8 (0.3–0.7)	
BMI at ART initiation[a] (kg/m^2)		
≤17[c]	3.3 (2.0–5.4)	
>17 and ≤18.5[d]	2.1 (1.3–3.6)	
>18.5 and ≤20	1.9 (1.1–3.4)	
>20	1	
Missing	1.3 (0.5–3.3)	
BMI at weight gain ≥10%[b] (kg/m^2)		
≤17	3.9 (2.6–5.7)	2.3 (1.5–3.5)
>17 and ≤18.5	1.4 (0.8–2.3)	1.0 (0.6–1.6)
>18.5 and ≤20	1.9 (1.2–2.8)	1.4 (0.9–2.1)
>20	1	1
Missing	1.0 (0.4–2.3)	0.8 (0.4–1.9)
CD4 cell count at ART initiation[a] (cells/μl)		
≤50	1.4 (0.9–2.4)	
51–100	1	
>100	0.6 (0.3–1.2)	
Missing	1.8 (1.0–3.0)	
CD4 cell count at weight gain ≥10%[b] (cells/μl)		
≤100	1	
101–200	0.3 (0.2–0.6)	
>200	0.3 (0.1–0.5)	
Missing	0.6 (0.4–1.0)	
Weight loss to ≤weight at ART initiation		
No	1	1
Yes	6.0 (4.3–8.5)	6.6 (4.7–9.3)

ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HR, hazard ratio; WHO, World Health Organisation.
[a]Measured within −1 month/+15 days around ART initiation.
[b]Measured within the month preceding a weight gain >10%.
[c]Severe-to-moderate malnutrition.
[d]Mild malnutrition.

However, the high mortality rate observed between 3 and 6 months makes the interpretation of the 'survivor' cohort data at 6 months more complex. Needless to say, the sooner excess mortality can be predicted, the sooner patient management can be improved, giving more relevance to the predictive value of weight gain at 3 months compared with 6 months.

The strength of this study lies in the use of data from two large (>5000 patients overall) and well characterized cohorts treated with ART in two different developing countries and with long follow-up (median >2.5 years). The magnitudes of the effects documented here were important and thus worth considering. The increase in risk of dying was six-fold when comparing patients with less than or equal to 5% to those with more than 10% weight gain at 3 months. CD4 cell count at ART initiation was no longer predictive of mortality between 3 and 6 months once weight gain at 3 months was taken into account; this is an interesting finding since in resource-limited settings, CD4 testing may not always be available.

An attractive feature of weight gain as a monitoring tool was its 'universality'. Its prognostic value on mortality was not statistically different across programme, sex, WHO clinical stage at ART initiation, CD4 level at ART initiation, and type of ART (NVP-based vs. EFV-based) provided that the initial BMI was taken into account. Clinicians and healthcare workers need simple clinical predictors that can be applied equally to large proportions of patients.

Although our findings are relevant for patients with low initial BMI, the number of patients concerned was not negligible (40% or more of the patients in both programmes). Additional studies in other countries are required to confirm that these findings can be generalized to other settings.

With ART becoming more widely available, it is hoped that patients initiate ART at an earlier stage of infection thus improving their prognosis and making weight monitoring less useful.

The use of weight gain as a monitoring tool for the management of HIV-infected patients is particularly relevant in resource-limited countries because of its simplicity and low cost. One may object that weight is subject to measurement error. However, our analysis was retrospective and based on routine measurements performed in field conditions, in which weight measurements may not be optimal, as may occur in study conditions. If anything, the predictive value of weight on mortality would have been improved had measurements been free of errors, since measurement errors were most likely nondifferential with regard to future mortality. Moreover, sensitivity analyses with average measurements performed over several visits gave results identical to those initially obtained.

Weight gain can be of great use in resource-limited settings, especially when decentralization of HIV care is required and access to well trained physicians is limited, for instance, under a scheme in which the ART initiation visit would be performed by a physician and subsequent visits by nurses. We chose to examine weight gains at 3 and 6 months, because we speculated these would be strategic time points at which patients could be referred to a higher level of care in case of suboptimal response to treatment.

Patients with insufficient weight gain at 3 and 6 months should undergo extensive clinical and laboratory assessments, as it could be explained by an underlying opportunistic infection. In these patients, testing in priority for tuberculosis (TB) could be implemented. Indeed, the experience from MSF in five countries showed a high incidence of TB under ART [28], and TB remains a leading causes of death in resource-limited settings [29,30]. Lack of adherence, which is believed to be the key element to acquisition of antiretroviral drug resistance [10], could also explain the poor weight gains observed. In patients with poor weight gain at 3 months, adherence should be assessed and patients with suboptimal adherence undergo counselling to improve it. Simple methods like pill counts have been identified as easy and reliable to assess adherence [31]. In resource-limited settings, in which the number of drugs available is limited, maximizing the duration of existing lines of treatment, and identifying and addressing the reasons for poor weight gain, are essential.

Studies are required to better characterize factors associated with poor weight gain, that is lack of adherence to treatment, opportunistic infections, or poor nutritional intake. Randomized trials are also needed to estimate the benefit in terms of survival associated with nutritional supplements.

World Health Organisation recommends looking at weight gain of at least 10% at 6 months to evaluate ART programmes [19]. Evaluating weight gain at 6 months is of interest, but our results, pertaining to individual and not programmatic evaluation of care, identified the 3-month time point as more critical for patient evaluation. In developing countries, where mortality within the first year of ART is high, early detection of patients with suboptimal ART response is crucial.

The prognostic value of weight gain on mortality was not restricted to the first 6 months of follow-up. Continuing weight monitoring beyond 6 months was informative. We showed that more than 60% of patients achieved a weight gain of at least 10% under ART, but some subsequently experienced a decrease in weight equal to or below their weight at ART initiation. This weight loss was associated with an increased risk of death, even after adjustment for BMI level at ART initiation.

Our results should not be interpreted as advocacy for minimal care and monitoring of patients taking ART in developing countries. CD4 cell count and viral load remain the gold standards for patient monitoring, and everything should be done to make these tests available in resource-limited settings. However, until they are broadly available, simple monitoring tools such as weight measurement can be of great help and should not be neglected since they provide meaningful patient information to healthcare providers.

Acknowledgements

The authors would like to thank the Ministry of Health of Cambodia and Kenya, the personnel of the Preah Bath Norodom Sihanouk hospital of Phnom Penh (Cambodia), and the district hospital of Homa Bay (Kenya), the MSF field teams, and the patients, for providing the data for this analysis. Thanks are also extended to Oliver Yun for his editorial support on the manuscript.

Contributors: Y.M. performed the analysis and drafted the manuscript; A.F. took overall responsibility for the project and assisted in the analysis and drafting of the manuscript; C.G. and L.F. were responsible for clinical care of patients at the study centres and data collection; E.S., S.B., and M.P. assisted in interpreting the results; all authors reviewed, edited and approved the manuscript.

References

1. UNAIDS. 2007: AIDS epidemic updates. http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007/default.asp.
2. World Health Organisation. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach; 2003 revision. Available at http://www.who.int/3by5/publications/documents/arv_guidelines/en/index.html.
3. Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, Mankhambo L, *et al*. **Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment.** *Lancet* 2006; **367**:1335–1342.
4. Stringer JS, Zulu I, Levy J, Stringer EM, Mwango A, Chi BH, *et al*. **Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes.** *JAMA* 2006; **296**:782–793.
5. Ferradini L, Laureillard D, Prak N, Ngeth C, Fernandez M, Pinoges L, *et al*. **Positive outcomes of HAART at 24 months in HIV-infected patients in Cambodia.** *AIDS* 2007; **21**:2293–2301.
6. Spacek LA, Shihab HM, Kamya MR, Mwesigire D, Ronald A, Mayanja H, *et al*. **Response to antiretroviral therapy in HIV-infected patients attending a public, urban clinic in Kampala, Uganda.** *Clin Infect Dis* 2006; **42**:252–259.
7. Madec Y, Laureillard D, Pinoges L, Fernandez M, Prak N, Ngeth C, *et al*. **Response to highly active antiretroviral therapy among severely immuno-compromised HIV-infected patients in Cambodia.** *AIDS* 2007; **21**:351–359.
8. Ivers LC, Kendrick D, Doucette K. **Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature.** *Clin Infect Dis* 2005; **41**:217–224.
9. Severe P, Leger P, Charles M, Noel F, Bonhomme G, Bois G, *et al*. **Antiretroviral therapy in a thousand patients with AIDS in Haiti.** *N Engl J Med* 2005; **353**:2325–2334.
10. Harries AD, Schouten EJ, Libamba E. **Scaling up antiretroviral treatment in resource-poor settings.** *Lancet* 2006; **367**:1870–1872.
11. Van Damme W, Kober K, Laga M. **The real challenges for scaling up ART in sub-Saharan Africa.** *AIDS* 2006; **20**:653–656.
12. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, *et al*. **The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings.** *Lancet* 2006; **368**:505–510.
13. Bagchi S, Kempf MC, Westfall AO, Maherya A, Willig J, Saag MS. **Can routine clinical markers be used longitudinally to monitor antiretroviral therapy success in resource-limited settings?** *Clin Infect Dis* 2007; **44**:135–138.

14. Calmy A, Ford N, Hirschel B, Reynolds SJ, Lynen L, Goemaere E, *et al*. **HIV viral load monitoring in resource-limited regions: optional or necessary?** *Clin Infect Dis* 2007; **44**:128–134.
15. Erikstrup C, Kallestrup P, Zinyama R, Gomo E, Mudenge B, Gerstoft J, Ullium H. **Predictors of mortality in a cohort of HIV-1-infected adults in rural Africa.** *J Acquir Immune Defic Syndr* 2007; **44**:478–483.
16. Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, Regensberg L, *et al*. **Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy.** *PLoS Med* 2008; **5**:e109.
17. Malvy E, Thiebaut R, Marimoutou C, Dabis F. **Weight loss and body mass index as predictors of HIV disease progression to AIDS in adults. Aquitaine cohort, France, 1985–1997.** *J Am Coll Nutr* 2001; **20**:609–615.
18. Paton NI, Sangeetha S, Earnest A, Bellamy R. **The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy.** *HIV Med* 2006; **7**:323–330.
19. World Health Organisation. Working Document on Monitoring and Evaluating of National ART Programmes in the Rapid Scale-up to 3 by 5. http://www.who.int/3by5/publications/documents/artindicators/en/index.html.
20. Silva M, Skolnik PR, Gorbach SL, Spiegelman D, Wilson IB, Fernandez-DiFranco MG, Knox TA. **The effect of protease inhibitors on weight and body composition in HIV-infected patients.** *AIDS* 1998; **12**:1645–1651.
21. Shikuma CM, Zackin R, Sattler F, Mildvan D, Nyangweso P, Alston B, *et al*. **Changes in weight and lean body mass during highly active antiretroviral therapy.** *Clin Infect Dis* 2004; **39**:1223–1230.
22. Tang AM, Forrester J, Spiegelman D, Knox TA, Tchetgen E, Gorbach SL. **Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2002; **31**:230–236.
23. Jerene D, Endale A, Hailu Y, Lindtjorn B. **Predictors of early death in a cohort of Ethiopian patients treated with HAART.** *BMC Infect Dis* 2006; **6**:136.
24. Saghayam S, Kumarasamy N, Cecelia AJ, Solomon S, Mayer K, Wanke C. **Weight and body shape changes in a treatment-naive population after 6 months of nevirapine-based generic highly active antiretroviral therapy in South India.** *Clin Infect Dis* 2007; **44**:295–300.
25. World Health Organisation. Global database on body mass index. Available at http://www.who.int/bmi/index.jsp?introPage=intro_3.htm.
26. Shetty PS, James WP. **Body mass index. A measure of chronic energy deficiency in adults.** *FAO Food Nutr Pap* 1994; **56**:1–57.
27. Diggle P, Liang K, Zeger S. **Fitting smooth curves to longitudinal data.** In: Atkinson ACCJC, Pierce DA, Schervish MJ, Titterington DM, editors. *Analysing longitudinal data*. Oxford: Oxford University Press; 1994. pp. 41–47.
28. Bonnet MM, Pinoges LL, Varaine FF, Oberhauser BB, O'Brien DD, Kebede YY, *et al*. **Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden.** *AIDS* 2006; **20**:1275–1279.
29. Etard JF, Ndiaye I, Thierry-Mieg M, Gueye NF, Gueye PM, Laniece I, *et al*. **Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study.** *AIDS* 2006; **20**:1181–1189.
30. Bonard D, Messou E, Seyler C, Vincent V, Gabillard D, Anglaret X. **High incidence of atypical mycobacteriosis in African HIV-infected adults with low CD4 cell counts: a 6-year cohort study in Cote d'Ivoire.** *AIDS* 2004; **18**:1961–1964.
31. San Lio MM, Carbini R, Germano P, Guidotti G, Mancinelli S, Magid NA, *et al*. **Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique.** *Clin Infect Dis* 2008; **46**:1609–1616.