# Differential effects of raltegravir, dolutegravir and bictegravir on human adipocytes

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## Background

Recent data have raised concerns about weight gain associated with the use of **integrase strand transfer inhibitors (INsTI)** [1-3]**.** The pathophysiological basis of this effect is unknown.

The **goal of our study** was to assess the potential direct effects of raltegravir (RAL), dolutegravir (DTG), and bictegravir (BIC) on human adipose cells.

## Methods

Human Simpson Golabi Behmel Syndrome (SGBS) adipose cells were used and cultured using standard procedures. In controls, sub-optimal differentiation was achieved with the use of 0.5 µM rosiglitazone at the time of differentiation induction. Drugs were included in the differentiation medium at concentrations ranging from 0.1 to 10 µM (which includes $C_{min}$ and $C_{max}$ in treated patients.

Morphological adipogenesis (accumulation of lipid droplets) was followed.

Gene expression for markers of adipogenesis, adipocyte metabolism, adipokines, and cytokines was determined using qRT-PCR twelve days after induction of differentiation.

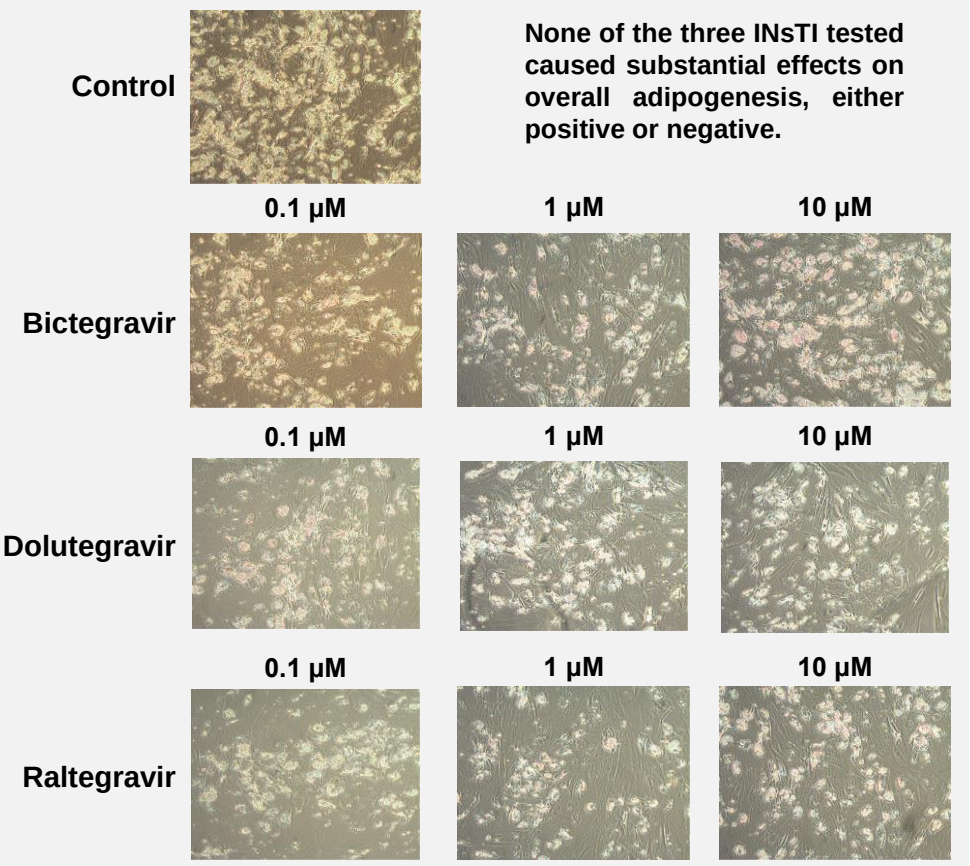
## Results

- Morphological differentiation of human adipose cells in culture was unaffected by the presence of BIC, DTG or RAL (Fig.1).
- Expression of marker genes of adipogenesis, such as glucose transporter GLUT4 (Fig.2a), lipoprotein lipase (Fig.2b), and also the adipokine leptin (Fig.2c), were unaltered.
- Expression of inflammation-related cytokines (IL-6, MCP-1) was not induced by INsTIs (Fig.2e and 2f), and even significantly decreased at 10 µM by BIC and DTG (only MCP-1).
- Both RAL and DTG lowered adiponectin gene expression in a dose-dependent manner (Fig.2d).
- Maximal inhibition noted at 10 µM (~ 60% and 40% inhibition for RAL and DTG, respectively), relative to expression in controls. In contrast, BIC did not show such an effect (Fig.2d).

## Conclusions

- INsTI did not cause large effects on human adipose cell differentiation (Fig.1; Fig.2a;2b;2c).
- BIC and DTG, but not RAL, reduced gene expression of pro-inflammatory cytokines (Fig.2e and 2f).
- RAL and DTG, but not BIC, reduced adiponectin gene expression (Fig.2d).
- Further studies are necessary to ascertain the pathophysiological relevance of these findings with respect to the effects of INSTI-containing treatments on body weight and metabolism in people living with HIV.

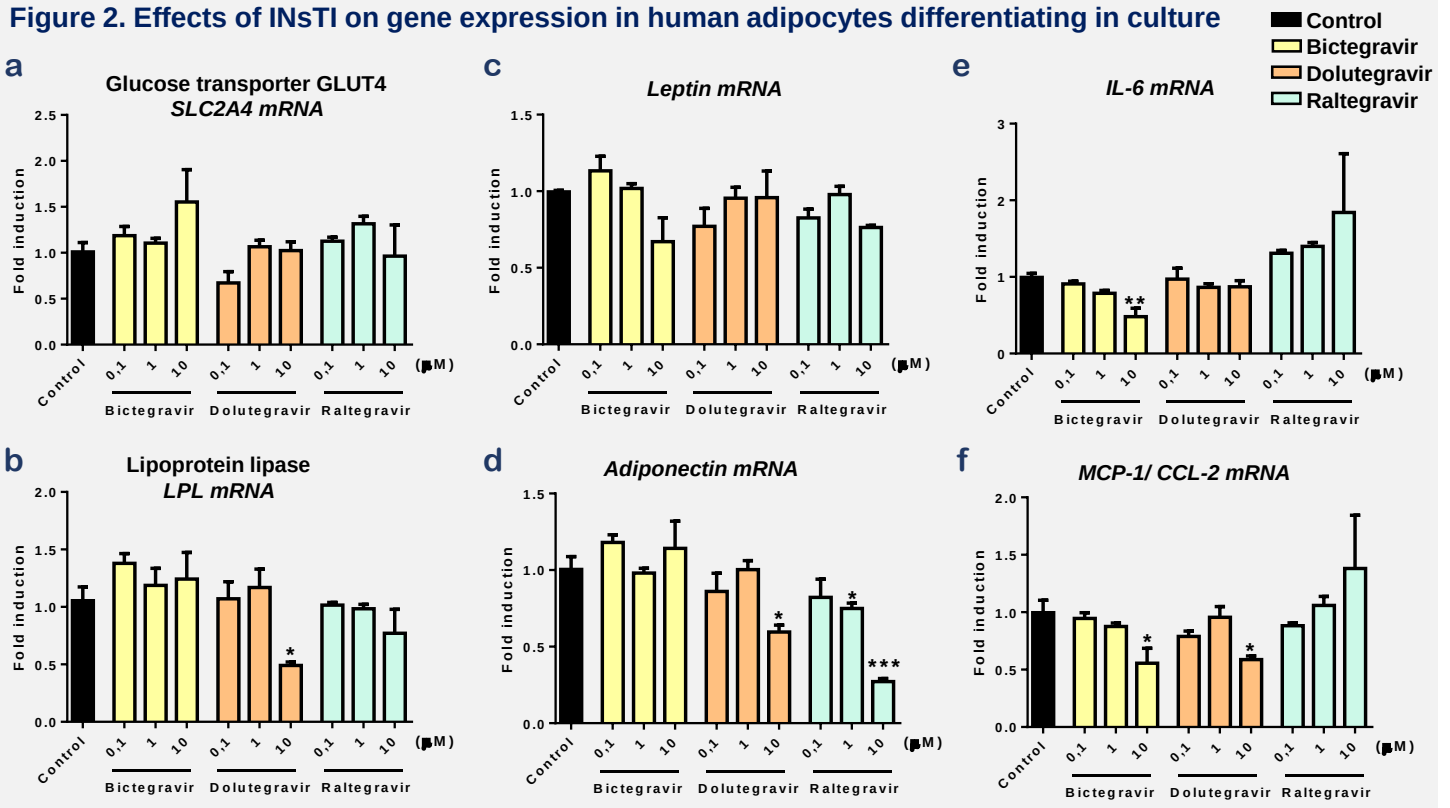
### Figure 1. Effects of INsTI on human adipose cell differentiation




**None of the three INsTI tested caused substantial effects on overall adipogenesis, either positive or negative.**

*Representative photomicrographs from three experiments of adipocyte cell cultures differentiating in the presence of the indicated concentrations of drugs.*

### Figure 2. Effects of INsTI on gene expression in human adipocytes differentiating in culture




*Data (means ± SEM) from three experiments, and expressed relative to values from untreated control cells. *P < 0.05 vs. control.*

## References

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