**Maraviroc (MVC) intensification can activate NFkB through CCR5 and the expression of its target genes in resting CD4$^+$-T-cells in suppressed HIV-1-infected patients**

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**Background:** Activation of CCR5 intracellular signaling pathways leading to transcription factors activation could promote HIV-1 transcription in resting CD4$^+$-T-cells. In previous experiments, we showed the activation of NFkB and specific target genes in resting CD4$^+$-T-cells cells from naïve patients with HIV-1 RNA>1,000 copies/mL who received 10 days of maraviroc (MVC) monotherapy in a clinical trial (TROPISMVC, NCT01060618). The present clinical trial aims to explore if MVC could trigger this effect in suppressed HIV-1-infected patients.

**Methods:** MARAVITRANS (Eudra CT: 2012-003215-66) is a clinical trial of 10 days MVC intensification. Blood samples were drawn at baseline, after 10 days of MVC and 18 days after MVC withdrawal. From 10 patients, activated and resting CD4$^+$-T-cells were separated by magnetic beads coupled to monoclonal antibodies (MACS® Technology) and aliquots of 5 million cells were frozen. NFkB and NFAT activity were detected by an ELISA-based kit consisting of plates coated with oligonucleotides mimicking consensus binding sites specific for each transcription factor (TransAM™ NFkB family and TransAM™ NFATc1, Actif Motif), following the manufacturer's instructions. NFkB activity was estimated measuring target genes' expression by real-time PCR of the extracted RNA.

| Patient | NF-κB Activity (FC) | | | |
|---|---|---|---|---|
| | Activated CD4+-T-cells | | Resting CD4+-T-cells | |
| | Day 10 (on MVC) | Day 28 (off MVC) | Day 10 (on MVC) | Day 28 (off MVC) |
| 1 | 2.32 | 1.8 | 0.88 | 1.07 |
| 2 | 0.3 | 0.4 | 0.4 | 0.5 |
| 3 | 1.4 | 1.4 | 0.5 | 0.7 |
| 4 | 0.8 | 1.3 | 1.3 | 0.9 |
| 5 | 0.5 | 15.4 | 3.5 | 20.1 |
| 6 | 0.5 | 1.3 | 4.3 | 2.4 |
| 7 | 1 | 0.7 | 1.8 | 1 |
| 8 | 1 | 0.1 | 2.4 | 2.2 |
| 9 | 1.17 | 0.8 | 1.8 | 1 |
| 10 | 1.45 | 0.95 | 1.36 | 1.29 |

*[Table 1]*

**Results:** NFkB activity was detected in resting CD4$^+$-T-cells in 6/10 patients; results expressed in fold change (FC) compared to baseline. The presence of MVC increased NFkB activity in resting CD4$^+$-T-cells, as summarized in the following table.

Upregulation of at least one NFkB targeted gene (IFN-g, IL-6, IL-10, TNF-a) was observed in cases where NFkB activity was detected. In case of NFAT, no significant activity was documented.

**Conclusion:** Our results suggest that MVC activates NFkB, and the subsequent expression of targeted genes, in resting $CD4^+$-T-cells from suppressed HIV-1-infected patients, as previously observed in treatment-naïve ones. Through this pathway, MVC could trigger HIV-1 transcription in resting cells thus accelerating the decay of the HIV-1 cell reservoir.