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A randomized open study comparing the impact of reducing stavudine dose vs. switching to tenofovir on mitochondrial function, metabolic parameters, and subcutaneous fat in HIV-infected patients receiving antiretroviral therapy containing stavudine.

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Background

- Peripheral lipoatrophy and dyslipidemia may complicate stavudine-containing antiretroviral therapy. Mitochondrial dysfunction has been suggested as at least one potential underlying mechanism in the pathogenesis of peripheral lipoatrophy and dyslipidemia associated with stavudine.

- Available data suggest that tenofovir has little effect on mitochondrial gamma polymerase and a lower risk for peripheral lipoatrophy and dyslipidemia than stavudine. Switching from stavudine to abacavir has shown an improvement on peripheral lipoatrophy without significant effects on plasma lipids. To date, the effects of switching from stavudine to tenofovir are unknown.

- Scarce data suggest that reducing stavudine dose may be as effective as standard dose but less toxic, although the effects of reducing stavudine dose on peripheral lipoatrophy and dyslipidemia are unknown.

Patients and methods

Type of study Prospective, randomized, open-label study

Inclusion criteria Clinically stable HIV-infected patients receiving antiretroviral therapy containing stavudine 40 mg bid with a plasma HIV RNA <200 copies/mL for at least the previous 6 months .

Treatment arms (while preserving the remaining drugs unchanged)

- d4T dose reduction to 30mg bid — d4T 30 arm
- Switch d4T to TDF — TDF arm
- Continue d4T 40mg bid — d4T 40 arm

Methods

Follow up 6 months

Study visits:

- **Baseline, 1, 3 and 6 months: glucose , triglycerides, total, HDL and LDL cholesterol, plasma HIV–1 RNA, CD4 cells count and lactate.**
- **Baseline and 6 months: mitochondrial analysis and body composition (DEXA).**
- **Statistical analysis: Kruskal-Wallis test , Bonferroni adjustment for the significance level , McNemar test , Fisher Chi-square test .**

Methods - mitochondrial function

Mitochondrial analysis in PBMCs

- Mitochondrial DNA content was determined by quantitative real time PCR.
- Mitochondrial Mass was determined through the measurement of Citrate Synthase (CS) Activity by spectrophotometry.
- Oxidative activity of intact cells (spontaneous cellular oxidation) was determined by polarography.
- Enzyme activity of the mtDNA-encoded complexes of the OXPHOS system (Complex IV and Complex III activity) was determined by spectrophotometry.
- Results were expressed as absolute values and as percentages with respect to the baseline value.

Baseline characteristics

	D4T-40 (n=22)	D4T-30 (n=19)	TDF (n=17)
Age			
(mean±SD)	45 ± 10	43 ± 7	46 ± 9
CD4 (/mm^3)			
HIV diagnosis	174 ± 120	197 ± 199	246 ± 207
Baseline study	568 ± 245	695 ± 317	529 ± 325
PIs *(n, %)*	7(32)	1(5)	2(12)
NNRTIs *(n, %)*	13 (59)	17(89)	13(76)
ddI *(n, %)*	6(27)	4(21)	1(6)
HIV-1 RNA (copies/mL)			
HIV diagnosis	278000	273000	202000
Baseline <20 copies/mL	22 (100%)	19 (100%)	17 (100%)

Baseline laboratory dates

	D4T-40 (n=22)	D4T-30 (n=19)	TDF (n=17)	P
Tgl (mg/dL)	141 ±116	207 ± 189	242 ± 234	0,15
Chl total (mg/dL)	222 ± 35	227 ± 40	205± 49	0,96
LDL-Chl (mg/dL)	142 ± 29	141 ± 33	137 ± 29	0,87
HDL-Chl (mg/dL)	48 ± 11	47 ±15	47 ± 9	0,65
Lactate (mg/dL)	13 ± 5	15 ±3	13 ±5	0,89

Baseline fat mass(DEXA)

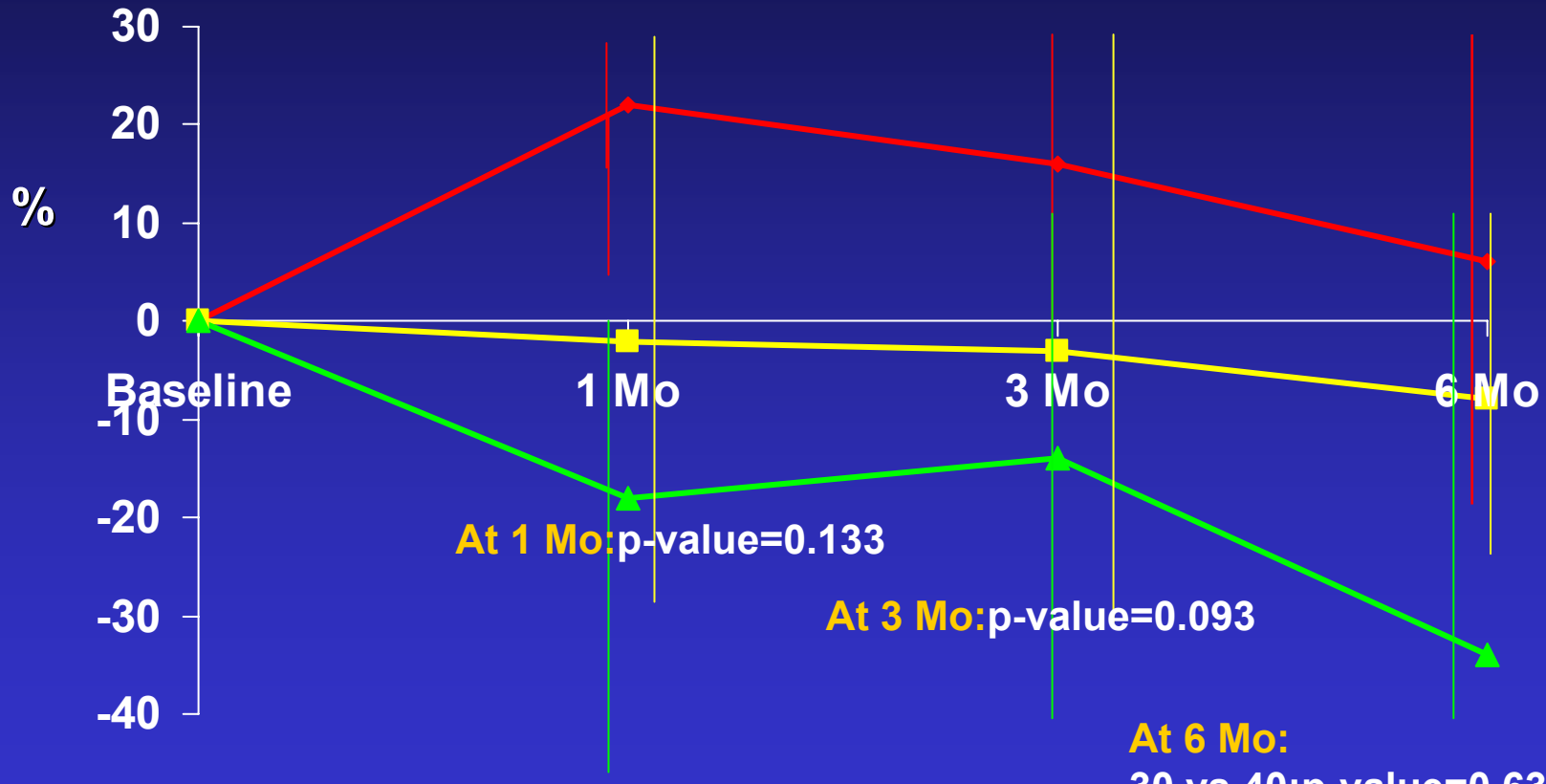
	D4T-40 (n=22)	D4T-30 (n=19)	TDF (n=17)	P
Peripheral (g)				
Median	3204	3295	4438	0,57
IQR	2238-4797	2785-4351	2585-5619	
Truncal (g)				
Median	7510	8220	9107	0,27
IQR	5742-10375	6833- 12090	7769-11850	
Total (g)				
Median	11843	11459	14000	0,31
IQR	8674-15061	9851-16990	10673-18848	

Baseline lean mass(DEXA)

	D4T-40 (n=22)	D4T-30 (n=19)	TDF (n=17)	P
Peripheral (g)				
Median	25218	24331	25212	0,38
IQR	22088-29285	21945-29121	23110-27143	
Truncal (g)				
Median	25184	26205	26652	0,55
IQR	23035-28547	24495-28146	25238-28591	
Total (g)				
Median	55008	53896	56134	0,75
IQR	48792-62588	52531-59918	53129-59874	

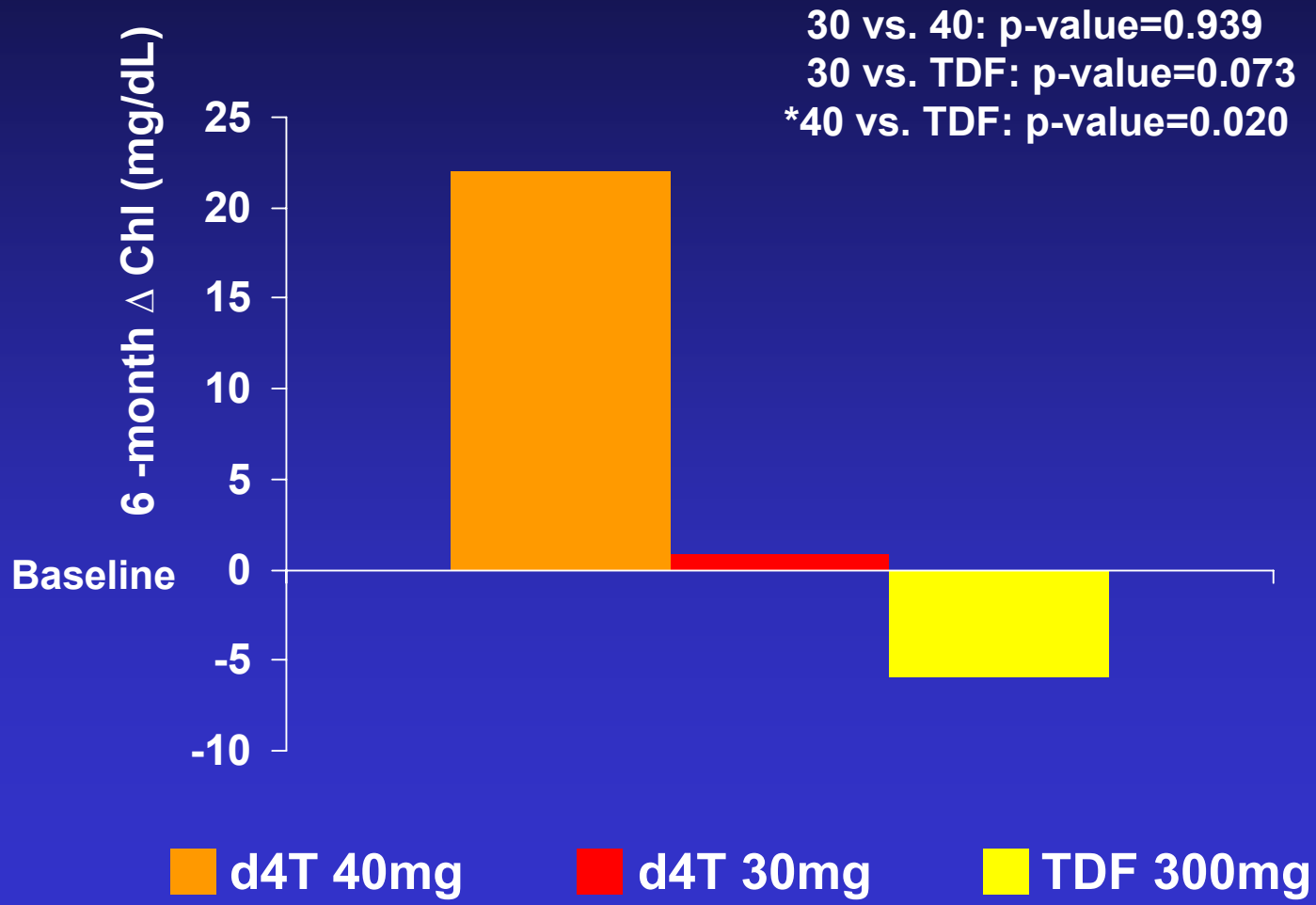
Triglycerides

Percentage of change from baseline

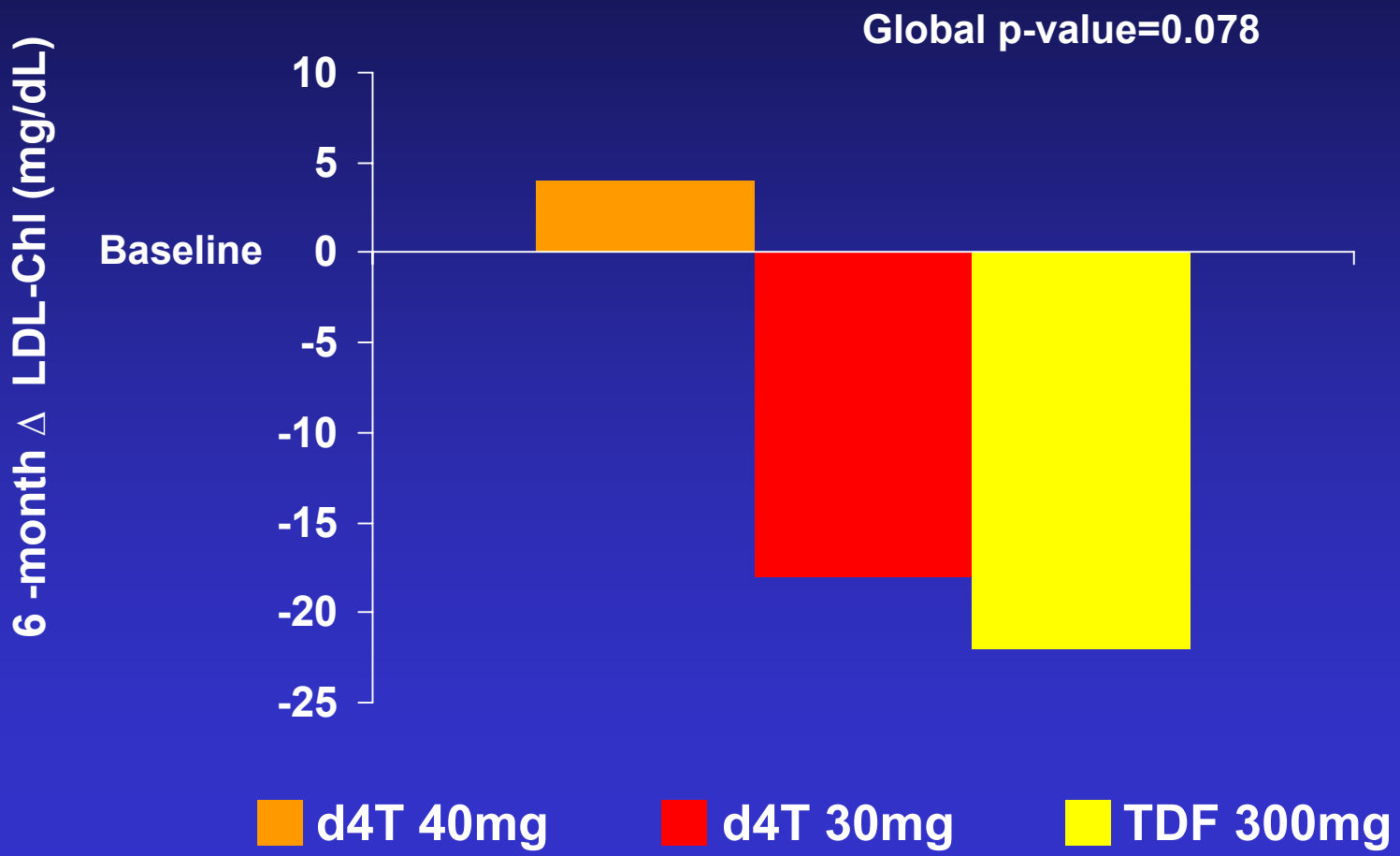


At 6 Mo:
30 vs.40:p-value=0.638
30 vs.TDF:p-value=0.152
* 40 vs. TDF=0.0390

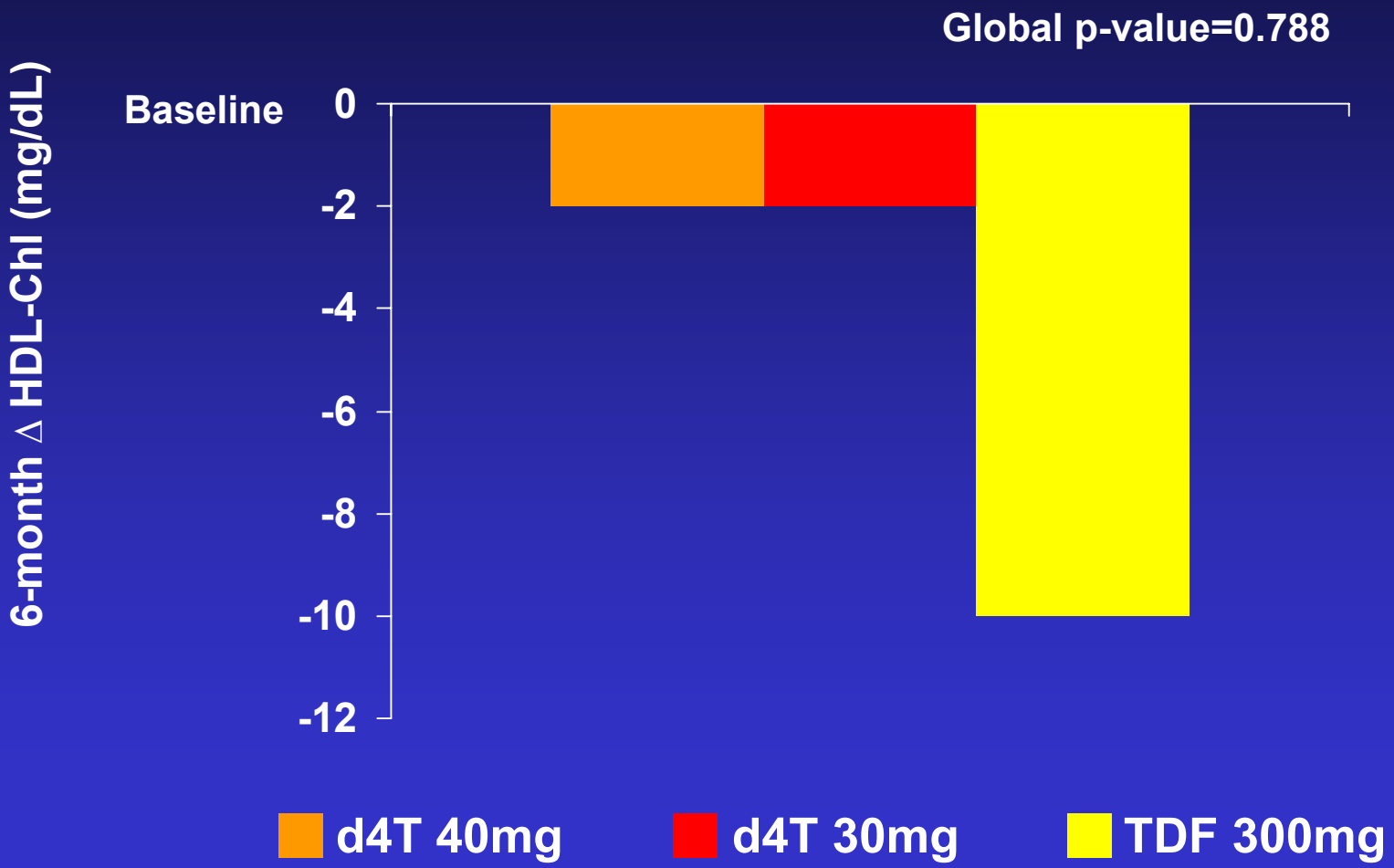
Cholesterol



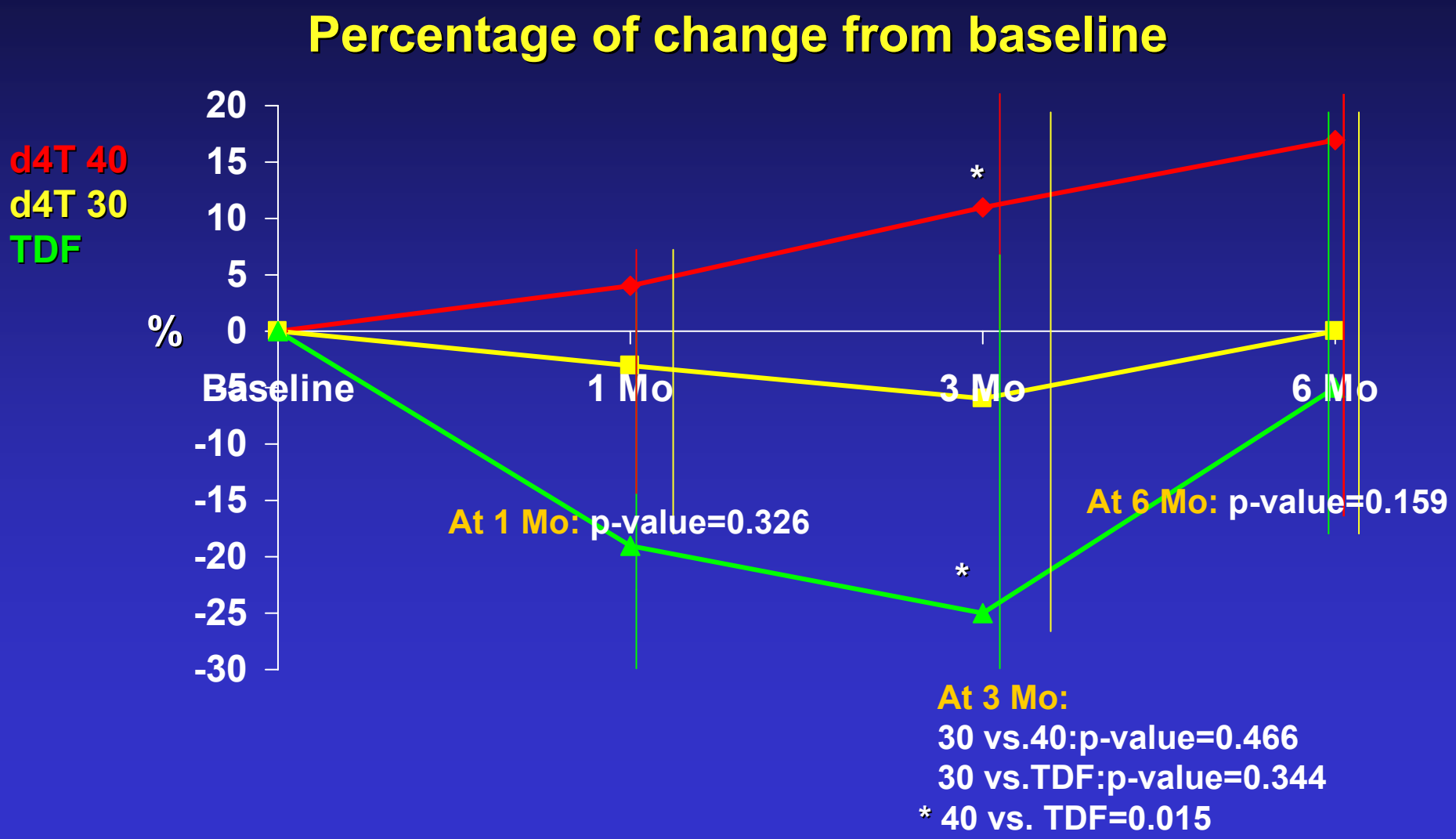
LDL-Cholesterol



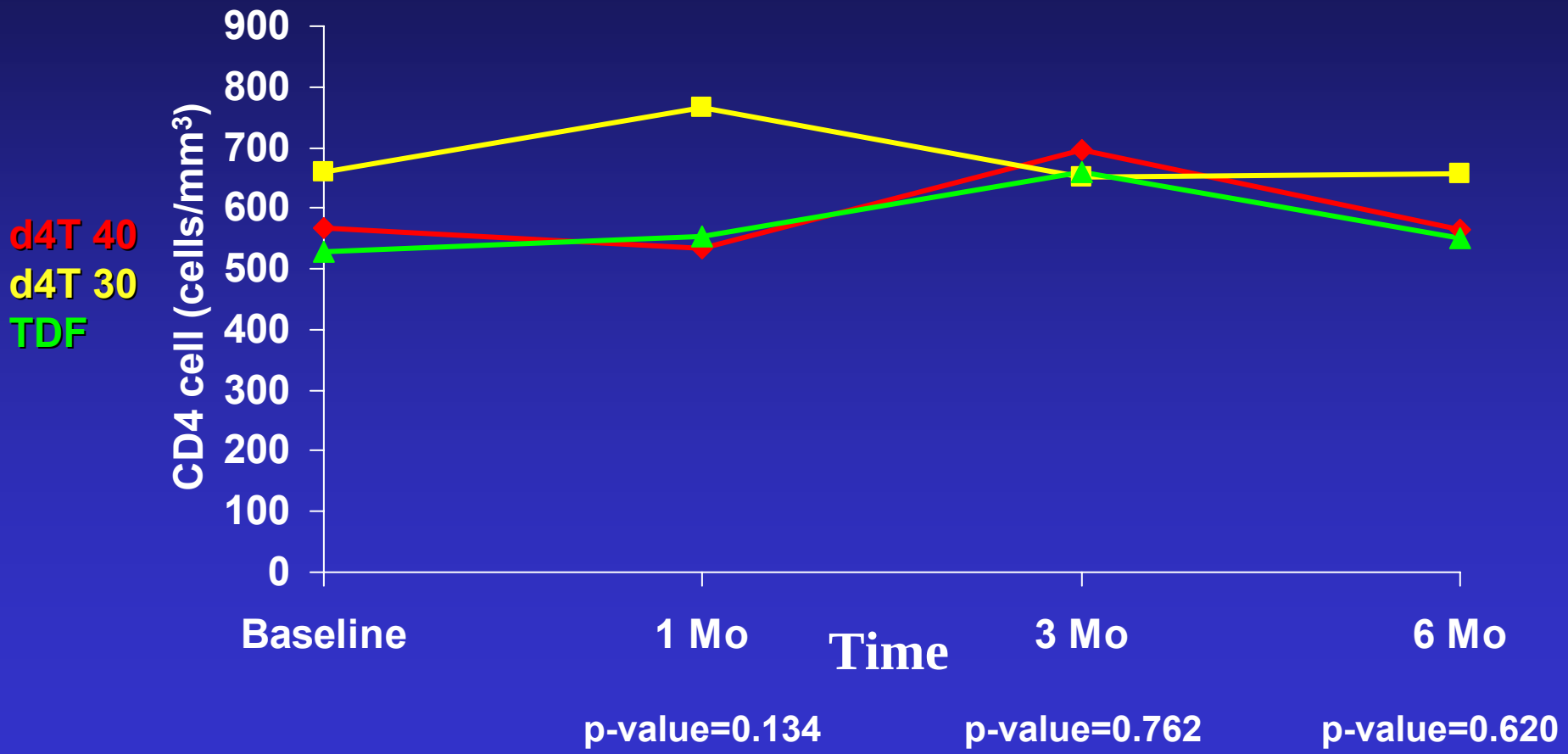
HDL-Cholesterol



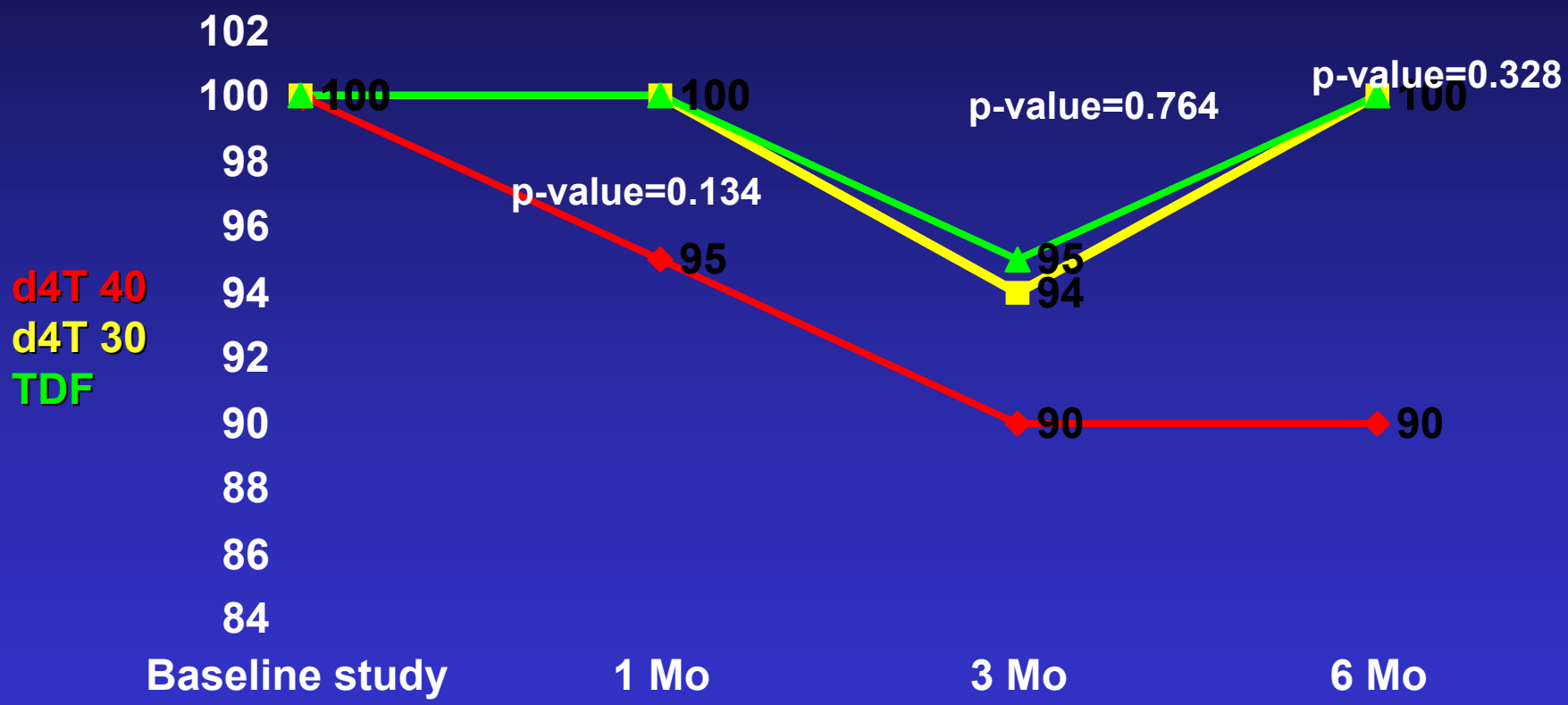
Lactate


Percentage of change from baseline
d4T 40
d4T 30
TDF
%
20
15
10
5
0
-5
-10
-15
-20
-25
-30
Baseline
1 Mo
3 Mo
6 Mo
*
*
At 1 Mo: p-value=0.326
At 6 Mo: p-value=0.159
At 3 Mo:
30 vs.40:p-value=0.466
30 vs.TDF:p-value=0.344
* 40 vs. TDF=0.015

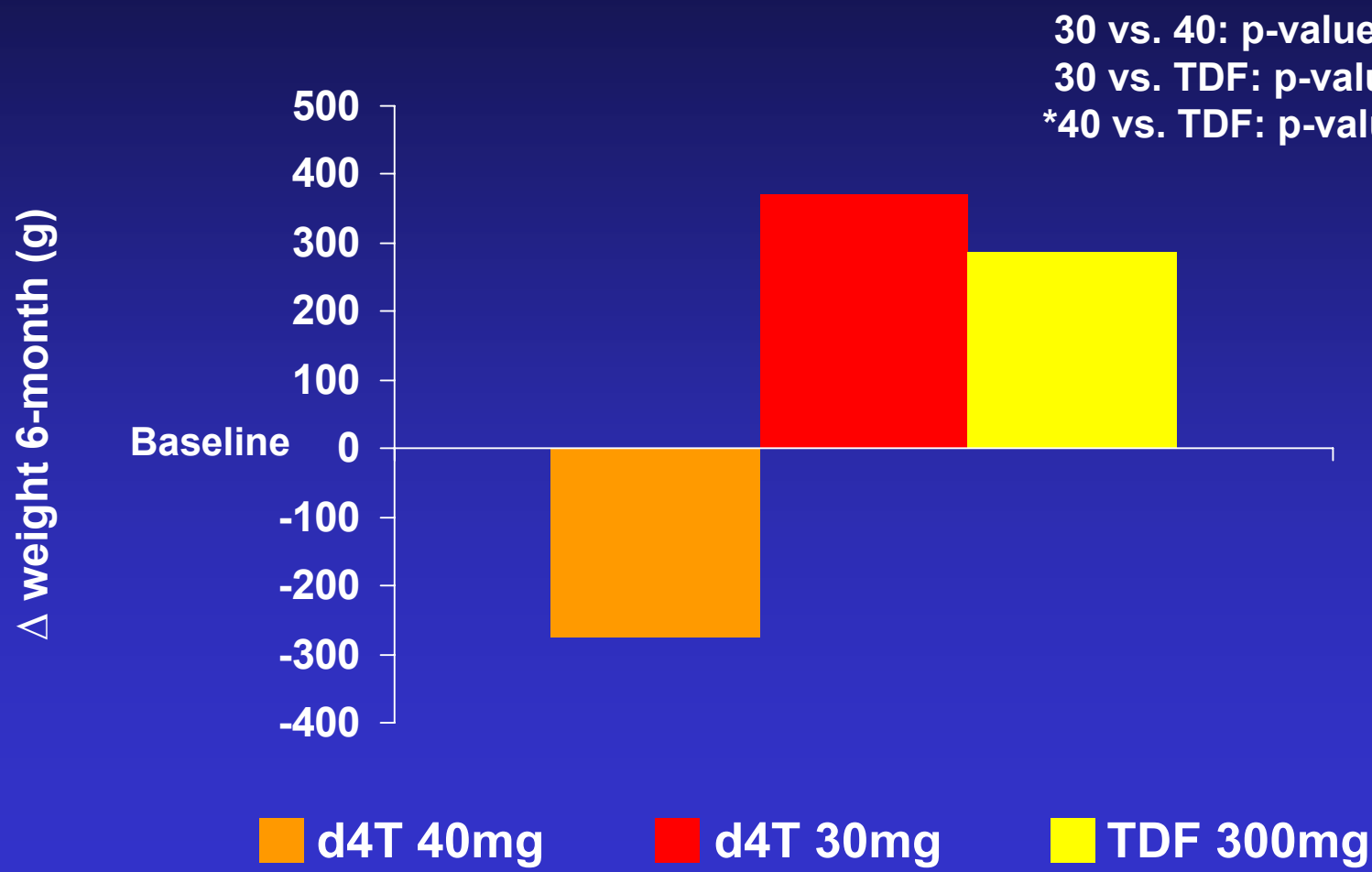
Change in mean CD4 cell count



% of patients with HIV-1 RNA<20

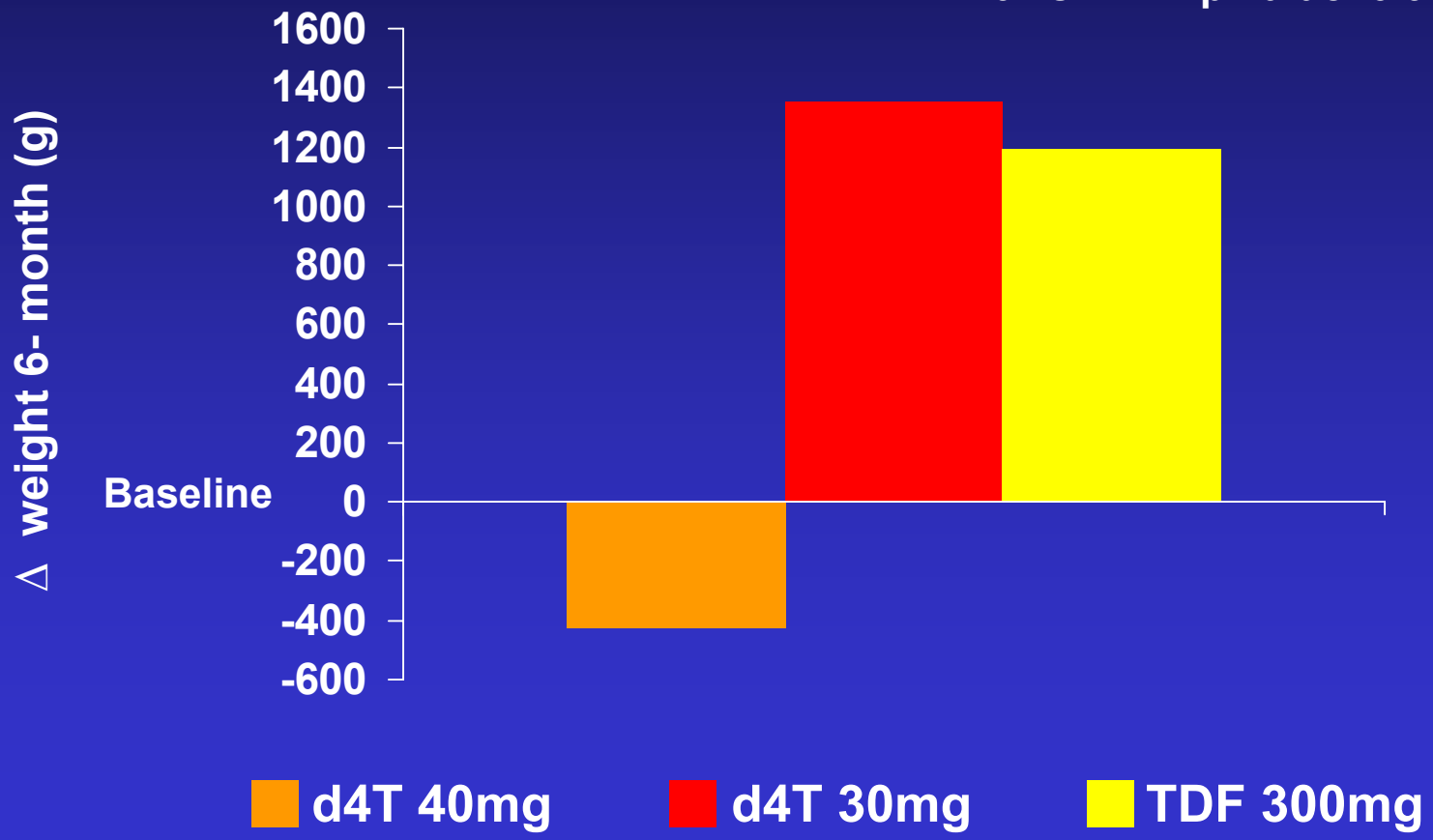


Peripheral fat

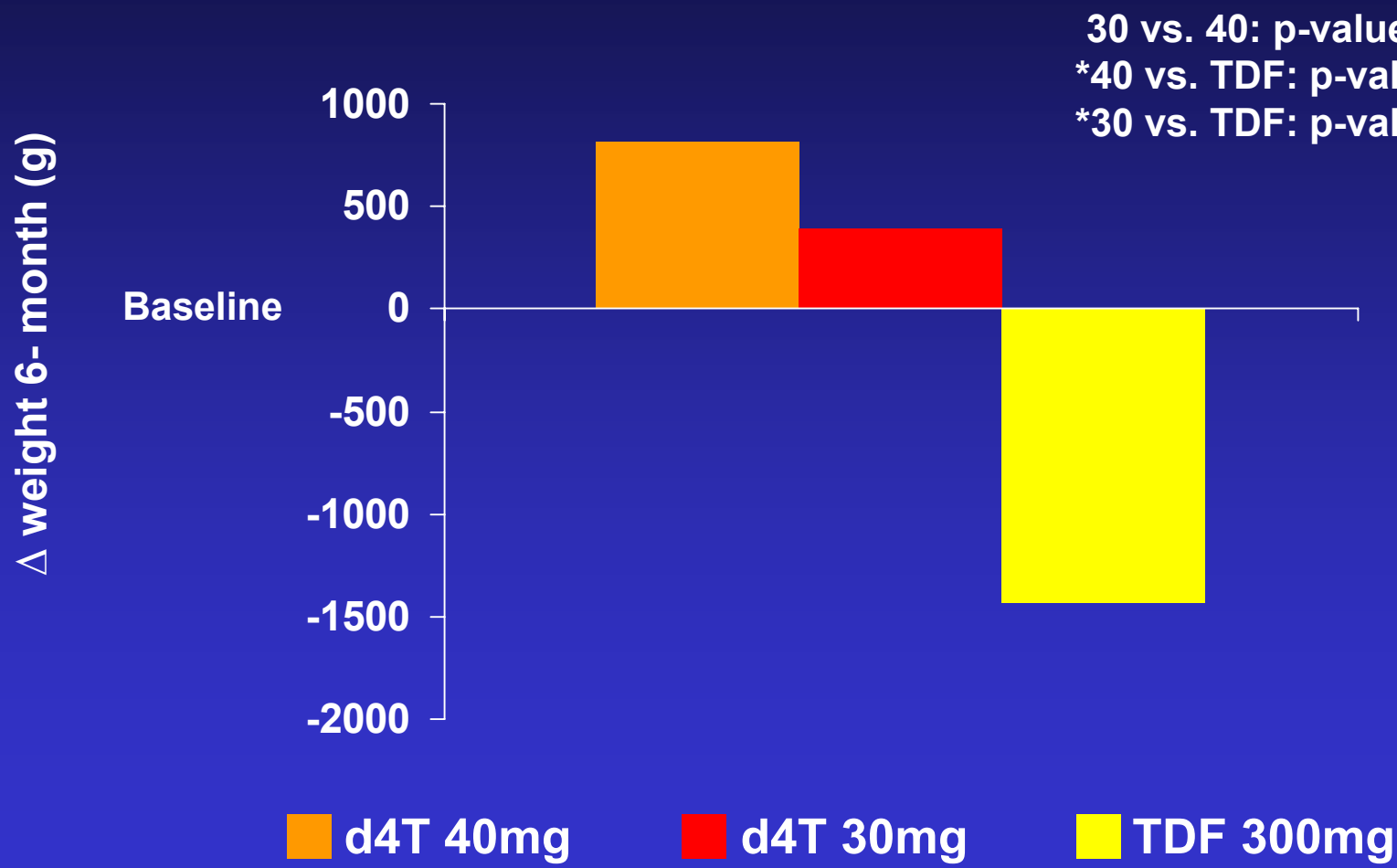


Total fat

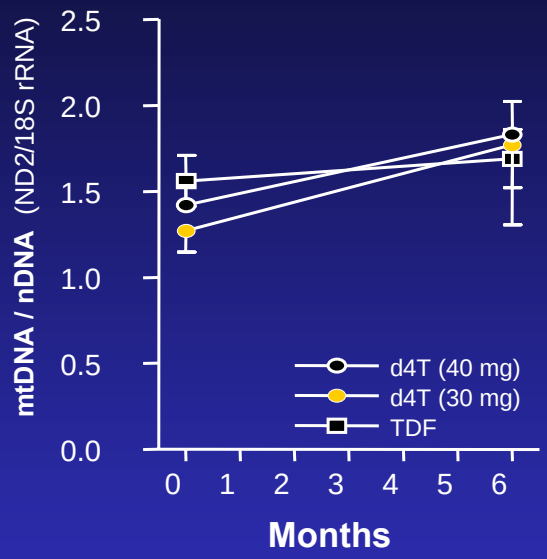
30 vs. 40: p-value=0.168
30 vs. TDF: p-value=0.998
*40 vs. TDF: p-value=0.032

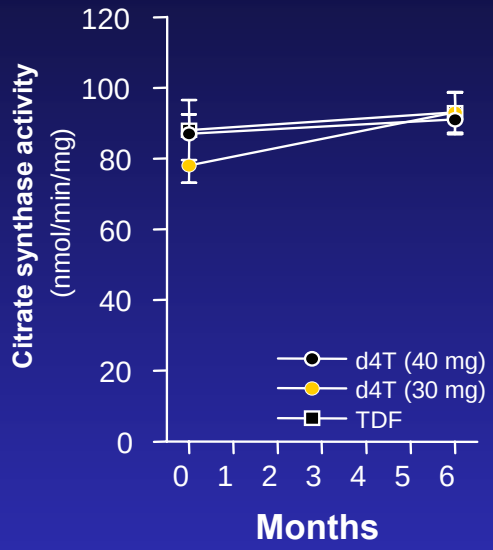


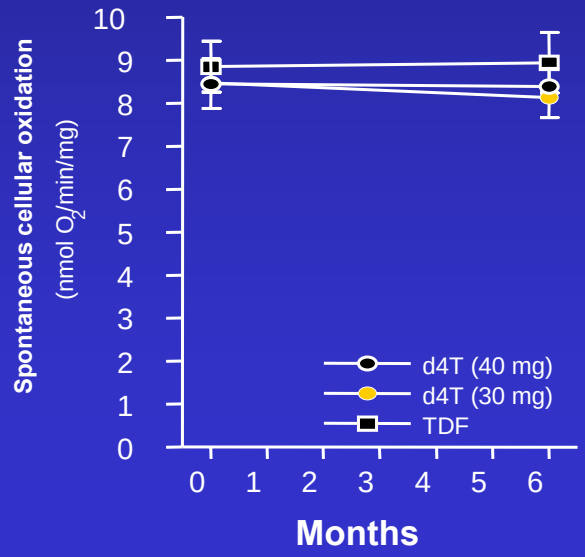
Total lean mass



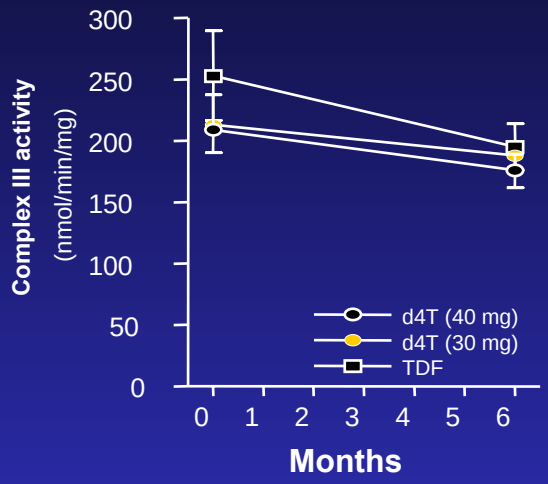
Mitochondrial function

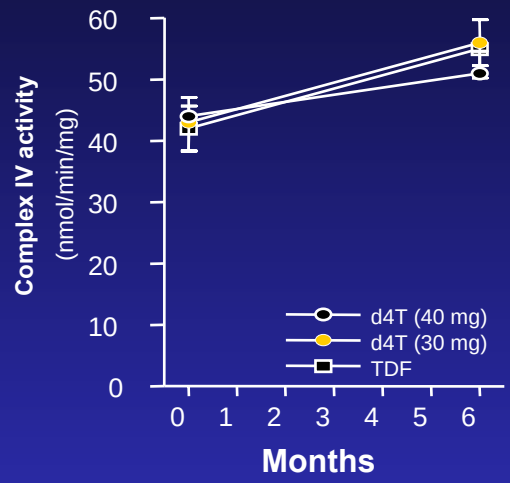


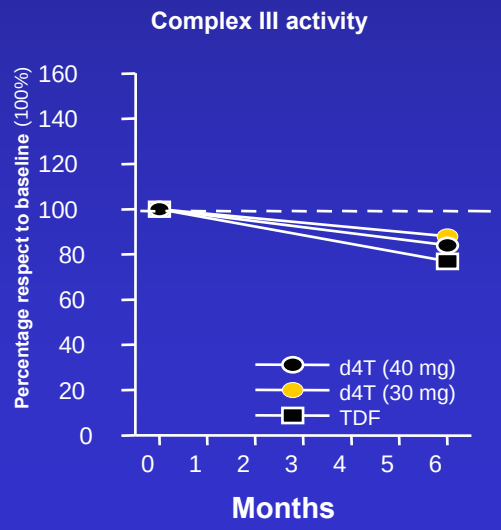


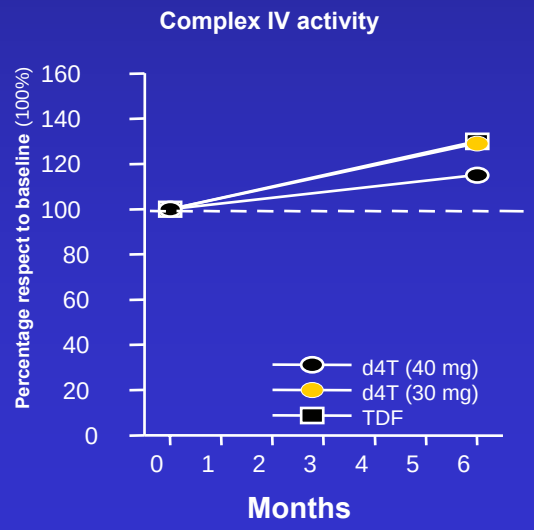


Mitochondrial function

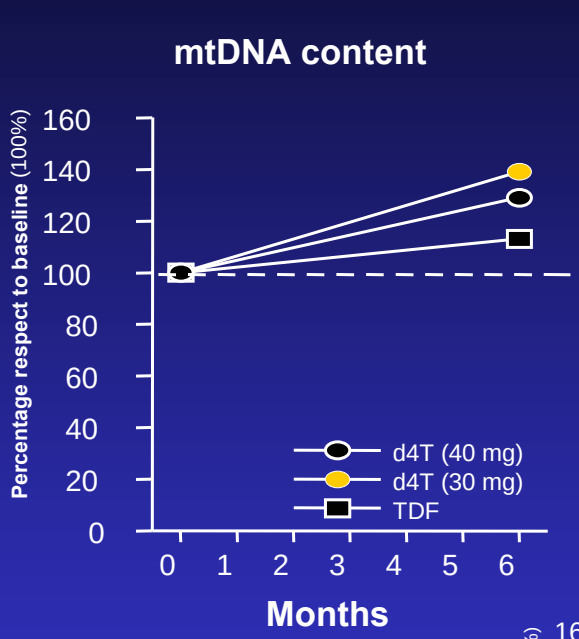


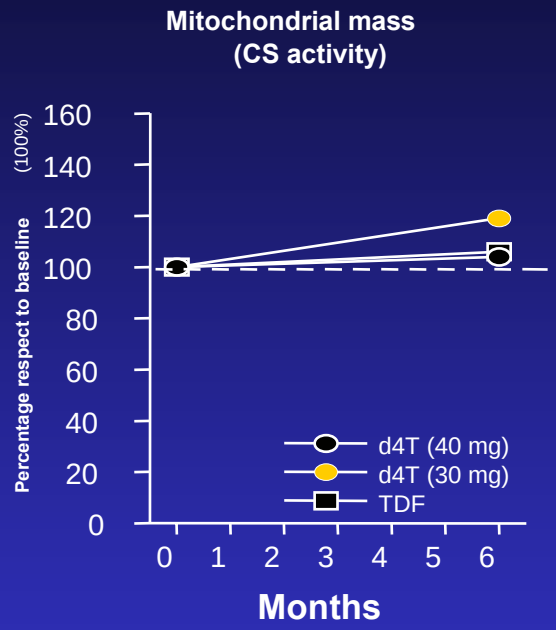


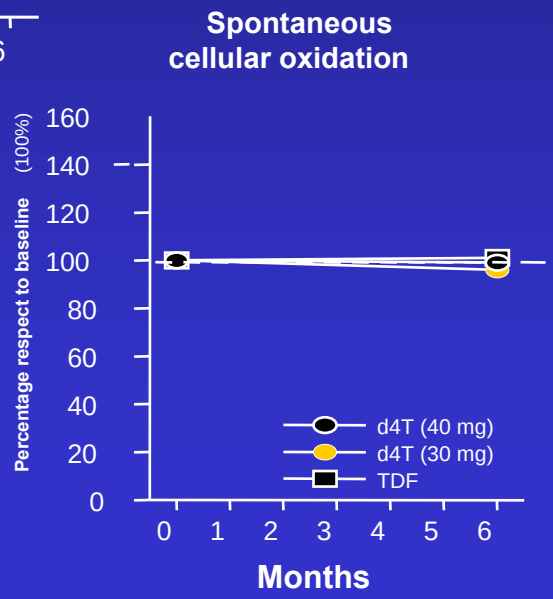




Mitochondrial function







Results

Virological safety and Adverse events

- Virological rebounds: 2 patient in d4T 40 arm
- No significant changes in CD4 cell count
- 2 cases of symptomatic hyperlactatemia in d4T 40 arm
  - 1case at baseline visit, another after 6 months.

Reasons for discontinuation:

- Pregnancy -1patient
- Lost to follow up-2 patients
- Poor adherence-1 patient

Conclusions

In patients receiving d4T 40 mg bid containing antiviral therapy and HIV-1 RNA<20 copies/mL:

- Switching from d4T 40 bid to TNF was associated with significant improvement in triglycerides, cholesterol and body fat at 6 months.
- Reduction in d4T 40 bid to d4T 30 mg bid was associated with an improvement in triglycerides, cholesterol and body fat at 6 months although the differences did not reached statistical significant.
- Both switch arms were at least as virologically effective as d4T 40 arm.

Conclusions

- No mitochondrial parameter from PBMCs studied differed among groups either at baseline or at 6 months suggesting either that fat and plasma lipid effects are not mediated via mitochondria, or if mediated by mitochondria not by those from PBMCs, or the mitochondrial tests used are not sensitive enough to detect potentially mitochondria-mediated changes.