



IAS 2021

Impact of ART on adipose tissue in HIV infection

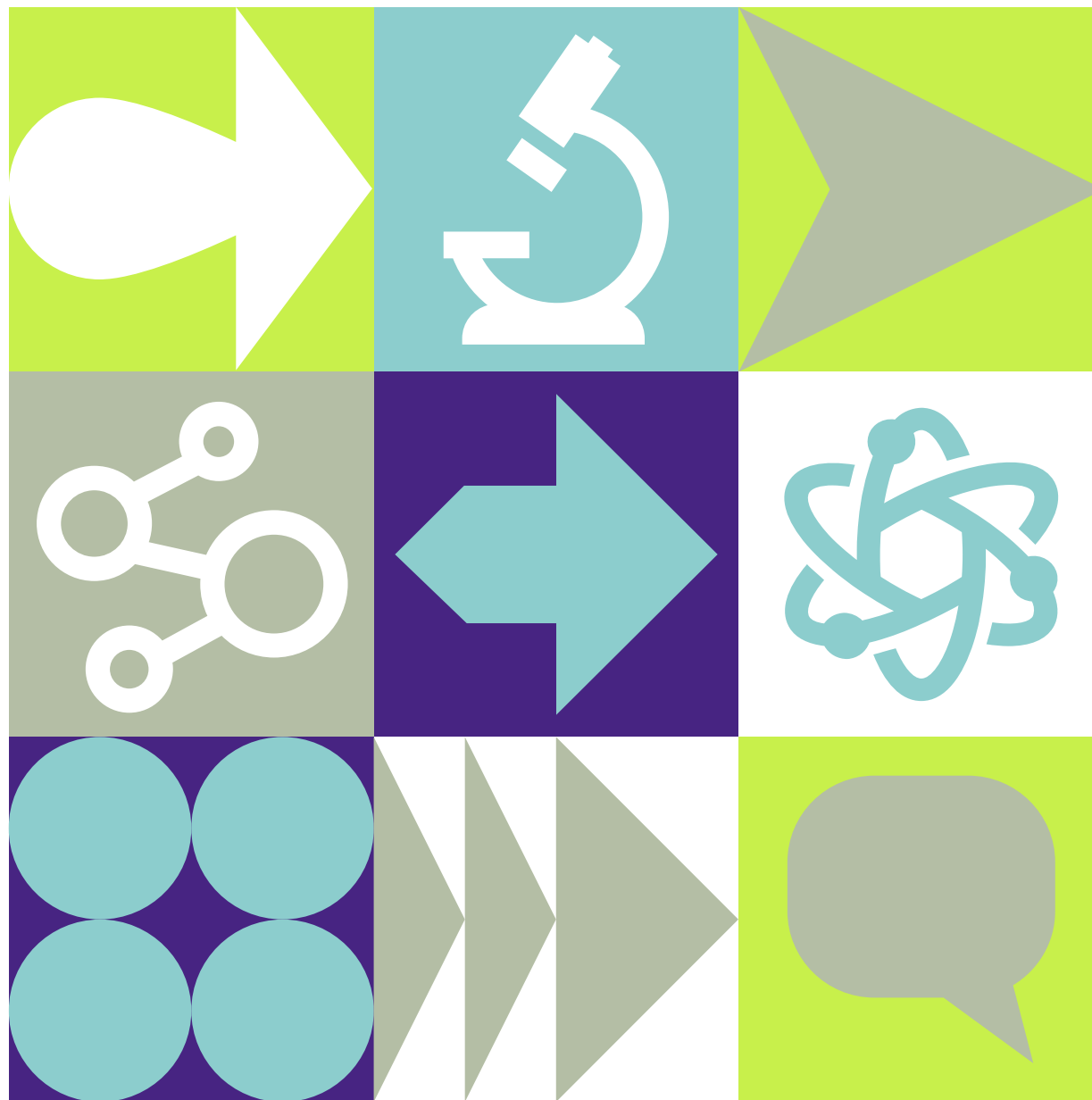
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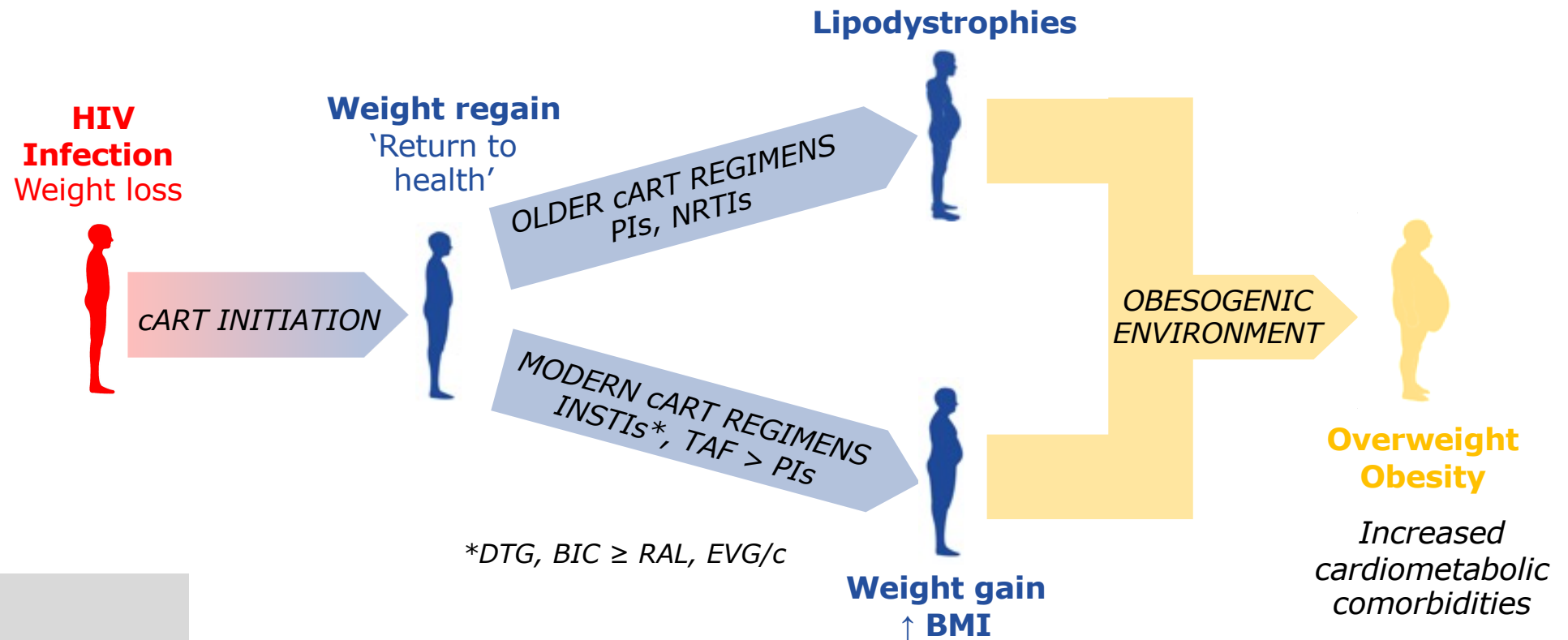
*Sorbonne Université, Inserm UMR_S938,
CRSA, ICAN*

*Lipodystrophies, Metabolic and Hormonal, & Aging
(Prof. B. fève Prof. J. Capeau)*

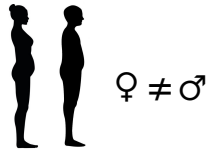
*Conflict of interest:
Personal fees for a lecture from MSD.*



Adipose tissue redistribution and gain in the context of HIV infection and ART



Adipose tissue alterations in the context of HIV infection and ART

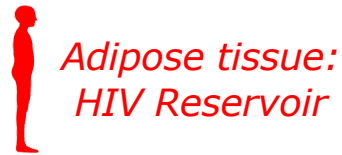


Insulin sensitivity
Storage capacity



SCAT VAT

VAT : visceral adipose tissue
SCAT: subcutaneous adipose tissue



HIV Infection

Adipose loss and redistribution?

Inflammation ++
Fibrosis ++
↓ Adipocyte size
↑ Oxidative stress

Obesogenic environment exacerbates HIV pathogenesis

T et al JCI 2019

Gorwood J *et al.* AIDS 2019
Gorwood J *et al.* Cells 2020

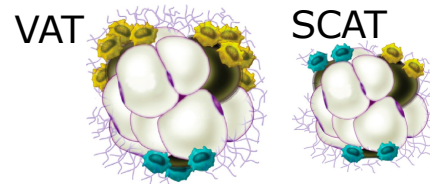


Lipodystrophy

Peripheral SCAT atrophy (NRTIs)
Trunk VAT hypertrophy (PIs)

Inflammation ++
Fibrosis +++
↑ or ↓ adipocyte size
↑ Oxidative stress
↓ mtDNA

Insulin resistance ++

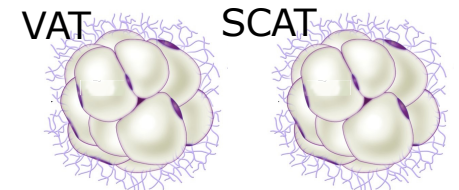


Weight gain/Obesity

Increase of both central and limb adipose tissue (INSTIs, TAF)

Inflammation ±
Fibrosis ++
Adipocyte hypertrophy

Insulin resistance ±



Koethe J *et al.* Nat Rev Dis prim 2020

Study of the impact of INSTIs on adipose tissue

In vivo
**VAT and SCAT from
 Cynomolgus macaques***
(Macaca fascicularis)



Control



**ART-treated uninfected
 TDF/FTC
 + DTG or RAL (2 weeks)**

14 macaques
 6.9±0.9 years
 7.6±0.9 kg

In vivo
**VAT and SCAT from
 Obese individuals
 undergoing bariatric
 surgery****



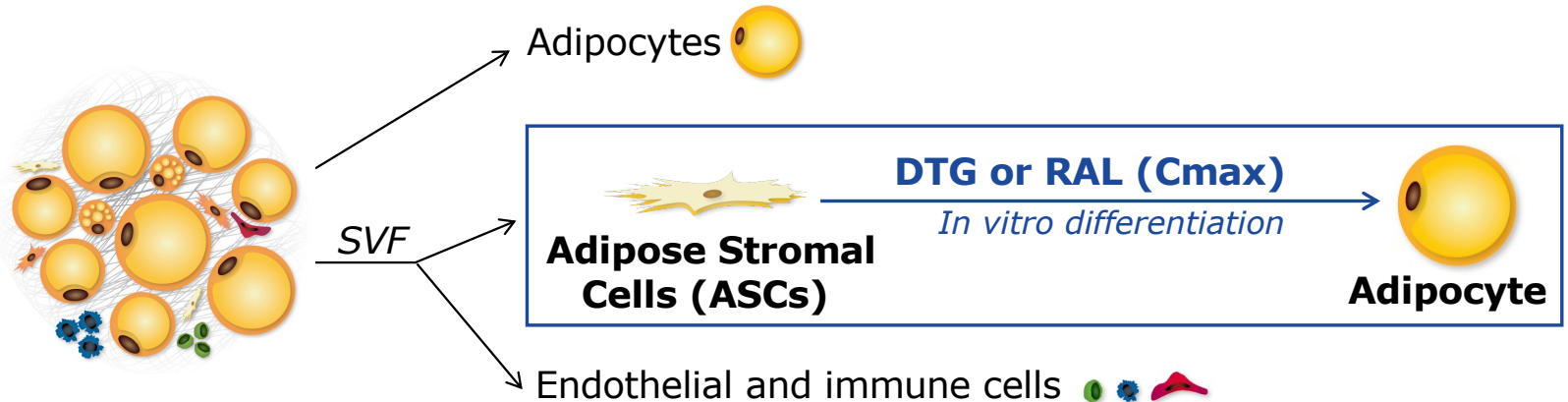
**INSTI-sparing
 regimens**



**INSTI-containing
 Regimens
 (29 months)**

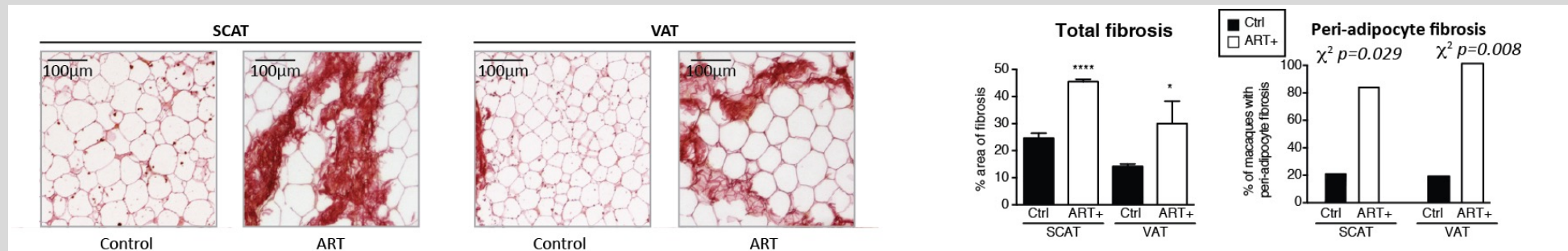
19 Patients
 Mean BMI: 41.5±1.3kg/m²
 46.9±2.0 years
 16.3±1.7 years of infection

In vitro
**Isolation of ASCs from
 Abdominal SCAT of
 Healthy donors**



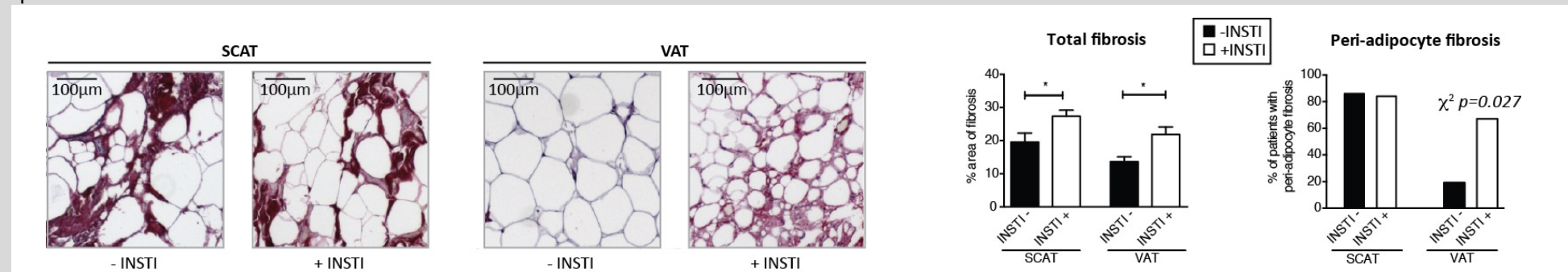
INSTI-containing regimens induce fibrosis in adipose tissue

In vivo



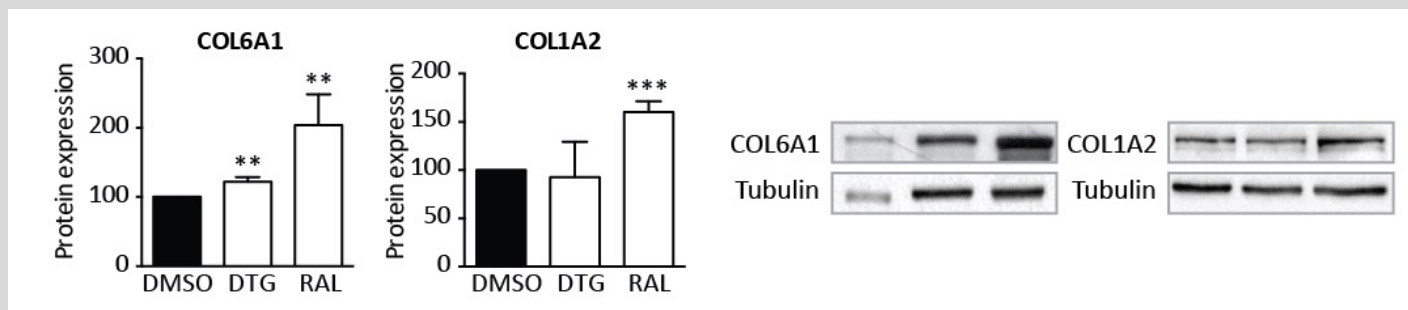
* $p < 0.05$, **** $p < 0.0001$ vs. control non-treated animals.

In vivo



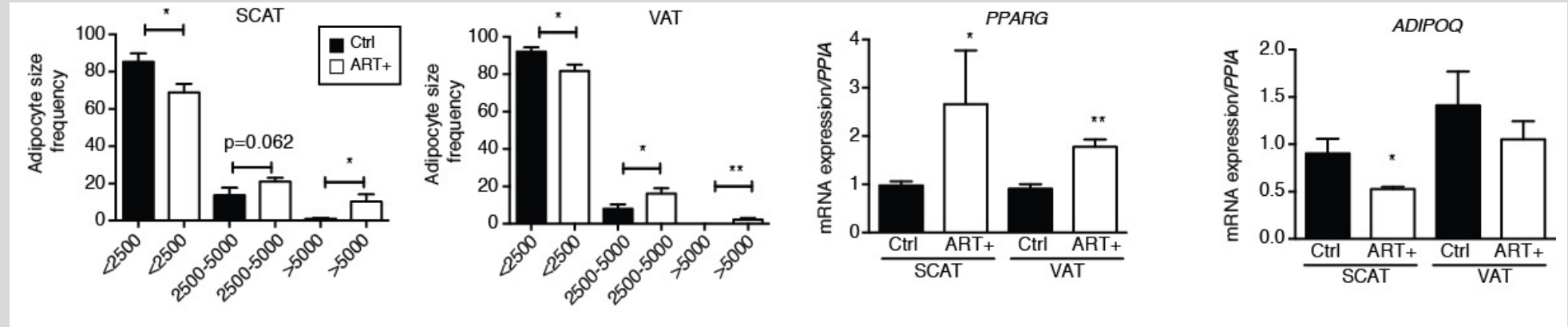
* $p < 0.05$ vs. non-INSTI-treated patients.

In vitro

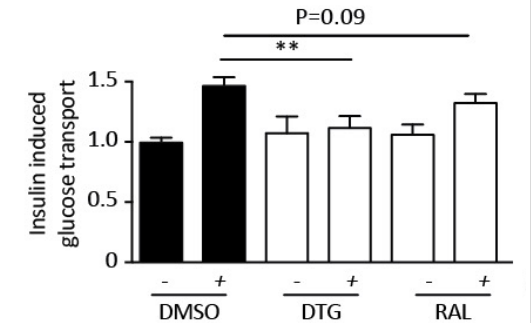
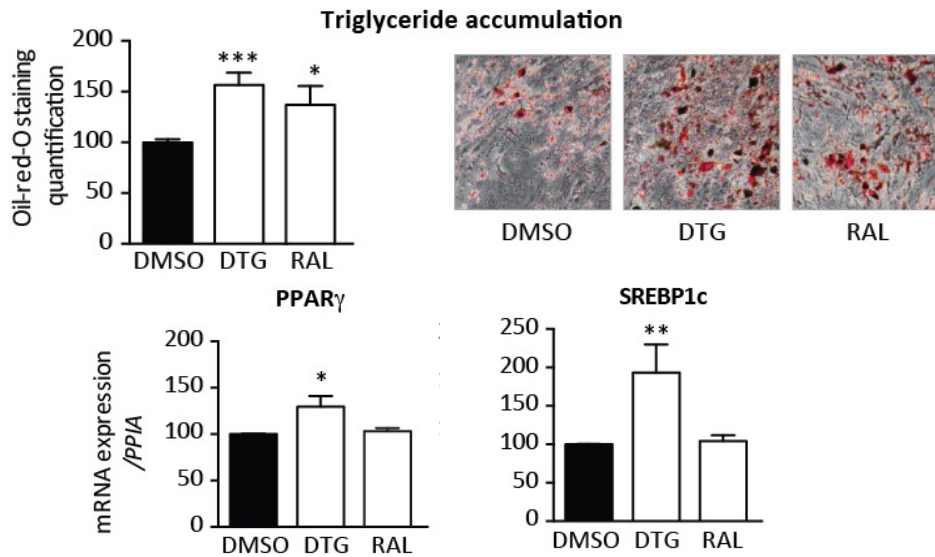


INSTI induce adipocyte hypertrophy and insulin resistance

In vivo

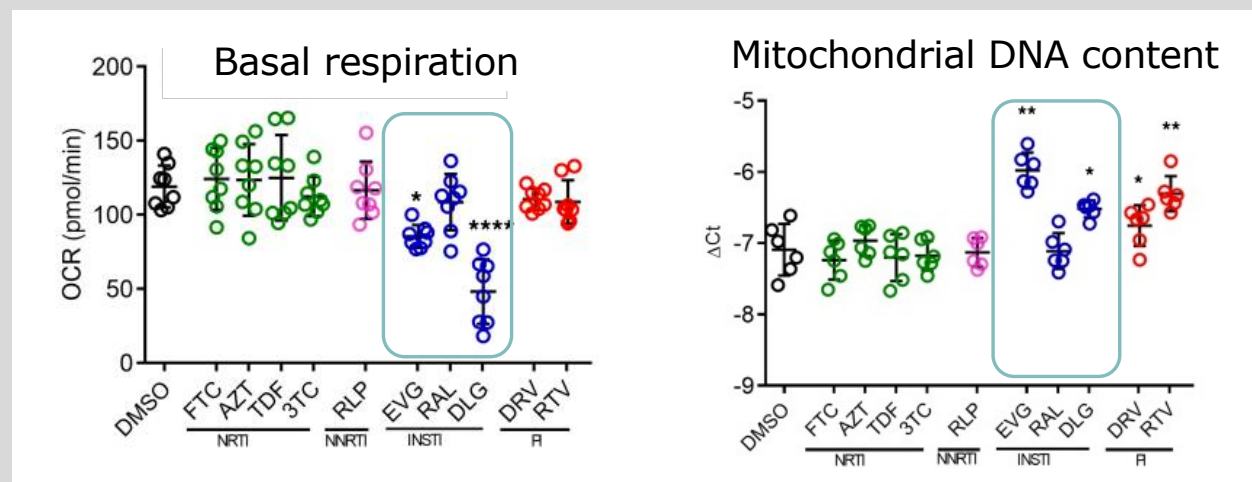


ASC-derived adipocytes



Mechanism of action of INSTI on adipose tissue: is mitochondria the target?

Effect of INSTI on Mitochondrial metabolism in immune cells



CD4 T cells exposed to ART for 3 days

Korencak M *et al.* JCI Insight 2019

Mechanism of action of INSTI on adipose tissue: Disruption of thermogenesis ?

White adipocyte

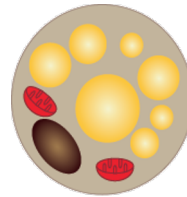
SCAT & VAT



**Storage
Mobilisation**

Beige adipocyte

VAT > SCAT

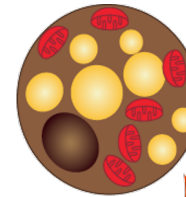


Mitochondria +++

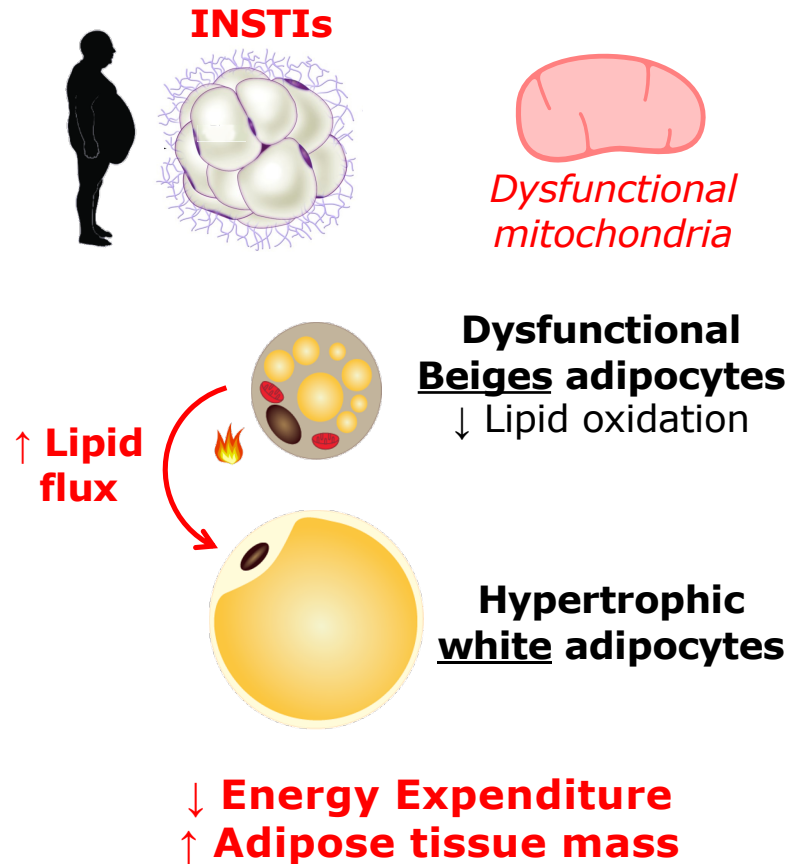
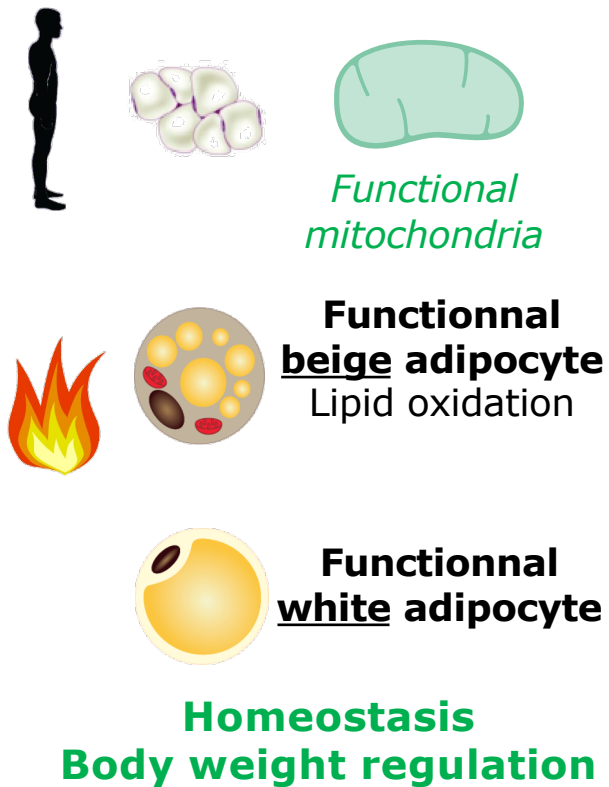
Thermogenesis (UCP1)
↑ **Energy expenditure** (↑ Lipid oxidation)

Brown adipocyte

Minor depots



Hypothesis: Loss of adipose tissue beiging/browning ? Impact on energy expenditure and weight gain



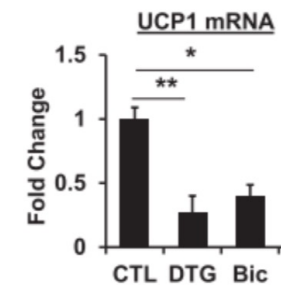
Clinical study

INSTI-containing regimens
↓ **Expression of beige markers in SCAT**

(Srinivasa I et al. JAIDS 2019)

Mice receiving INSTIs

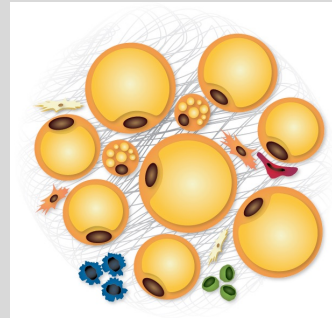
DTG & BIC enhance white & inhibit brown adipogenesis



(Jung I et al. CROI 2021)

Conclusion

Remaining questions



- 1) What is the impact of TAF on adipose tissue ?**
- 2) Are adipose tissue alterations reversible ?**

Aknowledgments



UMRS938, CRSA, ICAN

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