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Immunological alterations with GLP-1 receptor agonists in people living with HIV

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Background: Glucagon-like peptide 1 (GLP-1) receptor agonists (RA) are direct incretin mimetics and have become an important therapeutic option in the management of obesity. While a decrease of $CD4^+$ cells, a subset of T-lymphocytes, has been demonstrated in indirect incretin mimetics such as dipeptidyl peptidase IV (DPP-4) inhibitors[1], data on potential effects of GLP-1 RA on $CD4^+$ cells is lacking.

Objective: To investigate potential changes in circulating $CD4^+$ and $CD8^+$ cells in people with HIV (PWH) with obesity and/or typ 2 diabetes mellitus (T2D) who had initiated GLP-1 RA treatment.

Methods and Findings: This retrospective, longitudinal analysis used repeated measurements for $CD4^+$ and $CD8^+$ cells in PWH, within 56 weeks before and after initiation of dulaglutide or semaglutide once-weekly. Data was obtained from clinical routine in two large outpatient HIV centers. Analysis was restricted to subjects with stable viral suppression (< 50 copies/mL) and without evidence of malignant disease or exposure to immunosuppressive drugs during the observation period. Only patients with at least one determination during GLP-1 RA treatment were included. A sample size of 67 was calculated to detect the previously described decrease in CD4 cells of 100 cells/µL based on the pooled standard deviation for the change from baseline as found in the DPP-4 inhibitor study[1].

Overall, data from 70 subjects (semaglutide n=37, dulaglutide n=33) were analyzed, comprising 534 visits. Most subjects were male (84.3%), of caucasian ethnicity (90.0%) and in the age group of 50-59 years (44%). A diagnosis of T2D was present in 55.7%. Median absolute and relative CD4 T-cell nadir counts were 303 cells/µl (interquartile range, IQR, 189-421) and 20% (IQR, 14-26%), respectively. To analyze the effect of GLP-1 RA treatment on circulating $CD4^+$ and $CD8^+$ cells, mixed-model quantile regressions for the median of the distribution of the cell concentrations was fit. As a result of exploratory data analysis the preliminary main- and random-effects-structures were chosen to contain time and GLP-1 RA treatment as fixed effects, as well as random intercepts and random time effects. Extended models after adding T2D status and GLP-1 RA dosing were tested against the preliminary model using likelihood-ratio-tests; reduced models after eliminating the random time effect were tested against the preliminary model using modified likelihood-ratio tests for variance components. Following these tests, the preliminary models turned out to also be the final models. One-sided confidence intervals for the GLP-1 RA effect on $CD4^+$ cells were obtained by parametric bootstrapping.

For $CD4^+$ cells, there was no significant time effect (0.74 [-11.63; 13.10]), but a significant effect of GLP-1 RA treatment (-59.12 [-183.94; -5.31], one-sided). For $CD8^+$ cells, there was neither a significant effect of time (0.89 [-10.37; 12.15]), nor of GLP-1 RA treatment (-55.94 [-169.94; 58.05]). $CD4^+$ and $CD8^+$ cells alterations over time are displayed in **Figure 1**. Of note, in both models, there were neither

significant interactions between time and GLP-1 RA treatment status, nor significant effects for the GLP-1 RA dosing or diabetes status. We did not find significant differences with regard to the type of GLP-1 RA used, diabetes status, current or nadir CD4 cells as well as gender, age or ethnicity.

Discussion: For this explorative study, we took advantage of a large group of PWH with obesity and/or T2D in whom immune status is measured frequently in clinical routine care. Our data suggest a negative effect of GLP-1 RA treatment on circulating $CD4^+$ cells in PWH in a non-time-dependent manner and are therefore in line with previous findings in DPP-4 inhibitors as well as experimental findings of potential interactions of GLP-1 with T-lymphocytes[1–3].

The true effect of GLP-1 RA might have been diluted due to a shortage of GLP-1 RAs, potentially leading to unvoluntary pauses prior to the routine blood withdrawals and this might not have been fully captured due to the retrospective study design. As not all subjects seem to be affected equally, reproduction of our findings and identification of potential risk factors in larger study samples are warranted. Consequently, given the anticipated long-term use of GLP-1 RA in broad populations world-wide and beyond HIV, we strongly encourage further research to assess potential pathomechanisms and clinical implications of immune alterations during GLP-1 RA treatments.

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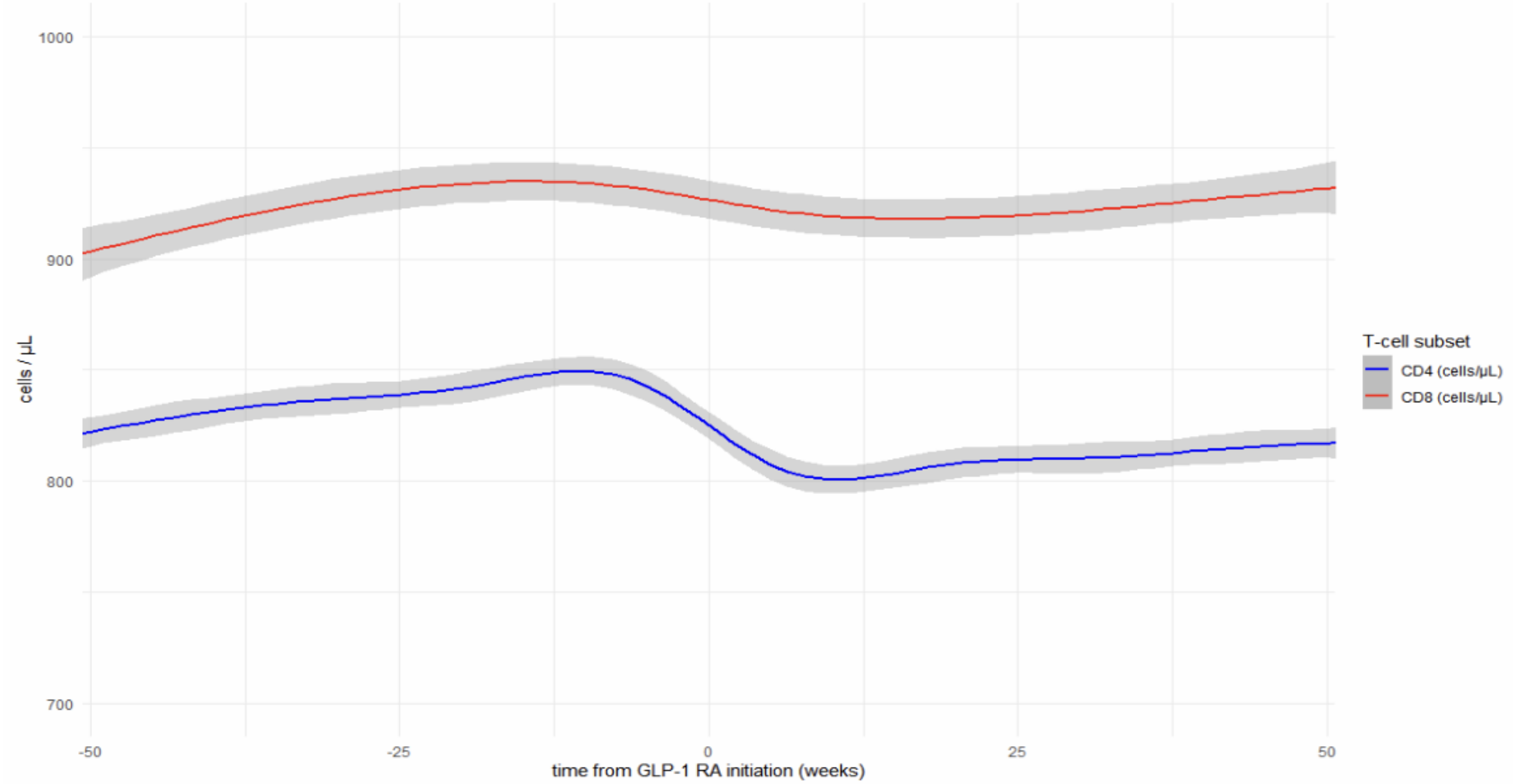

Figure 1: Models for the development of the median of the distributions of CD4+ and CD8+ cells with 95% confidence intervals (grey ribbons) over time in people with HIV, before and after initiation of GLP-1 RA treatment at timepoint '0'. Of note, the beginning decrease of CD4+ cells prior to initiation of GLP-1 RA treatment is an artefact, resulting from LOESS smoothing for the medians at each time point, obtained from parametric bootstrapping at each week, while the model predicts the decrease only after initiation of GLP-1 RA treatment.