Decreased adipose tissue gene expression after a 48-week switch from an INSTI regimen to TDF/3TC/DOR

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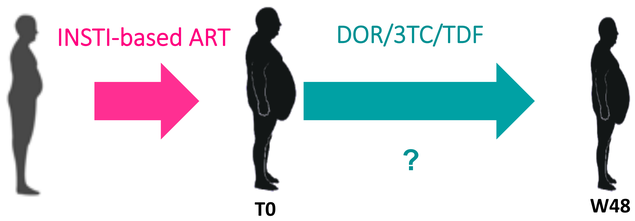
BACKGROUND

Integrase inhibitors (INSTIs) are known to induce weight and fat gain, the pathogenesis and reversibility of which remain unclear. In vivo and in vitro studies have previously demonstrated the ability of INSTIs to induce adipose tissue dysfunction including adipocyte hypertrophy (*J Gorwood CID 2020*).

The ADDORE study was designed to **evaluate the evolution of clinical, metabolic and adipose tissue parameters between baseline and week 48 in PWH with INSTI-associated weight gain who were switched to TDF/3TC/DOR.**

METHODS

- 22 PWH included, 20 followed at T0 and W48,
- Mean age 48.9 ± 3 years, 16 men/ 4 women
- ART at inclusion: 70% BIC/FTC/TAF,
- 25% DTG/3TC± ABC, 5% EVGc/FTC/TDF
- PWH underwent two surgical adipose tissue biopsies from subcutaneous fat at T0 and at W48.



- Samples were homogenized and RNA was isolated.
- 14 adipose tissue samples with sufficient RNA to perform RT-PCR analyses at T0 and W48
- Expression of 14 genes evaluated by RT-PCR compared to the expression of two reference genes (HPRT and PPIA)
- Statistical analysis performed by paired t-test and Wilcoxon test.

RESULTS

1/ Clinical and metabolic parameters

mean (SEM)	T0	W48	p
Weight kg N=20	102.8 ± 4.3	100.9 ± 4.6	**0.033**
BMI kg/m² N=20	32.6 ± 1.2	31.9 ± 1.3	**0.033**
Waist to Hip ratio N=20	0.99 ± 0.02	0.97 ± 0.02	**0.047**
Total Cholesterol mmol/L N=18	4.7 ± 0.3	4.3 ± 0.3	**0.010**
HDL-Cholesterol mmol/L N=18	1.2 ± 0.1	1.1 ± 0.1	0.170
LDL-Cholesterol mmol/L N=18	2.9 ± 0.3	2.6 ± 0.2	**<0.001**
Triglycerides mmol/L N=18	1.5 ± 0.2	1.4 ± 0.1	0.601
Glycemia mmol/L N=18*	5.7 ± 0.2	5.2 ± 0.1	**0.008**
Insulinemia mU/L N=18	29.6 ± 11.1	23.5 ± 6.0	0.413
HOMA-IR N=18	7.7 ± 3.1	4.5 ± 1.3	**0.016w**

Two PWH were excluded: one became diabetic and one glucose intolerant, w: Wilcoxon test

➔ At W48 : small reduction in weight (- 2 kg) and waist-hip-ratio.
➔ Improved metabolic profile : decreased total and LDL cholesterol, decreased glycemia and insulin resistance

2/ Adipose tissue expression of master adipocyte genes

Gene expression, relative to 2 control genes , mean ± SEM N=14	T0	W48	p
PPARG	1.42 ± 0.11	1.23 ± 0.13	**0.026**
CEBPA	1.36 ± 0.12	1.50 ±0.57	0.153
SREBF1	1.41 ± 0.18	1.03 ± 0.15	**0.049**
FASN	1.36 ± 0.18	1.02 ± 0.14	0.085
VEGFA	1.27 ± 0.11	1.02 ± 0.15	0.065w

➔At W48, reduced expression of master genes involved into:
- **adipogenesis** (*PPARG* encoding PPAR-γ, *SREBF1* encoding SREBP-1c),
- **lipid synthesis** (*SREBF1*, *FASN* encoding fatty acid synthase)
- and **vascularization** (*VEGFA* encoding the vascular growth factor VEGF-A)

➔ These results strongly suggests reduced adipose tissue hypertrophy, lipid accumulation and vascularization

3/ Adipose tissue expression of other genes

Gene expression, mean ± SEM N=14	T0	W48	p
PCK1	1.61 ± 0.19	1.33 ± 0.20	0.271
IRF8	0.60 ± 0.05	0.60 ± 0.07	0.670
MMP9	2.71 ± 0.70	2.51 ± 0.46	0.773
LEPTIN	1.07 ± 0.12	0.82 ± 0.12	0.355
ADIPOQ	1.79 ± 0.14	1.64 ± 0.21	0.405
COL1A2	1.98 ± 0.32	1.85 ± 0.33	0.640
COL6A1	2.54 ± 0.23	2.41 ± 0.22	0.848
TGFB	0.74 ± 0.06	0.9 ± 0.10	0.154
CD163	1.14 ± 0.12	1.15 ± 0.19	0.957

➔At W48, the expression of genes involved in fibrosis, adipokines (leptin, adiponectin) and macrophage infiltration was not modified.

CONCLUSION

- **A 48-week switch from an INSTI-based regimen to TDF/3TC/DOR in ART-controlled PWH resulted in an improved metabolic profile and modest weight loss.**
- **This switch allowed a partial reversal of the INSTI-induced gene expression profile associated with adipocyte hypertrophy, lipid accumulation and vascularization.**
- Larger clinical pathogenesis studies are needed to better understand the underlying mechanisms of INSTI-induced weight gain and its reversibility by doravirine.

CONTACT INFORMATION

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FUNDINGS

This study was funded by MSD