Determinants of Weight Evolution Among HIV-Positive Patients Initiating Antiretroviral Treatment in Low-Resource Settings

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Background: In resource-limited settings, clinical parameters, including body weight changes, are used to monitor clinical response. Therefore, we studied body weight changes in patients on antiretroviral treatment (ART) in different regions of the world.

Methods: Data were extracted from the "International Epidemiologic Databases to Evaluate AIDS," a network of ART programmes that prospectively collects routine clinical data. Adults on ART from the Southern, East, West, and Central African and the Asia-Pacific regions were selected from the database if baseline data on body weight, gender, ART regimen, and CD4 count were available. Body weight change over the first 2 years and the probability of body weight loss in the second year were modeled using linear mixed models and logistic regression, respectively.

Results: Data from 205,571 patients were analyzed. Mean adjusted body weight change in the first 12 months was higher in patients started on tenofovir and/or efavirenz; in patients from Central, West, and East Africa, in men, and in patients with a poorer clinical status. In the second year of ART, it was greater in patients initiated on tenofovir and/or nevirapine, and for patients not on stavudine, in women, in Southern Africa and in patients with a better clinical status at initiation. Stavudine in the initial regimen was associated with a lower mean adjusted body weight change and with weight loss in the second treatment year.

Conclusions: Different ART regimens have different effects on body weight change. Body weight loss after 1 year of treatment in patients on stavudine might be associated with lipoatrophy.

Key Words: HIV, body weight determinants, ART, low-resource settings

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INTRODUCTION

Monitoring HIV-positive patients on antiretroviral treatment (ART) remains a challenge in countries with limited resources. In many of them, routine viral load and even CD4 lymphocyte count monitoring is not possible or available.[1] Therefore, in these settings, clinical parameters, including body weight changes, are used to monitor clinical response.[2]

Significant body weight loss before the start of ART is usually associated with advancing HIV disease and the presence of opportunistic infections (in low-resource countries mainly tuberculosis).[3] Short-term weight evolution is an indicator of treatment success. Indeed, weight gain at 3 months was found to be strongly associated with survival[4] and weight loss as early as 1–6 months after ART initiation has been associated with a high risk of adverse outcomes.[5–7] Previous studies mainly focused on early periods during ART (generally less than 12 months).

The objective of our study was to describe body weight changes and associations with those changes across regions of the world among patients receiving up to 2 years of ART.

METHODS

Data were extracted from the "International Epidemiologic Databases to Evaluate AIDS," a large network of ART programmes that prospectively collects routine clinical data (IeDEA) (http://www.iedea.org/). Its aim is to collect baseline and follow-up characteristics on HIV-positive patients initiating ART worldwide.[8] These characteristics include demographic (age, gender, geographical region), clinical (weight, height, pregnancies, morbidity, medication), and biological (CD4 count, viral load) data. Adult patients (aged >18 years) on ART from the Southern, East, West, and Central African regions and the Asia-Pacific region were selected from the database if baseline data (within a 60-day window before start of ART) on body weight, gender, ART regimen, and CD4 count were available. Data for the study were collected from 140 sites, including 18 from Asia-Pacific, 10 from Central-Africa, 10 from East-Africa, 87 from Southern Africa, and 15 from West Africa. HIV-positive patients were included in this analysis if at ART initiation they were ART naive and starting first-line ART containing at least 3 different antiretroviral drugs. Pregnant women and patients on investigational study drugs or on implausible regimens [regimens containing the following combinations: zidovudine (AZT) and stavudine (D4T), AZT and tenofovir (TDF), D4T and TDF, and efavirenz (EFV) and nevirapine (NVP)] were excluded. All patients who had at least 1 baseline weight measure were included. Body weight change at time t is defined as body weight at time t minus body weight at ART initiation.

Statistical Analysis

The body mass index (BMI) was computed when body weight and height were both available; its 24-month evolution was graphically represented by region. As a significant proportion of patients had missing height, the main analytical models were based on body weight instead of BMI to avoid a selection bias. Individuals with complete and incomplete BMI data were compared.

Model 1

Body weight change was modeled over the first 2 years on ART using linear mixed models (LMMs) with no intercept and 2 slopes; the first slope over the first year of ART and the second slope over the second. To account for intraindividual correlation, we added random effects on the 2 slopes with an unstructured variance–covariance matrix. The LMMs were adjusted for geographical region, gender, age, initial body weight, initial clinical stage, first ART regimen, initial hemoglobin, calendar year of ART initiation, and initial CD4 count. The first body weight change slope was also adjusted for CD4 count changes between month 0 and month 12 and the second slope was adjusted for CD4 count change between 12 and 24 months. Moreover, we let the association between D4T and body weight change in the second year of ART to interact with baseline body weight, region, gender, age at ART initiation, and baseline CD4 count.

Model 2

This model studied risk factors for any weight loss larger than 5% in the second year of ART by fitting a multiple logistic model with weight loss larger than 5% during the second year as a binary outcome variable. Not all patients had a weight measurement exactly at 1 year and 2 years after start of ART treatment. Hence, we estimated the weight after the first year as the mean weight between 6 and 18 months and the weight after the second year as the mean weight between 18 and 30 months.

To account for missing data, missing CD4 counts were imputed using CD4 counts estimated with a predictive LMM, adjusted for geographical region, gender, age, initial body weight, clinical stage, ART, and initial hemoglobin.

RESULTS

Baseline Characteristics

Data from 212,795 patients were received from the IeDEA regions. Reasons for exclusion of 7224 (3.4%) patients were age under 18 years (n = 581) and implausible regimen (n = 6643) leaving 205,571 patients for analysis [139,174 (67.7%) from Southern Africa, 42,856 (20.8%) from East Africa, 17,202 (8.4%) from West Africa, 4700 (2.3%) from Central Africa, and 1639 (0.8%) from Asia Pacific] (see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/A690 for number of patients per country). Patient characteristics at ART initiation by geographical region are described in Table 1. Of the 205,571 patients included in the analysis of the first year of ART in 58,835 (28.6%) of them, only a weight measurement at baseline was available. In the remaining patients, the median number of weight measurements was 3 [interquartile range (IQR), 2–4]. In the second year of ART, 104,744 patients had at least 1 weight measurement. The median number of weight measurements was 3 (IQR, 2–5). Patients initiated ART between the years 2001 and 2010. The median (IQR) body weight at ART initiation was 55 kg (48–62), 58 kg (52–65) at 6

TABLE 1. Patient Characteristics at ART Initiation By Geographical Region (n = 205,571)

	Asia Pacific	Central Africa	East Africa	Southern Africa	West Africa	Total
N (%)	1639 (0.8)	4700 (2.3)	42,856 (20.8)	139,174 (67.7)	17,202 (8.4)	205,571 (100)
Year of enrollment, range	1994–2010	1998–2010	2001–2009	1997–2010	1998–2009	1994–2010
Female (%)	588 (35.9)	3297 (70.1)	27,106 (63.2)	84,078 (60.4)	11,075 (64.4)	126,144 (61.4)
Age, median (IQR), yrs	34 (29–40)	38 (31–44)	37 (31–43)	35 (30–42)	36 (30–43)	35 (30–42)
Clinical stage (%)						
WHO* I/II or CDC† ≥A	623 (38.0)	1413 (30.1)	13,263 (30.9)	45,194 (32.5)	6229 (36.2)	66,722 (32.5)
WHO III or CDC B	455 (27.8)	2615 (55.6)	18,383 (42.9)	68,408 (49.2)	7165 (41.7)	97,026 (47.2)
WHO IV or AIDS	561 (34.2)	652 (13.9)	6442 (15.0)	12,144 (8.7)	1795 (10.4)	21,594 (10.5)
Missing	—	20 (0.4)	4768 (11.1)	13,428 (9.6)	2013 (11.7)	20,229 (9.8)
Year of ART initiation (%)						
<2005	655 (40.0)	463 (9.9)	3070 (7.2)	7063 (5.1)	2741 (15.9)	13,992 (6.8)
2005–2006	567 (34.6)	870 (18.5)	19,321 (45.1)	35,178 (25.3)	8026 (46.7)	63,962 (31.1)
2007–2008	302 (18.4)	2094 (44.6)	20,085 (46.9)	53,071 (38.1)	6219 (36.2)	81,771 (39.8)
2009–2010	115 (7.0)	1273 (27.1)	380 (7.2)	43,862 (31.5)	216 (1.3)	45,846 (22.3)
First ART regimen, NRTI‡ (%)						
AZT-based	598 (36.5)	1857 (39.5)	9688 (22.6)	28,177 (20.2)	5751 (33.4)	46,071 (22.4)
D4T-based	953 (58.1)	2752 (58.6)	32,928 (76.8)	64,265 (46.2)	9320 (54.2)	110,218 (53.6)
Tenofovir-based	56 (3.4)	66 (1.4)	225 (0.5)	43,515 (31.3)	1872 (10.9)	45,734 (22.2)
Other NRTIs§	32 (2.0)	25 (0.5)	15 (0.0)	3217 (2.3)	259 (1.5)	3548 (1.7)
First ART# regimen, NNRTI‖ or PI (%)						
Efavirenz-based	487 (29.7)	715 (15.2)	8035 (18.7)	56,287 (40.4)	5514 (32.1)	71,038 (34.6)
Nevirapine-based	998 (60.9)	3933 (83.7)	34,724 (81.0)	82,314 (59.1)	10,119 (58.8)	132,088 (64.3)
PI#	154 (9.4)	52 (1.1)	97 (0.2)	573 (0.4)	1569 (9.1)	2445 (1.2)
CD4 count in cells/μL median (IQR)	95 (33–188)	135 (65–204)	102 (40–175)	134 (67–202)	139 (60–223)	128 (61–199)
CD4 count missing (%)	341 (20.8)	1316 (28.0)	16,212 (37.8)	33,497 (24.1)	4312 (25.1)	55,678 (27.1)
Hemoglobin in g/dL median (IQR¶)	12.1 (10.9–13.5)	10.2 (9.0–12.0)	11.2 (9.6–12.8)	10.9 (9.4–12.4)	10.2 (9.0–11.5)	10.9 (9.4–12.4)
Hemoglobin missing (%)	1314 (80.2)	3966 (84.4)	23,957 (55.9)	39,770 (28.6)	6203 (36.1)	75,310 (36.6)
Body weight in kg, median (IQR)						
At ART initiation	54 (47–61)	56 (49–64)	54 (48–61)	55 (48–62)	56 (49–64)	55 (48–62)
At 6 mo	56 (50–65)	59 (53–68)	59 (53–65)	58 (52–65)	60 (53–68)	58 (52–65)
At 12 mo	57 (51–65)	61 (54–70)	60 (54–67)	59 (53–67)	62 (55–70)	60 (53–67)
At 24 mo	57 (50–64)	62 (54–71)	60 (54–67)	60 (54–68)	62 (55–71)	60 (54–68)
BMI in kg/m^2, median (IQR)						
At ART initiation	20.1 (18.1–22.5)	20.6 (18.2–23.5)	19.7 (17.6–21.9)	20.0 (17.9–22.5)	20.6 (18.2–23.4)	20.0 (17.9–22.5)
At 6 mo	21.3 (19.5–23.7)	22.0 (19.8–24.7)	21.2 (19.4–23.5)	21.4 (19.5–23.9)	22.1 (20.0–24.9)	21.4 (19.5–23.9)
At 12 mo	21.7 (19.8–23.8)	22.6 (20.3–25.7)	21.7 (19.7–24.1)	21.9 (19.8–24.6)	22.8 (20.4–25.6)	21.9 (19.9–24.6)
At 24 mo	21.6 (19.8–23.7)	23.0 (20.3–26.2)	21.7 (19.7–24.1)	22.1 (19.9–24.9)	23.0 (20.5–26.0)	22.1 (19.9–24.8)

International Epidemiologic Databases to Evaluate AIDS (IeDEA).
*WHO, World Health Organization.
†CDC, Centers for Disease Control.
‡NRTI, nucleoside/nucleotide reverse transcriptase inhibitor.
§Other NRTIs: didanosine, lamivudine, abacavir, and emtricitabine.
‖NNRTI, nonnucleoside reverse transciptase inhibitor.
¶IQR, interquartile range.
#PI, protease inhibitor.

months, 60 kg (53–67) at 12 months, and 60 kg (54–68) at 24 months on ART (Table 1).

In all African regions, in contrast to the Asia-Pacific region, more women than men were enrolled in the cohorts (Table 1). The median CD4 lymphocyte count at ART initiation was 128 cells per microliter (IQR, 61–199) and the median CD4 lymphocyte count was below 150 cells per microliter in all cohorts. Most patients (57.7%) were in WHO stage III or IV. Over half of regimens contained D4T (n = 110,218, 53.6%) and roughly two-thirds contained NVP (n = 132,088, 64.3%). Only in Southern Africa, a relatively large proportion of patients (n = 43,515, 31.3%) were started on a TDF-containing regimen (Table 1).

BMI Evolution in Different Regions

BMI was computed for 165,804 individuals at baseline (80.7% of the sample), 89,762 at M6 (43.7%), 70,285 at M12 (34.2%), 56,350 at M18 (27.4%), and 44,598 at M24 (21.7%). Individuals with complete and incomplete BMI data were comparable at baseline (see Table S2, Supplemental Digital Content, http://links.lww.com/QAI/A690).

BMI evolution within the first 2 years of ART per region is shown in Figure 1. For all regions, median BMI increased in the first 12 months after ART initiation, after which it leveled off. Obesity (BMI >30 kg/m^2) was present in 4402 patients (2.6%) at baseline and in 2644 (5.9%) after 2 years on ART. Of those patients with a BMI >30 kg/m^2 after 2 years on ART, the BMI at baseline was ≤18 in 40 (1.5%), between 18 and 25 in 705 (26.7%), between 25 and 30 in 1016 (38.4%), and >30 kg/m^2 in 883 (33.4%).

Body Weight Change After ART Initiation

Adjusted body weight change slopes (kilograms per year) for all patients from 0 to 12 months and from 12 to 24 months after ART initiation (model 1) are shown in Table 2, taking as a reference in both analyses men aged <30 years who started ART in Southern Africa with TDF and EFV in 2009 or later, with an initial clinical stage WHO IV (or AIDS), with a baseline CD4 count <50 cells per microliter, a CD4 cell count change between 0 and 149 at month 12 and between 0 and 49 at month 24, hemoglobinemia <7.5 g/dL, and with an initial body weight of 55 kg.

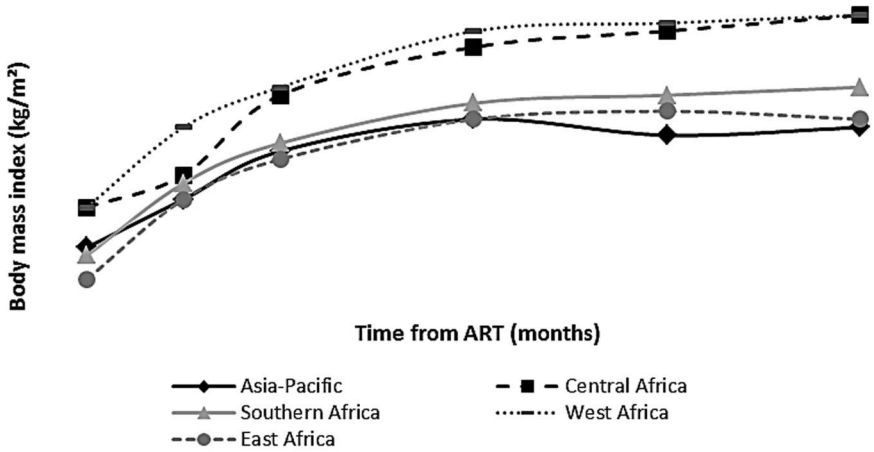
Gender

In the first year after ART initiation, the mean adjusted body weight change was greater in men than in women [−0.29, 95% confidence interval (CI): −0.38 to −0.20] but in the second year, it was greater in women (1.22, 95% CI: 1.09 to 1.35).

ART Regimen

Patients initiating TDF-containing regimens had a higher mean adjusted body weight change in the first 2 years compared with patients who started on a regimen containing AZT or other nucleoside/nucleotide reverse transcriptase inhibitors. Patients started on a D4T-containing regimen had a significant lower mean adjusted body weight change in the first year on ART (−0.16, 95% CI: −0.29 to −0.02). In the second year on ART, there was no significant difference in mean adjusted body weight change between patients on D4T and TDF. However, the effect on mean adjusted body weight change in the second year of D4T in initial ART regimen (Table 3) was more negative for patients from Eastern Africa (−0.77 kg/yr, 95% CI: −1.04 to −0.50), women (−1.13 kg/yr, 95% CI: −1.29 to −0.96), elder patients (aged above 39 years) (−1.16 kg/yr, 95% CI: −1.38 to −0.94), and patients with a higher baseline body weight (−0.34 kg/yr, 95% CI: −0.38 to −0.30, for every 5 kg more) and a CD4 cell count below 50 cells per microliter at baseline (compared with a baseline CD4 count above 199 cells/μL) (Table 3).

Patients who started EFV had a higher mean adjusted body weight change in the first year than patients starting NVP (−0.69, 95% CI: −0.78 to −0.59) or a protease inhibitor (PI) (−1.41, 95% CI: −1.79 to −1.03) but patients on a PI-based ART regimen had a higher median baseline body weight: 57 kg (IQR, 49.6–66) versus 55 kg (IQR, 48–62, $P = 0.0000$) compared with patients on a nonnucleoside reverse transciptase inhibitor (NNRTI) regimen. There was no



Time from ART	M0	M6	M12	M18	M24
Asia-Pacific (N)	1,434	1,056	925	892	839
Central Africa (N)	4,602	1,086	964	913	782
East Africa (N)	29,603	20,788	16,166	12,301	8,761
Southern Africa (N)	117,385	59,317	46,186	37,363	30,326
West Africa (N)	12,780	7,515	6,044	4,881	3,890
Total (N)	165,804	89,762	70,285	56,350	44,598

FIGURE 1. Evolution of BMI within the first 2 years of ART per region in the study population (n = 165,804). International Epidemiologic databases to Evaluate AIDS (IeDEA).

TABLE 2. Body Weight Change Slopes Within the First 24 Months After ART Initiation Modeled With the Adjusted LMM: Main Effects (n = 205,571; Observations = 1,785,439)

	From Month 0–12		From Month 12–24	
	Body Weight Change, kg/yr	95% CI	Body Weight Change, kg/yr	95% CI
Body weight change in reference group*	9.12	8.81 to 9.42	−0.08	−0.50 to 0.34
Gender (versus ref*)				
Men	Ref*	—	Ref*	—
Women	−0.29	−0.38 to −0.20	1.22	1.09 to 1.35
NRTI† in first ART regimen (versus ref*)				
Tenofovir (TDF)	Ref*	—	Ref*	—
Tavudine (D4T)	−0.16	−0.29 to −0.02	0.01	−0.30 to 0.32
Zidovudine (AZT)	−0.29	−0.43 to −0.15	−0.45	−0.61 to −0.28
Other NRTIs‡	−0.35	−0.70 to −0.004	−0.59	−1.09 to −0.09
NNRTI§ or PI‖ in first ART regimen (versus ref*)				
Efavirenz (EFV)	Ref*	—	Ref*	—
Nevirapine (NVP)	−0.69	−0.78 to −0.59	0.34	0.23 to 0.44
PIs	−1.41	−1.79 to −1.03	−0.25	−0.62 to 0.12
Geographical region (versus ref*)				
Southern Africa	Ref*	—	Ref*	—
Asia-Pacific	−0.41	−0.81 to −0.01	−0.68	−1.23 to −0.12
Central Africa	1.85	1.54 to 2.16	−0.63	−1.19 to −0.07
East Africa	0.46	0.35 to 0.56	−0.28	−0.53 to −0.03
West Africa	1.56	1.40 to 1.71	−0.08	−0.30 to 0.15
Year of ART initiation (versus ref*)				
2009–2010	Ref*	—	Ref*	—
2007–2008	0.56	0.43 to 0.69	−1.46	−1.72 to −1.21
2005–2006	1.45	1.31 to 1.60	−1.43	−1.70 to −1.16
ART <2005	1.56	1.36 to 1.75	−0.93	−1.22 to −0.64
Age at ART initiation (versus ref*), yrs				
18–29	Ref*	—	Ref*	—
30–34	0.41	0.30 to 0.53	0.15	−0.03 to 0.33
35–39	0.64	0.52 to 0.76	0.28	0.09 to 0.47
>39	0.68	0.57 to 0.79	0.27	0.09 to 0.45
Baseline body weight (per 5 kg) (versus ref*)				
55 kg	Ref*	—	—	—
For each 5 kg higher	−0.90	−0.92 to −0.88	0.29	0.26 to 0.32
Initial clinical stage (versus ref*)				
AIDS or WHO IV	Ref*	—	Ref*	—
CDC B or WHO III	−0.30	−0.43 to −0.16	0.003	−0.14 to 0.14
CDC A or WHO I/II	−2.26	−2.41 to −2.12	0.40	0.26 to 0.55
Clinical stage missing	−0.49	−0.68 to −0.30	0.08	−0.12 to 0.28
Baseline CD4 count in cells/μL (versus ref*)				
0–49	Ref*	—	Ref*	—
50–199	−2.04	−2.15 to −1.92	0.08	−0.11 to 0.28
>199	−3.56	−3.70 to −3.42	0.24	0.02 to 0.45
CD4 count change between M0 and M12 in cells/μL (versus ref*)				
<0	−0.92	−1.09 to −0.75	—	—
0–149	Ref*	—	—	—
150–249	0.56	0.47 to 0.65	—	—
>249	1.43	1.33 to 1.54	—	—

TABLE 2. (*Continued*) Body Weight Change Slopes Within the First 24 Months After ART Initiation Modeled With the Adjusted LMM: Main Effects (n = 205,571; Observations = 1,785,439)

	From Month 0–12		From Month 12–24	
	Body Weight Change, kg/yr	95% CI	Body Weight Change, kg/yr	95% CI
CD4 count change between M12 and M24 in cells/μL (versus ref*)				
<0	—	—	−0.16	−0.27 to −0.04
0–49	—	—	Ref*	—
50–99	—	—	−0.06	−0.17 to 0.05
>99	—	—	0.44	0.33 to 0.55
Baseline hemoglobin in g/dL (versus ref*)				
<7.5	Ref*	—	Ref*	—
7.5–10	−0.84	−1.08 to −0.60	0.28	0.04 to 0.52
≥10	−2.17	−2.41 to −1.94	0.33	0.10 to 0.56
Missing	−2.36	−2.60 to −2.13	0.32	0.08 to 0.56

*Reference group: men aged <30 years who started ART in Southern Africa with tenofovir and efavirenz in 2009 or later, with an initial clinical stage WHO IV (or AIDS), with a baseline CD4 count <50 cells per microliter, a CD4 count change = 0–149 at M12 and 0–49 at M24, hemoglobinemia <7.5 g/dL and with an initial body weight = 55 kg.
†NRTI, nucleoside/nucleotide reverse transcriptase inhibitor.
‡Other NRTIs: didanosine, lamivudine, abacavir, and emtricitabine.
§NNRTI, nonnucleoside reverse transciptase inhibitor.
||PI, protease inhibitor.

significant difference in CD4 cell count at baseline between patients started on a PI compared with an NNRTI regimen (117 versus 128 cells/μL, $P = 0.3502$).

In the second year, patients initiated on NVP had a greater mean adjusted body weight change than patients started on EFV (0.34, 95% CI: 0.23 to 0.44) (Table 2).

Geographical Regions

In the first year, mean adjusted body weight change was 1.85 (95% CI: 1.54 to 2.16), 1.56 (95% CI: 1.40 to 1.71), and 0.46 kg/yr (95% CI: 0.35 to 0.56) higher in patients from the Central, West, and East African regions, respectively, and 0.41 kg/yr (95% CI: −0.81 to −0.01) lower in the Asia-Pacific region compared with the Southern African region. In the second year, mean adjusted body weight change was lower in patients from the Central African (−0.63, 95% CI: −1.19 to −0.07), East African (−0.28, 95% CI: −0.53 to −0.03), and Asia-Pacific (−0.68, 95% CI: −1.23 to −0.12) regions compared with the Southern African region.

Clinical and Biological Status

The mean adjusted body weight change in the first year was higher in patients with a poorer clinical status, reflected by higher WHO stage [WHO stage I/II: −2.26 (95% CI: 2.12 to 2.41) compared with WHO stage IV], lower baseline CD4 lymphocyte count [baseline CD4 cell count larger than 199: −3.56 (95% CI: 3.42 to 3.70) compared with baseline CD4 cell count 0–49 cells/μL], lower hemoglobin level [baseline hemoglobin ≥10 g/dL: −2.17 (95% CI: 1.94 to 2.41) compared with a hemoglobin <7.5 g/dL] and lower initial body weight [for every 5 kg higher −0.90 (95% CI: −0.92 to −0.88)]. Furthermore, mean adjusted body weight change in the first year was higher in patients with a CD4 lymphocyte count change of more than 249 cells per microliter [1.43 (95% CI: 1.33 to 1.54)] compared with patients with a CD4 cell count change between 0 and 149 cells per microliter. Contrary to the first year, the mean adjusted body weight change in patients with a poorer clinical state (lower CD4 count, higher WHO stage and lower adjusted body weight) at baseline was lower than in patients with the better clinical state at baseline, but patients with the highest CD4 cell count change (>99 cells/μL) between 12 and 24 months of treatment still had the highest mean adjusted body weight change (0.44, 95% CI: 0.33 to 0.55, compared with 0–49 cells/μL CD4 cell count change).

Weight Loss in the Second Year of Treatment

In both the 130,427 patients in the 6–18-month period as in the 84,394 patients in the 18–30-month period with at least 1 weight measurement, the median number of weight measurements was 3 (IQR, 2–5). Between 12 and 24 months of ART treatment, 45.8% of patients lost weight overall. The median weight loss in this subgroup of patients was 2.0 kg (IQR, 1.0–3.6). At 24 months of treatment, 68.7% of these patients lost between 0% and 5% of their body weight at 12 months, 23.4% between 5% and 10% and 7.9% lost more than 10% of their body weight at 12 months. The median weight gained in the subgroup of patients who gained weight in the second year of therapy was 2.1 kg (IQR, 0.9–4.0). A higher probability for weight loss larger than 5% between 12 and 24 months of treatment (model 2, Table 4) was associated with the use of D4T [adjusted odds ratio (aOR), 1.28; 95% CI: 1.19 to 1.39] or other NRTIs (aOR, 1.54; 95% CI: 1.22 to 1.96) compared with TDF and with PIs (aOR, 1.43; 95% CI: 1.19 to 1.72) or NVP (aOR, 1.06; 95% CI: 1.01 to 1.12) compared with EFV in initial ART regimen; with women (aOR, 1.48; 95% CI: 1.41 to 1.55)

TABLE 3. Body Weight Change Slopes Within the First 24 Months After ART Initiation Modeled With the Adjusted LMM: Interactions Terms With D4T in Second Year (n = 205,571; Observations = 1,785,439)

	Body Weight Change, kg/yr	95% CI
Gender (versus ref*)		
Men	Ref*	—
Women	−1.13	−1.29 to −0.96
Geographical region (versus ref*)		
Southern Africa	Ref*	—
Asia-Pacific	−0.59	−1.24 to 0.07
Central Africa	1.86	1.21 to 2.51
East Africa	−0.77	−1.04 to −0.50
West Africa	0.05	−0.23 to 0.33
Age at ART initiation (versus ref*), yrs		
18–29	Ref*	—
30–34	−0.60	−0.83 to −0.37
35–39	−0.78	−1.02 to −0.54
>39	−1.16	−1.38 to −0.94
Baseline body weight (per 5 kg) (versus ref*)		
55 kg	Ref*	—
For each 5 kg higher	−0.34	−0.38 to −0.30
Baseline CD4 count in cells/μL (versus ref*)		
0–49	Ref*	—
50–199	0.20	−0.03 to 0.43
>199	0.50	0.24 to 0.77

*Reference group: men aged <30 years who started ART in Southern Africa with a baseline CD4 count <50 cells per microliter and with an initial body weight = 55 kg.

compared with men; with a higher baseline body weight (aOR, 1.05 per 5 kg; 95% CI: 1.04 to 1.06), with a CD4 count change less than 0 in the second year (aOR, 1.11; 95% CI: 1.04 to 1.18), with a WHO stage IV and year of ART initiation before 2009 (Table 4). A lower probability of weight loss larger than 5% between 12 and 24 months of treatment was associated with West African (aOR, 0.76; 95% CI: 0.69 to 0.82) and East African (aOR, 0.91; 95% CI: 0.86 to 0.97) regions compared with the Southern African region; age between 35 and 40 years (aOR, 0.88; 95% CI: 0.82 to 0.94) compared with age younger than 29 years and a baseline CD4 cell count above 199 cells (aOR, 0.87; 95% CI: 0.81 to 0.94) (Table 4).

When comparing baseline characteristics between patients with complete data availability and patients where CD4 counts were imputed, results were similar (see Tables S3-S4, Supplemental Digital Content, http://links.lww.com/QAI/A690).

DISCUSSION

Our study shows that persons with HIV infection experienced the most weight gain during the first year after ART initiation and that the second year weight changes were equally distributed between losses and gains. The study showed that weight gain was more pronounced in patients with a poorer clinical condition at the start of ART, reflected by a low pretreatment CD4 cell count, a more advanced WHO clinical stage, lower hemoglobin level, and lower baseline body weight. This has also been reported previously.[9,10] Hurley et al[11] also reported that the lower the BMI of patients was at start of ART, the higher the weight gain was after 1 year of treatment in a single cohort in South Africa.

Almost half of the patients lost weight in the second year of treatment, with almost 8% of these patients losing more than 10% of their weight at 12 months of treatment. It might be due, among other reasons, to therapy failure, opportunistic infection (tuberculosis), or intentional weight loss (diet or exercise). A study from Rwanda also showed that with D4T-based ART, a high proportion of patients had a progressive decline of body weight in the second year of treatment.[12] There are not enough data available in our study to fully explain this weight loss. There was however a difference in total weight change after 2 years of treatment according to the antiretroviral drugs in the initial regimen, within the nucleoside/nucleotide reverse transcriptase inhibitor category the highest weight gain in patients on a TDF-containing regimen. Certain patients on a D4T regimen had a smaller weight gain or even lost weight after 1 year of ART. This has also been observed in a study from Rwanda where such weight loss was probably due to lipoatrophy, a consequence of mitochondrial toxicity.[13] In our analysis adjusted for CD4 cell count change over the 12–24-month period, the smaller weight gain in patients on a D4T-containing regimen was still seen. Indeed, not only treatment failure but also adverse events such as painful neuropathies can contribute to weight loss. Others also showed that the impact of virological failure on weight evolution during the second year of ART was not significant.[11] Although lipoatrophy measurements were not available in our database, our hypothesis is that this D4T-related weight loss is indeed due to lipoatrophy. The lower weight gain in patients on D4T was mainly seen in patients from East-Africa, females, patients with a higher baseline body weight, older patients, and patients with a CD4 cell count below 50 cells per microliter at baseline. This corresponds to the findings of van Griensven et al,[12] who showed that being female, a longer duration of ART, a baseline BMI ≥25 kg/m^2, a D4T-based ART-regimen (compared with an AZT-based regimen) but also (in contrast to our findings) a baseline CD4 cell count ≥150 cells per microliter, were significantly associated with lipoatrophy. A South African study showed that lactic acidosis, another consequence of mitochondrial toxicity, was also associated with female gender, increased BMI, and D4T therapy.[14]

Our study showed, in contrast to other studies,[15] that patients started on a PI-based therapy (mostly boosted lopinavir) had on average a lower body weight increase than patients starting on an NNRTI-based regimen. The group of patients started on a PI-based ART regimen seems to be a diverse group; in West Africa, patients on PI-based therapy have a lower CD4 cell count than those not on PIs, whereas in Asia-Pacific, the opposite is the case. Patients who started a PI-boosted ART regimen might have been patients previously exposed to an NNRTI, for example, because of pregnancy (and therefore already had a higher CD4 cell

TABLE 4. Adjusted Odds Ratio on Weight Loss ≥5% in the Second Year of ART of Each Variable Compared With Its Reference Level

Variables	aOR	95% CI	*P*
Body weight loss in reference group*	0.11	0.09 to 0.13	<0.0001
Gender (versus ref*)			
Men	Ref*	—	—
Women	1.48	1.41 to 1.55	<0.0001
NRTI† in first ART regimen (versus ref*) ($P < 0.0001$)			
Tenofovir	Ref*	—	—
Stavudine	1.28	1.19 to 1.39	<0.0001
Zidovudin	0.97	0.89 to 1.05	0.420
Other NRTIs‡	1.54	1.22 to 1.96	0.0004
NNRTI§ or PI‖ in first ART regimen (versus ref*) ($P = 0.0005$)			
Efavirenz	Ref*	—	—
Nevirapine	1.06	1.01 to 1.12	0.032
PI	1.43	1.19 to 1.72	0.0001
Geographical region (versus ref*) ($P \leq 0.0001$)			
Southern Africa	Ref*	—	—
Asia-Pacific	0.88	0.73 to 1.06	0.169
Central Africa	0.82	0.67 to 1.01	0.055
East Africa	0.91	0.86 to 0.97	0.001
West Africa	0.76	0.69 to 0.82	<0.0001
Year of ART initiation (versus ref*) ($P < 0.0001$)			
<2005	1.23	1.03 to 1.46	0.021
2005–2006	1.38	1.18 to 1.63	<0.0001
2007–2008	1.30	1.11 to 1.52	0.001
2009–2010	Ref*	—	—
Age at ART initiation (versus ref*) ($P = 0.0002$), yrs			
18–29	Ref*	—	—
30–35	0.96	0.91 to 1.02	0.220
35–40	0.88	0.82 to 0.94	0.0001
≥40	0.99	0.94 to 1.05	0.791
Baseline body weight (per 5 kg) (versus ref*)			
55 kg	Ref*	—	—
For each 5 kg higher	1.05	1.04 to 1.06	<0.0001
Initial clinical stage (versus ref*)			
AIDS or WHO IV	Ref*	—	—
CDC B or WHO III	0.84	0.78 to 0.90	<0.0001
CDC A or WHO I/II	0.93	0.87 to 1.00	0.047
Clinical stage missing	1.00	0.91 to 1.10	0.982
Baseline CD4 count in cells/μL (versus ref*)			
0–49	Ref*	—	—
50–199	0.96	0.90 to 1.02	0.159
>199	0.87	0.81 to 0.94	0.0002
CD4 count change between M12 and M24 in cells/μL (versus ref*)			
<0	1.11	1.04 to 1.18	0.002
0–49	Ref*	—	—
50–99	1.03	0.97 to 1.10	0.322
>99	0.98	0.92 to 1.04	0.546
Baseline hemoglobin in g/dL (versus ref*)			
<7.5	Ref*‡	—	—
7.5–10	0.93	0.83 to 1.04	0.212
≥10	0.91	0.81 to 1.02	0.095
Missing	0.92	0.82 to 1.04	0.180

*The reference group: baseline body weight = 55 kg, TDF, EFV, region = Southern Africa, men, WHO IV, start year 2009–2010, age: 18–30, baseline CD4 cell count <50, CD4 change during second year 0–50, hb <7.5.
†NRTI, nucleoside/nucleotide reverse transcriptase inhibitor.
‡Other NRTIs: didanosine, lamivudine, abacavir, and emtricitabine.
§NNRTI, nonnucleoside reverse transciptase inhibitor.
‖PI, protease inhibitor.

count), or were patients from more wealthy Asian countries where PIs may be used as first-line therapy and at higher CD4 count. Excluding from the analysis, patients with HIV-2 infection on PIs did not change the results.

Although weight gain is mostly regarded as being beneficial in patients with HIV, we have to take into account the current obesity epidemics in several resource-limited settings.[16] Overweight and obesity are indeed important health risk factors predisposing for cardiovascular and metabolic diseases and certain cancer types.[17] Overweight and obese patients with HIV were found to have a higher prevalence of multimorbidity than patients with normal or underweight.[18]

The strength of our study lies in its large number of participants from various resource-limited countries. This is a strong advantage to detect statistical significant differences between treatment regimens. However, it is unclear how clinically significant some of these differences are. Indeed, our study had several limitations. HIV treatment centers participating in the IeDEA network cannot be considered to be representative of all the HIV treatment centers in the regions included in the study. The majority of patients were included in the Southern African region (67.7%) (with almost 75% of patients coming from Zambia) and only 0.80% from the Asia-Pacific region. We did however correct the outcomes for region, but cannot prevent some bias of data. Moreover, data were collected during routine care and therefore were not of the same quality as data collected during clinical trials. Our cohort data contained many missing variables and no information was available on adherence to drugs, drug switches or discontinuations, coinfections, lipodystrophy, access to food programs, pregnancies during follow-up, and number of patients who were lost to follow-up, transferred, or who died. HIV RNA plasma viral load measurements were available in a subgroup of patients. However, in some regions of all measured viral loads, the majority (up to 96.1% in the East African region) was 50 copies per milliliter or higher at month 24 after initiation of ART. This suggests that viral load measurements were only performed if there were clinical clues of failure (or nonadherence).

In conclusion, body weight increase, particularly in the first year of ART, is correlated with CD4 count increase and therefore may suggest that a patient is on an effective ART regimen. After the first year of ART, the body weight increase is leveling off, and in certain patients on a D4T regimen, body weight may even decrease because of lipoatrophy. Hopefully, with the 2013 WHO treatment guidelines, where D4T is not advised as the preferred first-line therapy, and with patients starting ART much earlier, there will be less thymidine-related side effects.[14] Weight and ideally BMI measurements may then become more meaningful to monitor treatment response from a clinical standpoint and basic program success indicator.

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