**Viral replication capacity influences HIV-1-induced metabolic and cytokine reprogramming of T Cells**

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**Background:** High replicative capacity (RC) HIV-1 strains are associated with higher viral loads and faster disease progression in the absence of antiretroviral therapy. Understanding the mechanisms by which high RC strains impact the host is crucial for developing novel HIV interventions. This study explores cellular metabolism, cytokine induction, and cell-to-cell spread as mechanisms underlying the differential clinical outcomes between high and low RC HIV-1 strains.

**Materials & Methods:** We generated chimeric viruses by inserting patient-derived *gag-protease* regions from HIV-1 subtypes B and C into the NL4-3 backbone. Viral RC was measured using a GFP-reporter T-cell line assay. Cytokine production was quantified using Luminex assays, while flow cytometry detection of p24 determined virus cell-to-cell spread efficiency. T-cell metabolism and mitochondrial function were evaluated via nutrient uptake assays, glutamine/glutamate bioluminescent assays and mitotracker dye detection.

**Results:** Subtype C chimeric viruses exhibited significantly lower RC than subtype B viruses (p=0.0008). Cytokine profiling in T cells revealed distinct signatures for low RC subtype C viruses, including higher TNF-α, and IL-8 levels. Viral RC negatively correlated with TNF-α, IL-8, and IL-13 induction, but positively correlated with PDGF-bb, IL-7, MCP-1, FGF-basic levels, cell-to-cell spread efficiency (p=0.008, r=0.5) and cellular glucose uptake (p=0.02, r=0.5). A significant negative correlation between RC and glutamine levels (p=0.001, r=-0.7) indicated an association with nutrient utilization. In addition, mitochondrial depolarization was notably higher in subtype B infections than in subtype C (p=0.0008).

**Conclusions:** High replicative capacity (RC) HIV-1 strains trigger unique cellular responses, altering metabolism and cytokine profiles to accelerate disease progression. These findings underscore the importance of developing therapeutic strategies targeting the distinct cellular reprogramming induced by high RC strains to mitigate HIV-1 pathogenesis.