Predictors of weight gain in the ADVANCE, NAMSAL and WRHI trials: EFV, TDF and baseline CD4 count

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BACKGROUND

Post-ARV initiation weight gain is prevalent in PLHIV, especially among women and those of black race. Use of TDF or EFV can suppress weight gain. People with lower baseline CD4 count show greater weight gains, but this might be associated with lower baseline weight.

METHODS

Data were pooled from three clinical trials: ADVANCE (n=1053), NAMSAL (n=613), and WHRI001 (n=536). The trials used first-line ARV regimens (TAF/XTC/DTG, TDF/XTC/DTG, and TDF/XTC/EFV) and enrolled in Cameroon, India, Uganda and South Africa. BMI over 96 weeks was assessed, stratified by baseline CD4 count as a marker for disease stage (<100, 100-200, 200-350, ≥350 cells/mm^3). Multivariate models at week 96 assessed factors associated with BMI and clinical obesity (BMI ≥30), adjusting for baseline CD4 category, age, sex, TDF, EFV and trial. Models were assessed with/without interactions between baseline CD4 category and TDF/EFV use.

RESULTS

At baseline, mean age was 34.5 (SD 8.9), 60% were female, 14% had CD4 <100, and 31% had CD4 ≥350. Lower baseline BMI was strongly correlated with lower CD4 count (p<0.001). At week 96, mean unadjusted BMI change was highest in the <100 CD4 group (+3.2 kg/m^2; SD 3.1) and lowest in the CD4≥350 group (+1.1; SD 2.4). Individuals with advanced disease on TAF-based regimens experienced greater BMI increases compared to those on TDF-based regimens (Figure 1). For participants on TAF-based treatment (ADVANCE only), increases in BMI were significantly higher in participants with CD4<100 (+5.0; SD 3.1) compared to those in the ≥350 group (1.6; SD 2.2). In the adjusted model, for those not on TDF or EFV regimens, predicted BMI at week 96 was significantly higher for CD4<100 (28.4 [95%CI 26.7-30.1]) overshooting that seen in CD4≥350 (25.3 [95%CI 24.4-26.3]; p=0.001). However, on TDF or EFV regimens, there was no difference in BMI across the CD4 categories. Analyses using clinical obesity (BMI >30 kg/m^2) showed consistent results: despite having the lowest baseline weight, people taking TAF/FTC/DTG with CD4<100 were significantly more likely to become obese after 96 weeks of first-line treatment.

CONCLUSIONS

For people taking TAF/FTC/DTG, baseline CD4<100 cells/mm^3) at treatment initiation was associated with significantly higher BMI and clinical obesity at Week 96. Use of TDF and EFV were associated with smaller rises in weight. Effective weight management is required with current regimens to avoid complications associated with significant weight increases, particularly for individuals with low baseline CD4 counts.

Low baseline CD4 count associated with higher risks of clinical obesity on first-line TAF/FTC/DTG. This may be "HIV-related weight gain" and not "Return to Health"

Table 1 Baseline demographic and health characteristics of the participants of each trial

	Pooled	ADVANCE	NAMSAL	WHRI001[1]
Randomisation period	-	Feb2017 – May2018	Jul2016 – Aug2019	Jul2012 – Jan2014
Study country	-	South Africa	Cameroon	South Africa (56%), Uganda (36%), India (8%)
Number of participants	2,202	1053	613	536
Treatment arms		TAF/FTC+DTG: 351 TDF/FTC+DTG: 351 TDF/FTC/EFV: 351	TDF/3TC+DTG: 310 TDF/3TC+EFV 400mg: 303	TDF/3TC/EFV: 536
Age, years				
Median (IQR)	33 (28-40)	32 (27-37)	37 (29-44)	34 (29-40)
Mean (SD)	34.5 (8.9)	32.5 (7.7)	37.6 (10.3)	35.0 (8.1)
Female sex	1,320 (60)	623 (59)	404 (66)	293 (55)
Black African race	1,543/1,589 (97)	1,051 (100)	NR	492 (92)
Baseline weight, kg				
Median (IQR)	64.5 (57.0-73.5)	66.2 (58.9-77.0)	64.0 (57.0-72.0)	61.8 (55.0-70.0)
Mean (SD)	66.4 (13.4)	68.7 (14.2)	65.2 (12.1)	63.1 (12.2)
Baseline BMI, kg/m^2				
Median (IQR)	23.0 (20.5-26.5)	23.1 (20.2-26.9)	23.2 (20.8-26.2)	22.8 (20.7-25.8)
Mean (SD)	23.9 (4.8)	24.1 (5.3)	23.7 (4.0)	23.7 (4.5)
Underweight (<18.5)	189 (9)	114 (11)	42 (7)	33 (6)
Normal (18.5-24.9)	1,266 (58)	559 (53)	367 (60)	340 (63)
Overweight (25-29.9)	518 (24)	252 (24)	156 (26)	110 (21)
Obese (≥30)	227 (10)	128 (12)	46 (8)	53 (10)
Baseline HIV RNA viral load, $\log_{10}$ copies/mL				
Median (IQR)	4.7 (4.1-5.3)	4.4 (3.8-4.9)	5.3 (4.8-5.8)	4.9 (4.4-5.3)
Mean (SD)	4.7 (0.9)	4.3 (0.8)	5.3 (0.8)	4.9 (0.7)
Baseline HIV RNA viral load, copies/mL				
<100,000	1,339 (61)	825 (78)	206 (34)	308 (57)
≥100,000	863 (39)	228 (22)	407 (66)	228 (43)
Baseline CD4 cell count, cells/mm^3				
Median (IQR)	258 (151-393)	293 (173-451)	281 (154-444)	205 (124-270)
Mean (SD)	297.3 (205.9)	336.6 (227.1)	315.0 (209.5)	199.7 (99.1)
<100	311 (14)	123 (12)	84 (14)	104 (20)
100-199	471 (21)	196 (19)	120 (20)	155 (29)
200-349	736 (33)	310 (29)	177 (29)	249 (46)
≥350	684 (31)	424 (40)	232 (38)	28 (5)[2]

Data are no. (%) unless otherwise indicated.
[1]Only the TDF/3TC/EFV arm is included in the analysis.
[2]CD4>350 at screening was an exclusion criterion but 5% of participants had a CD4 cell count 350-500 at randomisation.
Abbreviations: IQR, interquartile range; NR, not reported; SD, standard deviation

Table 2 Predictors of weight gain and obesity

Variable	Weight change Coefficient (95%CI)	p-value	Obesity Odds ratio (95%CI)	p-value
Baseline CD4 category				
<100	2.31 (1.83,2.79)	<0.001	16.0 (6.48,40.17)	<0.001
100-199	1.30 (0.89,1.71)	<0.001	2.75 (1.28,5.90)	0.006
200-349	0.41 (0.05,0.77)	0.024	1.91 (0.98,3.71)	0.057
≥350	Ref.		Ref.	
HIV RNA (>100,000 vs ≤100,000 cp/mL)	0.93 (0.61,1.25)	<0.001	3.45 (1.86,6.40)	<0.001
TAF regimen (TAF vs TDF)	1.50 (1.05,1.95)	<0.001	2.05 (0.92,4.55)	0.077
DTG regimen (DTG vs EFV)	1.31 (0.96,1.66)	<0.001	3.70 (1.90,7.20)	<0.001
Baseline BMI (continuous)	-0.03 (-0.06,0.00)	0.077	5.28 (4.51,6.18)	<0.001
Age (continuous)	0.01 (-0.01,0.02)	0.311	0.97 (0.94,0.99)	0.022
Sex (female vs male)	0.83 (0.54,1.12)	<0.001	3.48 (1.90,6.39)	<0.001

Results are from longitudinal regression models including all listed predictors, with week and trial as fixed effects and participant as a random effect. The weight change model is a linear mixed-effect model with weight change from baseline as the outcome. The obesity model is a mixed-effect logistic regression model with obese (BMI ≥30 kg/m2) as the outcome measure.

Figure 1 – Pooled analysis showing BMI change for those on TAF vs TDF containing regimens across the three studies

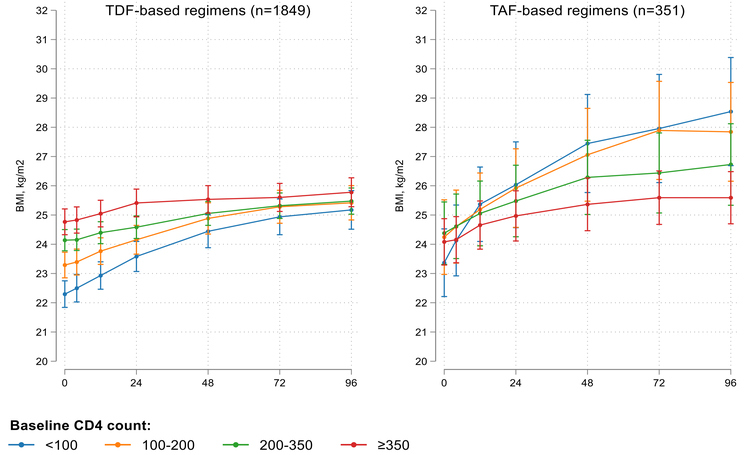

Figure 2 – *Weight and obesity outcomes by baseline CD4 category*