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Protective HLA alleles fail to predict immune control of HIV after ART interruption in chronically infected patients with low HIV-DNA from the ULTRASTOP Study

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Background: In an effort to further understand the determinants influencing HIV remission in chronically-infected patients, we investigated the impact of HLA background and HIV-specific T-cell responses on viral control after ART-interruption in the ULTRASTOP study.

Methods: The Ultrastop study consisted in treatment interruption in ten chronically-infected patients enrolled with median 5.3 years ART, undetectable pVL< 1cp/ml, HIV-DNA < 66 cp/106 PBMC and 1,118 CD4/mm3. ART was resumed if pVL>400 cp/mL, CD4< 400/mm3 or HIV-related clinical event monitored at W2, W4 and every 4 weeks off-ART, and W4, W12 and W24 after ART-resumption (RxR). HLA-class-I genotyping was performed and HIV-specific CD8 T cells were evaluated by IFNγ-ELISpot at D0, RxR and W24 post-RxR with 15-mers HIV-Gag, Nef and RT or optimal peptides covering the HLA-B*27 and B*57 epitopes

Results: Five of the ten enrolled patients were HLA-B*27+ and/or B*57+ (3B*27, 1B*57 and 1B*27/57) and three were HLA-B*35+. Nine patients lost viral control between W2-W12 while only one post-treatment controller (PTC) (HLA-B*27) controlled viremia up to W48. All HIV-specific CD8-T-cell responses were weak at D0 (median 95 SFC/106 PBMC). The CD8-T-cells directed against the HLA-B*27 restricted KK-10 epitope were detectable at baseline in only two B*27 non-controllers (180 & 735 SFC/106 PBMC) and strongly boosted after virus relapse (1800 & 4500 SFC/106 PBMC), though unable to control viremia. Responses against KK10-epitope mutants were also boosted suggesting viral escape. In contrast KK10-responses were undetectable at D0 in the HLA-B*27+ PTC but boosted at W24 and W48 (215 and 800 SFC/106 PBMC) together with a modest increase in HIV-RNA. The HLA-B*57 restricted CD8-T-cells were undetectable at baseline in the 2 HLA-B*57+ patients who relapsed. Boosted responses persisted 12W following RxR while the increased pVL and HIV-DNA levels observed during ART-interruption returned to baseline values.

Conclusions: Despite protective HLA-alleles and low reservoirs in HIV chronically treated patients, modest HLA-B*27-restricted HIV-specific T-cells and lack of HLA-B*57-restricted ones were associated to viral rebound after ART-interruption in all but one patients. Our results suggest that protective HLA-alleles in treated patients with low HIV reservoirs fail at conferring immune control of the virus after ARV-cessation, thus providing rationale for additional immune interventions.