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Increased Baseline Body Weight Is a Risk Factor Associated With Virological Failure While on Antiretroviral Treatment

To the Editor:

We read with interest the article of Best et al[1] revealing higher baseline body weight as an independent risk factor for subtherapeutic antiretroviral (ARV) drug levels, potentially putting patients at risk of antiretroviral treatment (ART) failure and calling for therapeutic drug monitoring. This is particularly interesting because low body weight/body mass index has generally been associated with poor treatment outcomes and has been highlighted as a potential predictor of treatment failure in resource-constrained settings.[2,3]

We have been interested in the association of body weight with nucleoside reverse transcriptase inhibitors–related toxicity and had observed increased stavudine-related toxicity (lipoatrophy, lactic acidosis) with higher baseline body weight and body mass index within our program in Kigali, Rwanda.[4,5] However, while assessing the role of CD4 count measurements in predicting ART failure,[6] we had observed increased body weight at baseline to be associated with virological failure as well. Given the findings of Best et al,[1] we considered it relevant to report on our findings because it seems to add to the clinical relevance of their observations.

Médecins Sans Frontières is supporting the ART program in 2 urban government health centers in Kigali, Rwanda.[4,7] The ART program was launched in October 2003, with currently >3000 patients started on treatment. Approximately 90% of this cohort started on generic fixed-dose combination regimens containing stavudine, lamuvudine, and nevirapine. Viral load measurement was performed routinely after 1 year of treatment.

We aimed to further elaborate the association of body weight and virological failure (defined for the purpose of this study as a viral load >1000 copies/mL after >1 year of ART), using the data of 1166 adult patients who had been on ART for at least one year. A multivariate logistic regression model was generated using the variables specified in Table 1. Statistical analysis was performed using Intercooled Stata software version 9 (Stata Corp College Station, TX).

In bivariate analysis, apart from low baseline CD4 count, poor adherence, and treatment initiation with zidovudine (vs stavudine), a baseline body weight over 65 kg was associated with virological failure. Given the documented positive correlation of high baseline body weight with stavudine-related toxicity,[2,3,8] we thought that the most obvious explanation for the association of body weight with virological failure might have been confounding by toxicity. Alternatively, differences in the nonnucleoside reverse transcriptase inhibitors used as initial therapy or ARV drug substitutions could potentially explain these findings. However, increased body weight remained an independent risk factor for treatment failure after adjustment for multiple factors (Table 1). No significant interactions were observed. As such, the association seems to hold after controlling for ARV regimen and ARV toxicity/changes and other baseline characteristics. The same was true if mean on treatment body weight or body mass index (significantly increased risk if >25kg/m^2) was entered as main risk factor (instead of baseline body weight), although the association tended to be less strong. Hypothetically, higher body weight at the time of nevirapine initiation (with the vast majority of patients starting on a nevirapine-containing regimen in our setting) might be a more important risk factor than the body weight later on treatment, when full dosing is given.

One of the main limitations of this assessment is that it is an observational study performed retrospectively on existing data, and as such, residual confounding cannot be excluded (in particular, more detailed data on adherence, clinical events, and baseline viral load measurements might have been informative).

Few studies have specifically addressed the association of body weight and the risk of virological failure. However, the metabolism of nonnucleoside reverse transcriptase inhibitors is known to be positively correlated with body weight, and subtherapeutic drug levels are associated with virological failure,[9,10] as also suggested by the observed tendency of a lower virological treatment response for patients with subtherapeutic drug levels, reported by Best et al.[1] Given the article of Best et al,[1] our observation might require further exploration because it could potentially reveal the consequences of subtherapeutic drug levels for patients with higher body weight. With the vast majority of patients on ART living in resource-constrained settings, this finding might even be more concerning for these settings as therapeutic drug monitoring is generally not available, and the relevance of using alternative strategies like weight-adjusted dosing might need to be explored. With earlier access to ART becoming a growing reality in many settings, more patients are also likely to have a relatively higher body weight on ART initiation, thereby increasing the relevance of this issue. As such, we would like to invite other researchers to assess this potentially important clinical and operational problem in their setting.

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TABLE 1. Risk Factors Associated With Virological Failure in Adults on ART, Kigali, Rwanda (N = 1166)

Risk Factors	Virological Failure*	OR	P	Adjusted OR	P
Sex					
Male	32/276 (10.4)	1	—	1	—
Female	67/791 (7.8)	0.76 (0.49–1.16)	0.205	0.70 (0.42–1.17)	0.180
Age					
≤35 yrs	51/474 (9.7)	1	—	1	—
>35 yrs	48/593 (7.5)	0.76 (0.51–1.13)	0.175	0.68 (0.43–1.09)	0.113
Baseline body weight†					
<55 kg	34/506 (6.3)	1	—	1	—
55–65 kg	37/391 (8.6)	1.35 (0.84–2.16)	0.218	1.54 (0.91–2.60)	0.109
>65 kg	26/164 (13.7)	2.25 (1.32–3.81)	0.003	2.90 (1.59–5.27)	0.001
Baseline CD4 count (cells/μL)‡					
<100	40/296 (11.9)	1	—	1	—
100–200	32/394 (7.5)	0.56 (0.35–0.91)	0.018	0.54 (0.32–0.90)	0.019
>200	21/317 (6.2)	0.49 (0.29–0.84)	0.009	0.38 (0.20–0.69)	0.002
Time on ART					
≤1.5 yrs	55/664 (7.6)	1	—	1	—
>1.5 yrs	44/403 (9.8)	1.37 (0.92–2.04)	0.123	1.20 (0.76–1.89)	0.446
Baseline WHO clinical stage					
I	4/40 (9.1)	1	—	1	—
II/III/IV	95/1026 (8.5)	1.14 (0.40–3.22)	0.805	1.01 (0.32–3.20)	0.990
NNRTI at start of treatment					
Efavirenz	10/71 (12.3)	1	—	1	—
Nevirapine	89/996 (8.2)	0.55 (0.30–1.00)	0.051	1.22 (0.49–3.02)	0.673
NRTI at start of treatment					
Zidovudine	12/64 (15.8)	1	—	1	—
Stavudine	87/1003 (8.0)	0.55 (0.31–0.99)	0.045	0.46 (0.21–1.01)	0.052
NNRTIs change					
No	90/950 (8.6)	1	—	1	—
Yes§	9/117 (7.1)	0.78 (0.38–1.58)	0.487	0.67 (0.31–1.47)	0.323
NRTIs change					
No	83/903 (8.4)	1	—	1	—
Yes§	16/164 (8.9)	1.10 (0.65–1.88)	0.716	1.05 (0.57–1.94)	0.874
Adherence‖					
100%	31/486 (6.0)	1	—	1	—
95%–99%	23/250 (8.4)	1.71 (0.99–2.92)	0.052	1.38 (0.76–2.51)	0.293
<95%	45/331 (12.0)	2.33 (1.46–3.71)	0.001	1.99 (1.18–3.36)	0.009

OR, odds ratio; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors.

*Defined as a viral load >1000 copies/mL after 1 year of therapy; values are expressed as n with virological failure/n without virological failure; the percentage of patients with virological failure is given in parentheses.

†χ^2 test for trend: 9.5; P value: 0.002.

‡χ^2 test for trend: 7.0; P value: 0.008.

§Treatment changes for all kind of reasons (toxicity, tuberculosis, pregnancy, etc.).

‖Based on clinical attendance as a measure of adherence to therapy: being punctual for 100%, 95%–99%, or <95% of the visits; χ^2 test for trend: 9.9; P value: 0.002.

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