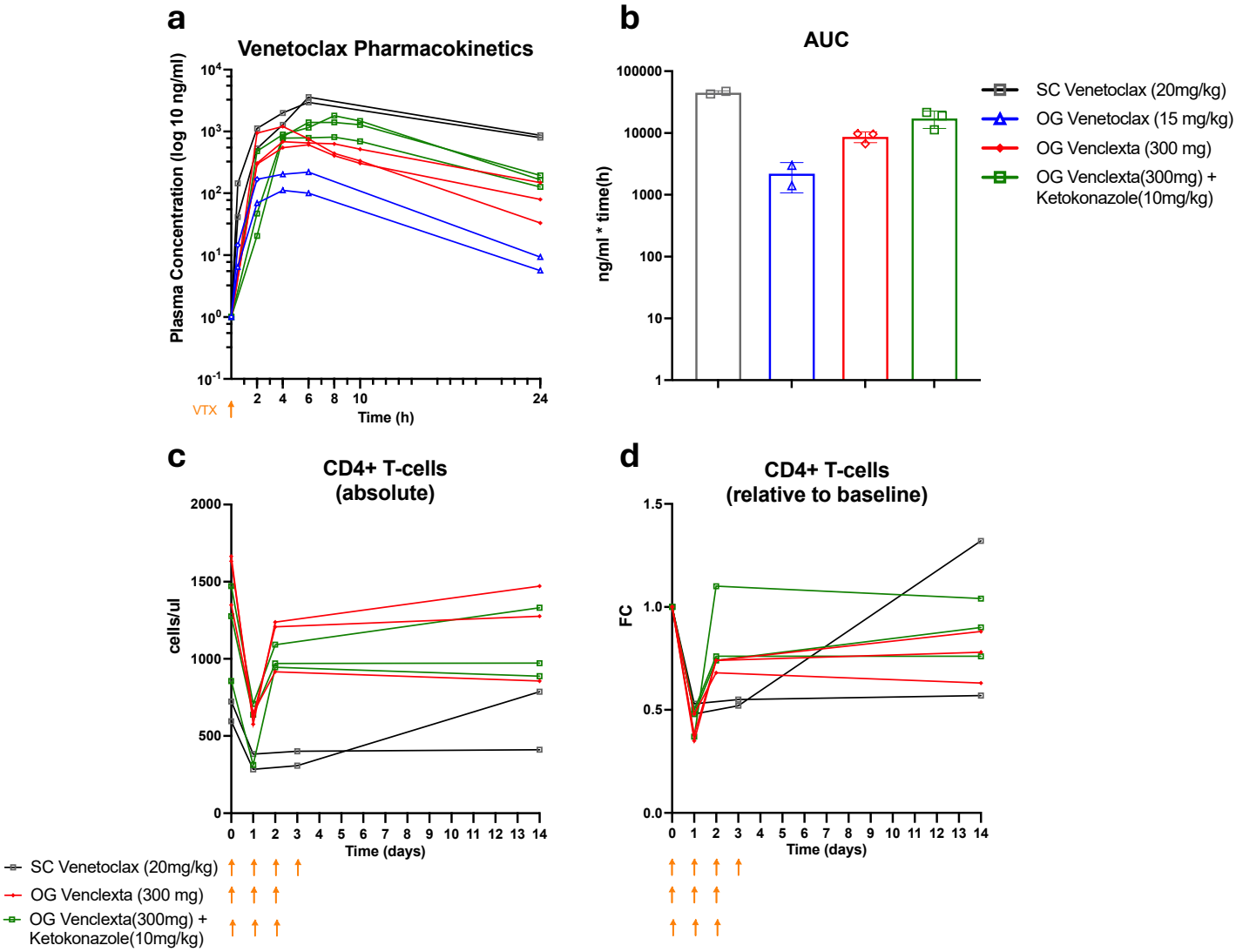
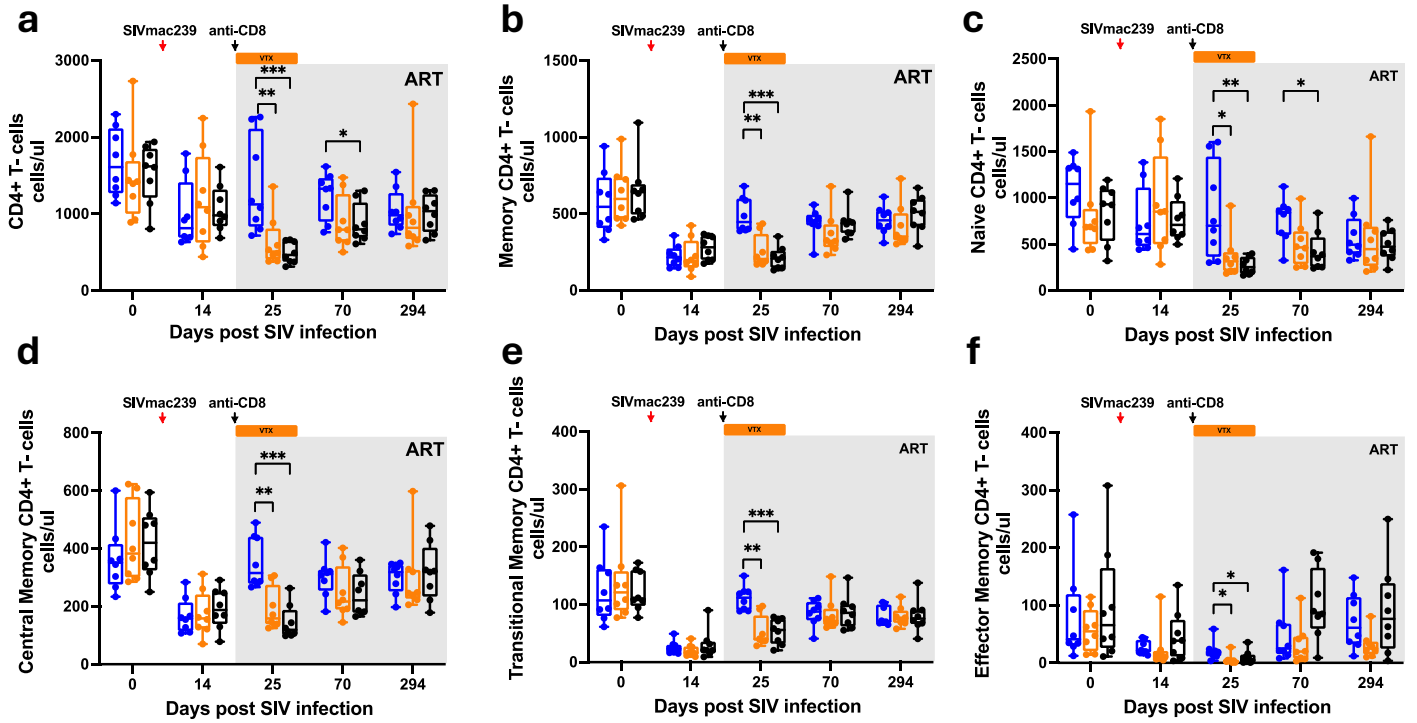
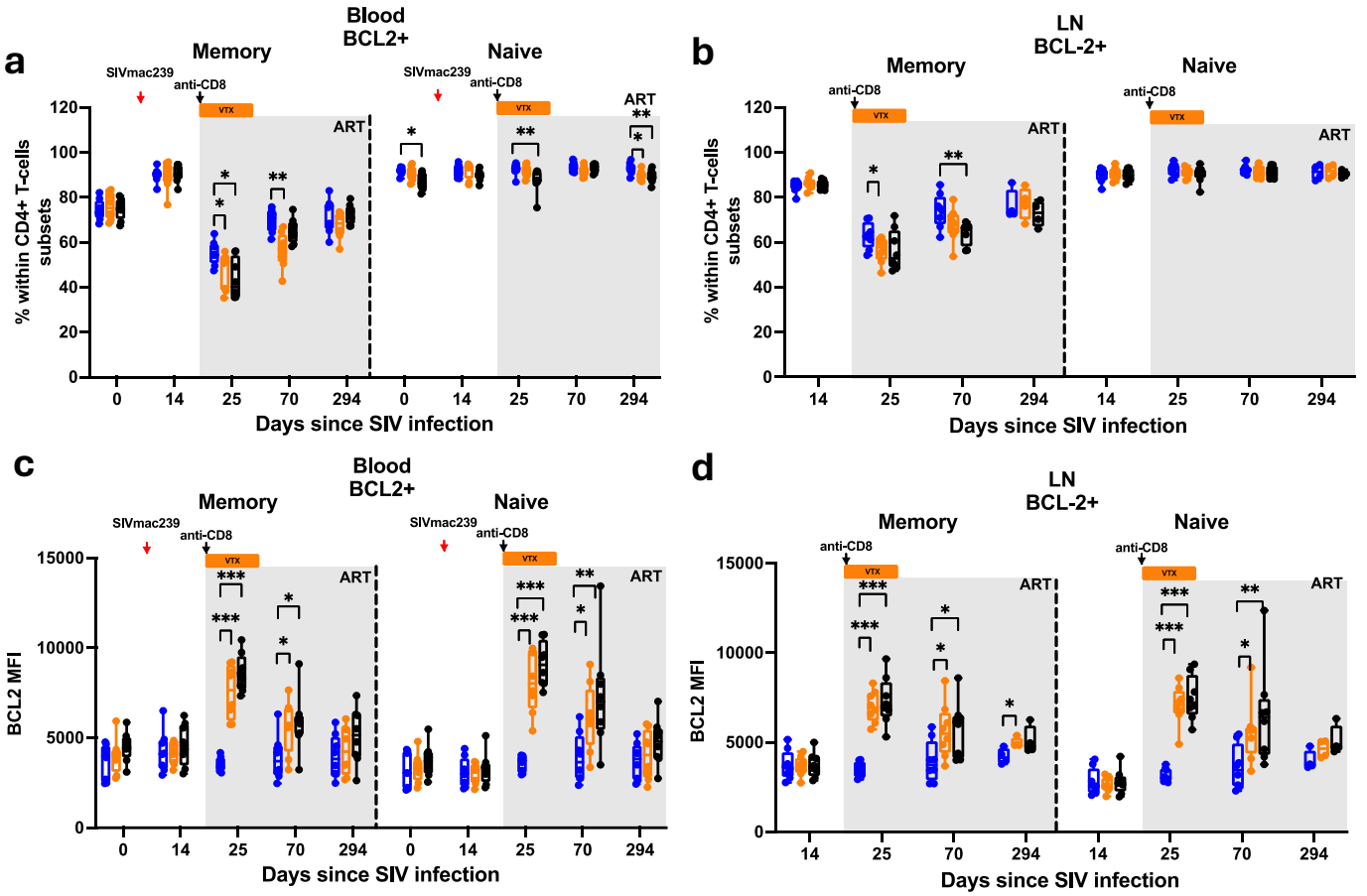


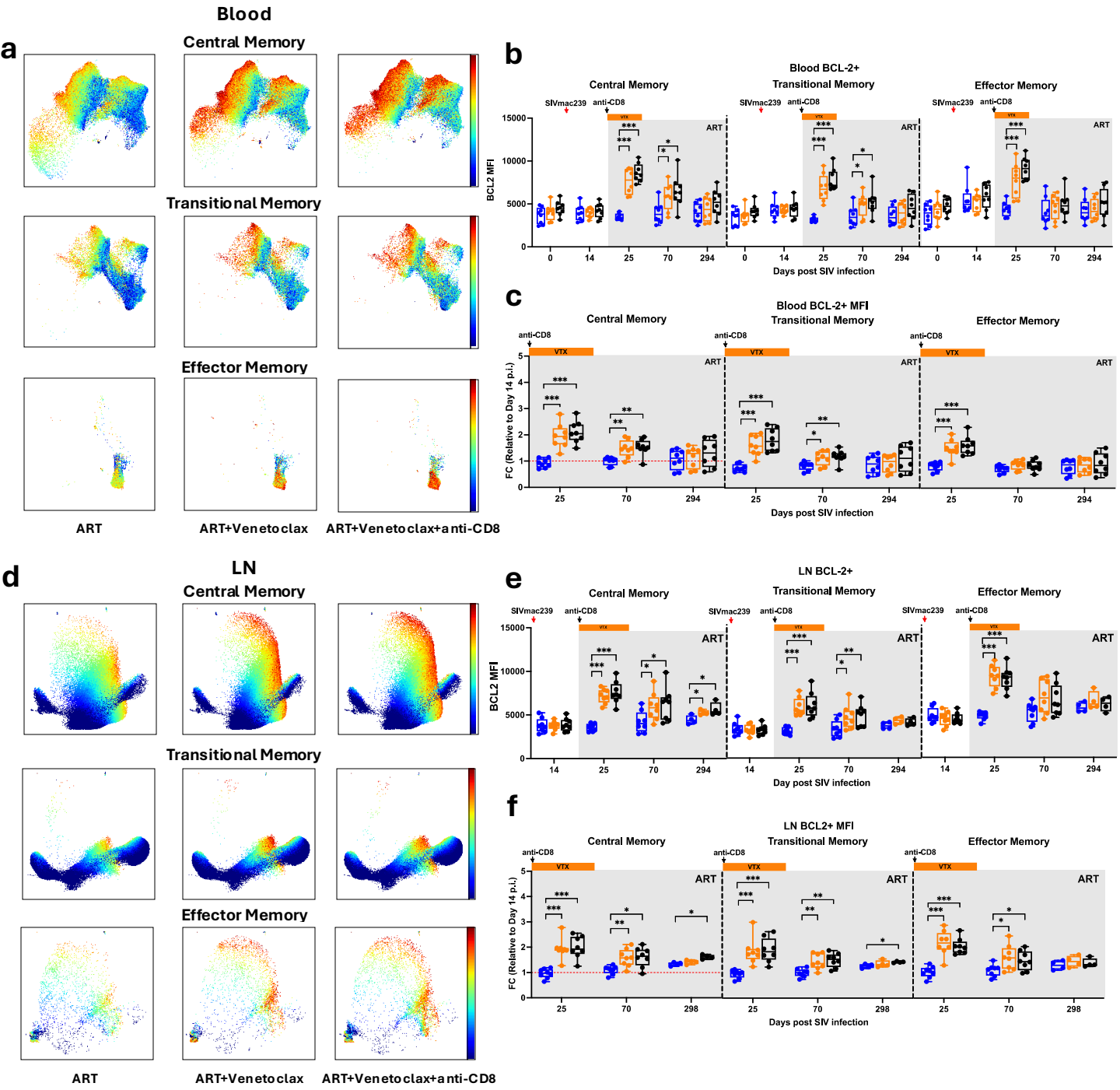
Supplementary Fig.1. Pharmacokinetics and immunological impact of venetoclax administered via different routes and formulations in SIV-uninfected RMs. a, b, Pharmacokinetic profiles of venetoclax**.** Plasma venetoclax concentrations were measured at 2, 4, 6, 8, 10, and 24 hours after administration via subcutaneous injection (20 mg/kg), oral gavage (15 mg/kg), 300 mg Venclexta tablets, or 300 mg Venclexta tablets combined with the CYP3A inhibitor ketoconazole (10 mg/kg) (a). Area under the curve (AUC) of plasma venetoclax concentration (ng/ml × time) for each treatment condition(b). c, d, Immunological impact of venetoclax. Absolute $CD4^+$ T cells counts measured at baseline and at 1, 2, and 3 days post-administration in blood(c). Fold change of $CD4^+$ T cells counts relative to baseline (d). RMs are grouped by treatment arm, with population sizes indicated for all analyses: subcutaneous (n = 2), gray; oral gavage (n = 2), blue; Venclexta 300 mg (n = 3), red; Venclexta 300 mg + ketoconazole (n = 3), green.



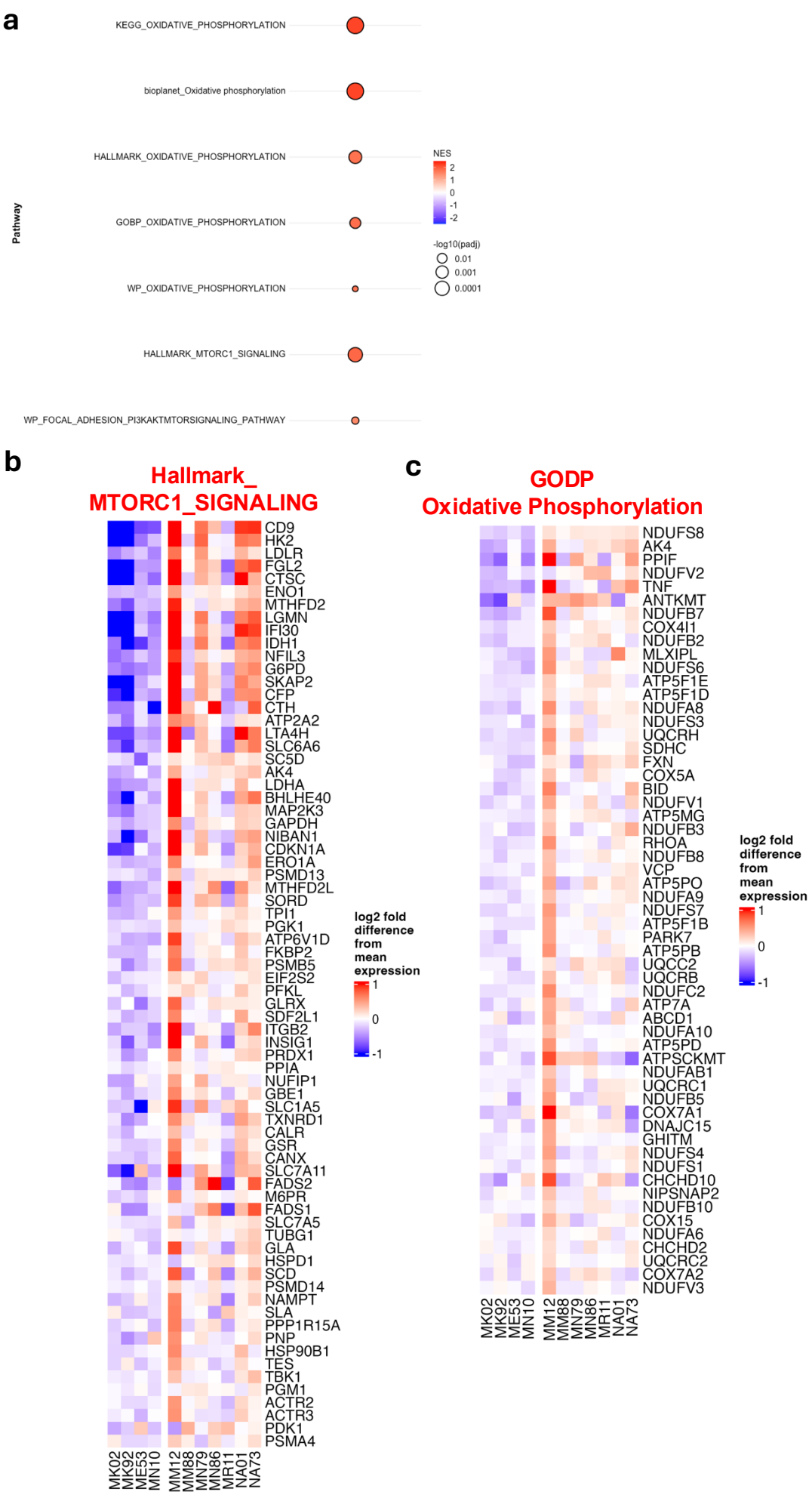
Supplementary Fig 2. Effect of venetoclax on CD4+ T cells subsets in blood. a–f, Absolute counts of $CD4^+$ T cells in blood, including total (a), memory (b), naïve (c), central memory (d), transitional memory (e), and effector memory (f) $CD4^+$ T cells. RMs are color-coded and grouped according to treatment arm: vehicle (n = 8), blue; venetoclax (n = 8), orange; venetoclax + anti-CD8 (n = 8), black. All data are presented as median ± 25th and 75th percentile and were analyzed using a two-sided Mann–Whitney U test. *P ≤ 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.



Supplementary Fig. 3. Frequency of BCL-2$^+$ CD4$^+$ T cells and quantification of BCL-2 MFI in blood and LNs after venetoclax treatment. a, b, Frequency of BCL-2$^+$ cells within memory and naïve CD4$^+$ T cells in blood (a) and LNs (b). c, d, BCL-2 MFI in BCL-2$^+$ memory and naïve CD4$^+$ T cells in blood (c) and LNs (d). RMs color-coded by treatment: vehicle (n = 8), blue; venetoclax (n = 8), orange; venetoclax + anti-CD8 (n = 8), black. All data are presented as median ± 25th and 75th percentile and were analyzed using a two-sided Mann–Whitney U test. *P ≤ 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

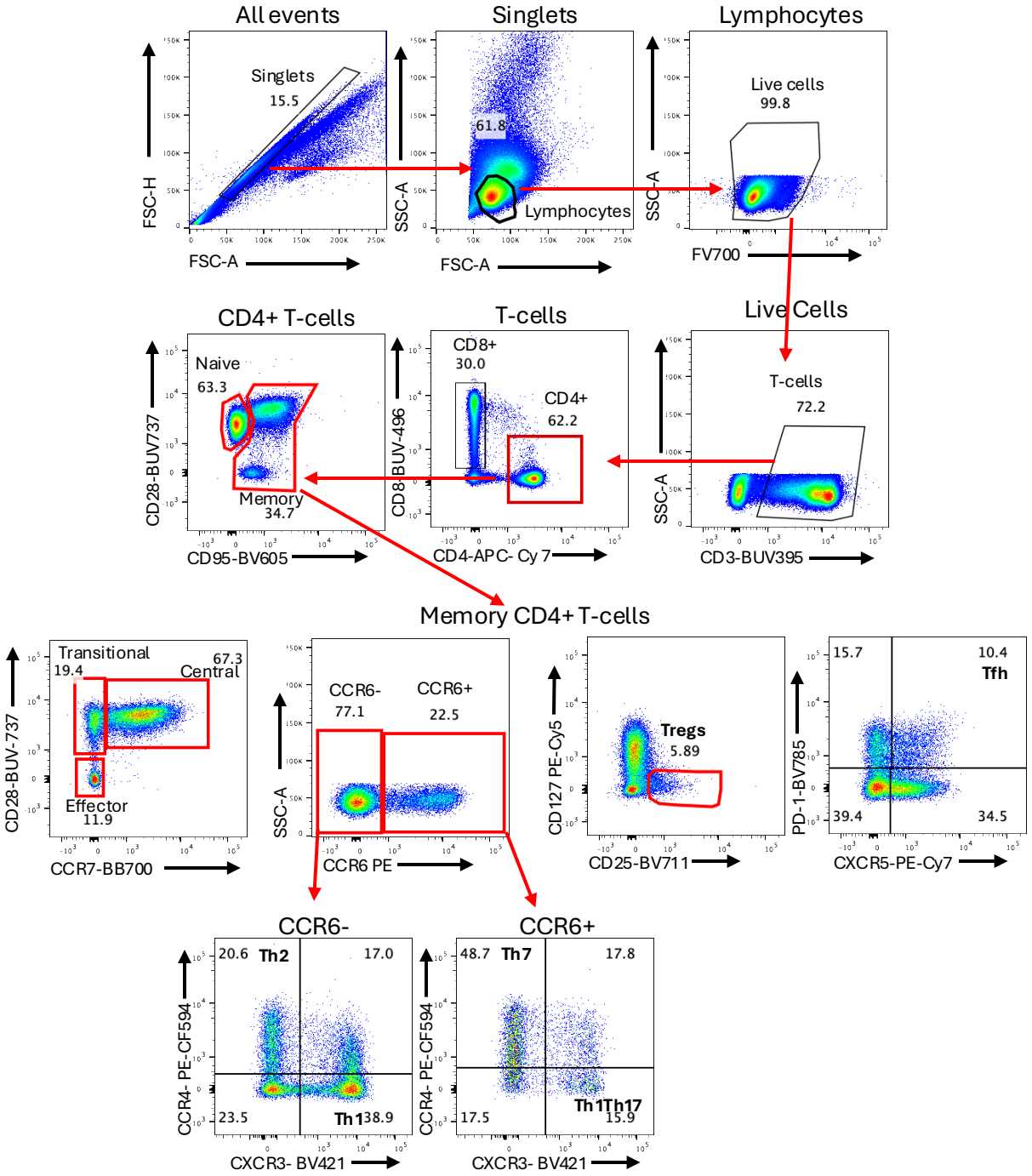


Supplementary Fig. 4. BCL-2 expression in memory CD4⁺ T-cells subsets in blood and LNs after venetoclax treatment. a, d, UMAP visualization showing BCL-2 expression patterns in T_{CM}, T_{TM}, and T_{EM} $CD4^+$ T cells in blood (a) and LNs (d) of vehicle, venetoclax, and venetoclax + anti-CD8-treated RMs. b, e, BCL-2 MFI in T_{CM}, T_{TM}, and T_{EM} $CD4^+$ T cells in blood (b) and LNs (e). c, f, FC of BCL-2 MFI relative to day 14 p.i. in T_{CM}, T_{TM}, and T_{EM} $CD4^+$ T cells in blood (c) and LNs (f). RMs color-coded by treatment: vehicle (n = 8), blue; venetoclax (n = 8), orange; venetoclax + anti-CD8 (n = 8), black. All data are presented as median ± 25^{th} and 75^{th} percentile and were analyzed using a two-sided Mann–Whitney U test. *P ≤ 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

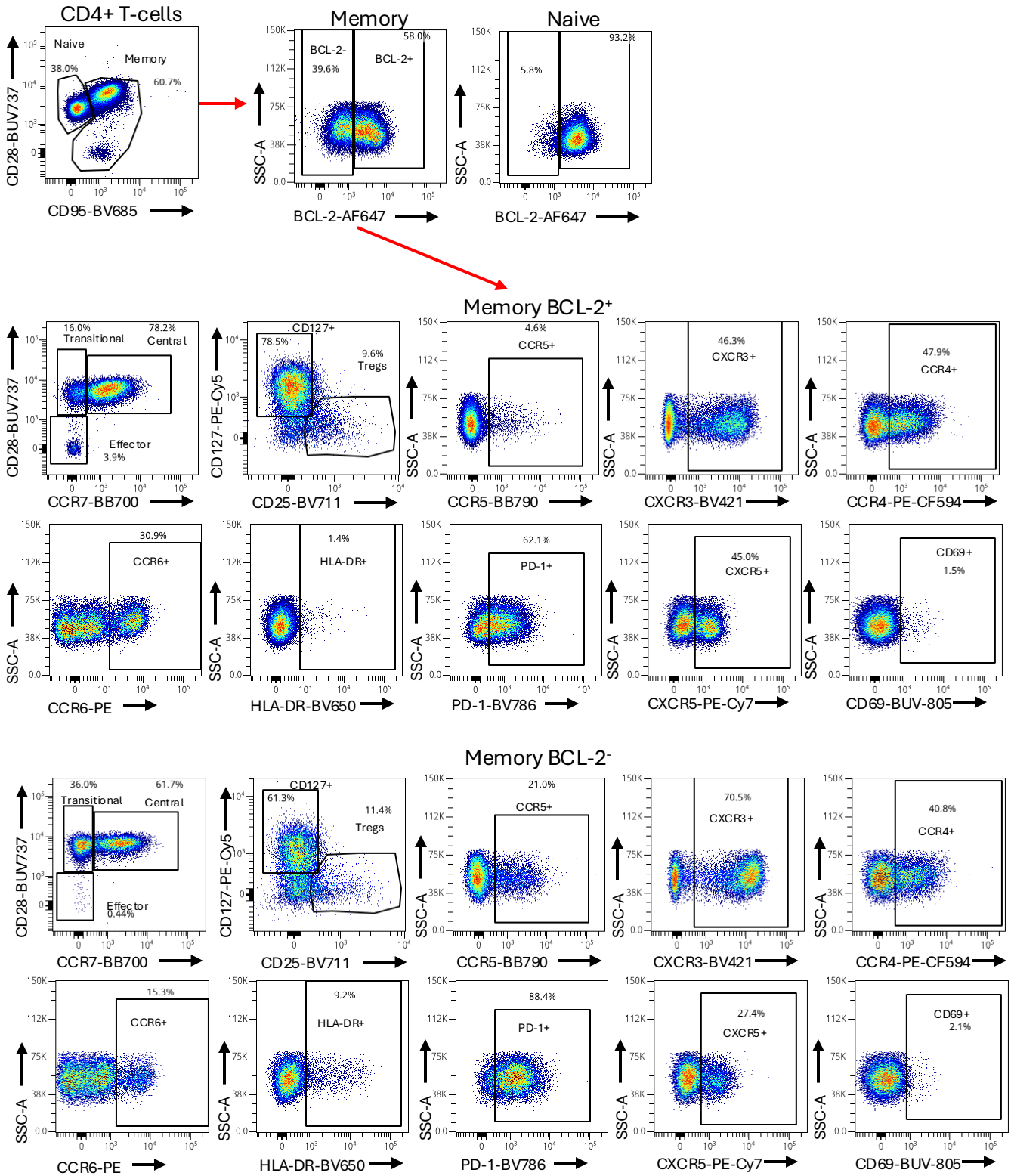


Supplementary Fig. 5. Upregulation of oxidative phosphorylation pathways in venetoclax-treated RMs. a, GSEA results for oxidative phosphorylation pathways in CD4$^+$ T cells isolated from

venetoclax-treated as compared to vehicle-treated RMs at day 25 p.i.; color indicates NES, circle size indicates p value. b, Heatmap showing genes from the HALLMARK_MTORC1_SIGNALING gene set; color indicates $\log_2$ fold difference from mean expression. c, Heatmap showing genes from the GO: oxidative phosphorylation (GODP) gene set; color indicates $\log_2$ fold difference from mean expression. Analyses were performed on samples from vehicle (n = 4), venetoclax (n = 4), and venetoclax + anti-CD8 (n = 3) treated RMs. Genes with adjusted $P < 0.05$ were included for heatmaps and GSEA results.



Supplementary Fig. 6. Gating strategy used to identify CD4$^+$ T cell subsets in blood.



Supplementary Fig. 7. Gating strategy used to phenotypically characterize BCL-2^{+} and BCL-2^{-} memory CD4^{+} T cells in blood and LN.