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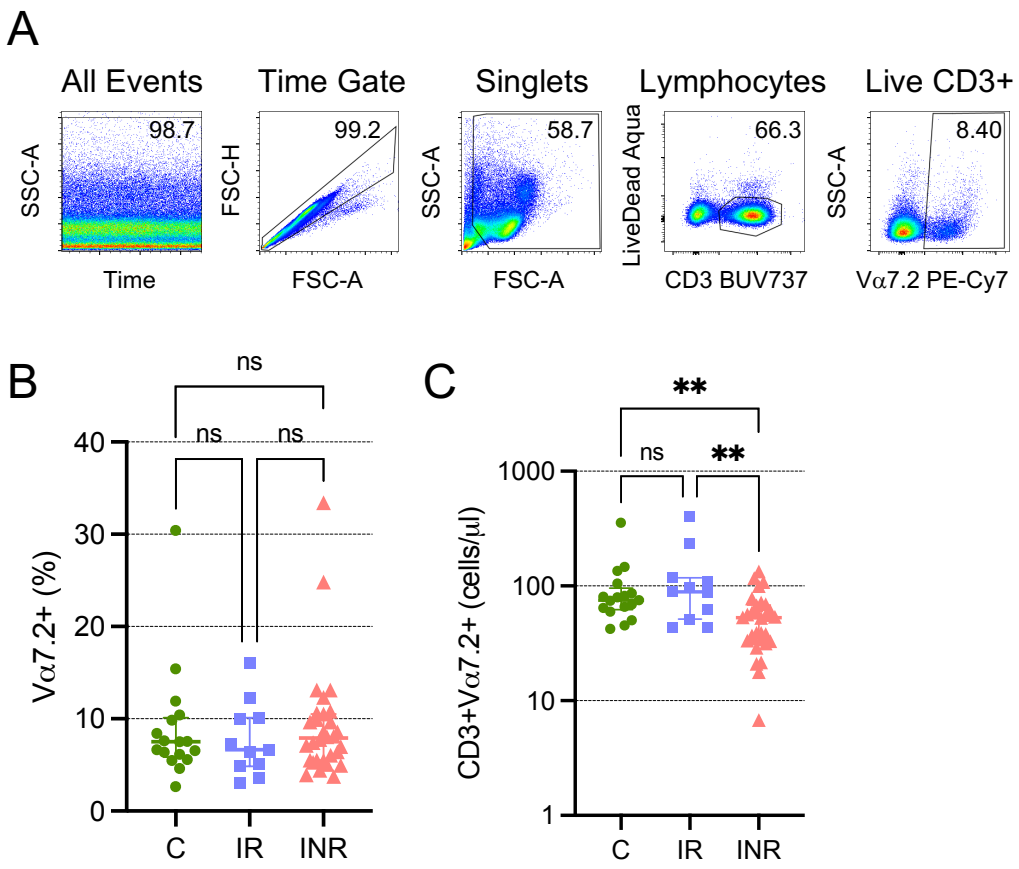

Supplementary Figure 1. Reduced number of TCR Vα7.2+ CD3+ T cells in PWH with poor CD4 T cell recovery. Cryopreserved peripheral blood mononuclear cells (PBMCs) from Cleveland Immune Failure (CLIF) study control (C, n=17), immune responder (IR, n=11), and immune non-responder (INR, n=30) donors were thawed and stained with surface antibodies. (**A**) Representative pseudocolor plots showing gating strategy to identify live CD3+ T cells expressing the Vα7.2 T cell receptor (TCR). Numbers on plots indicate the percent of cells in the indicated gate. (**B**) Proportion of $CD3^+$ T cells that are $V\alpha7.2^+$. Lines and error bars indicate the median ± IQR. (**C**) Number of $V\alpha7.2^+$ $CD3^+$ T cells per μL of peripheral blood. Lines and error bars indicate the median ± IQR. Statistics were calculated using Kruskal-Wallis test with Dunn's correction for multiple comparisons. ns, not significant; $^{**}P<0.01$.

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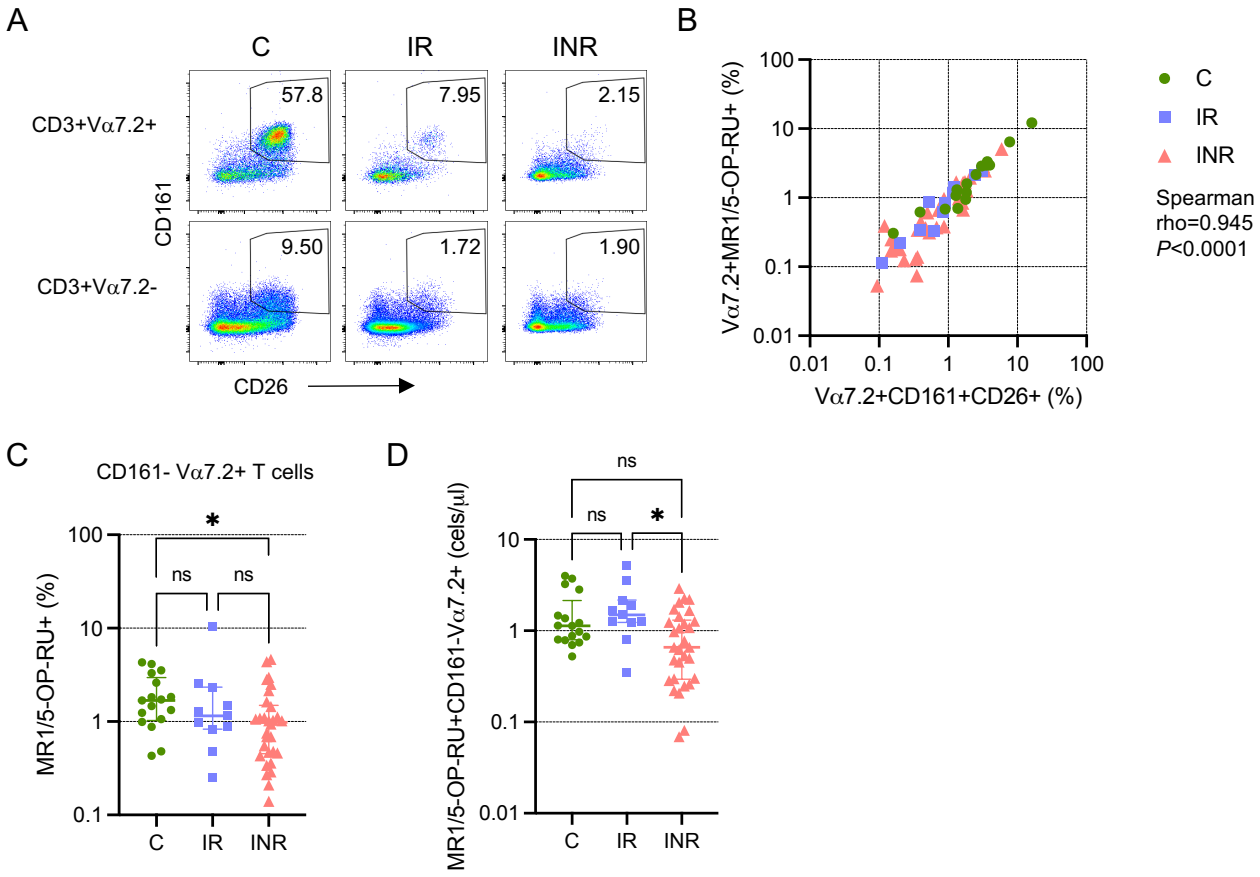

Supplementary Figure 2. There is no accumulation of MR1/5-OP-RU+ cells among Vα7.2+ T cells lacking CD161. Cryopreserved peripheral blood mononuclear cells (PBMCs) from Cleveland Immune Failure (CLIF) study control (C, n=17), immune responder (IR, n=11), and immune non-responder (INR, n=30) donors were thawed, labeled with MR1/5-OP-RU tetramers, and stained with surface antibodies. (**A**) Representative pseudocolor plots showing CD161 and CD26 staining on Vα7.2$^+$ CD3$^+$ T cells (top row) or Vα7.2$^-$ CD3$^+$ T cells (bottom row). Numbers on plots indicate the percent of cells that co-express CD161 and CD26. (**B**) Correlation of the percent of Vα7.2$^+$CD3$^+$ T cells that are CD161$^+$CD26$^+$ and the percentage of Vα7.2$^+$CD3$^+$ T cells that bind the MR1/5-OP-RU tetramer. (**C**) Proportion of Vα7.2$^+$CD161$^-$ CD3$^+$ T cells that are MR1/5-OP-RU tetramer$^+$. Lines and error bars indicate the median ± IQR. (**D**) Number of MR1/5-OP-RU tetramer$^+$Vα7.2$^+$CD161$^-$ CD3$^+$ T cells per μL of peripheral blood. Lines and error bars indicate the median ± IQR. Statistics for **B** were calculated using Spearman correlation. Statistics for **C** and **D** were calculated using Kruskal-Wallis test with Dunn's correction for multiple comparisons. ns, not significant; *P<0.05.

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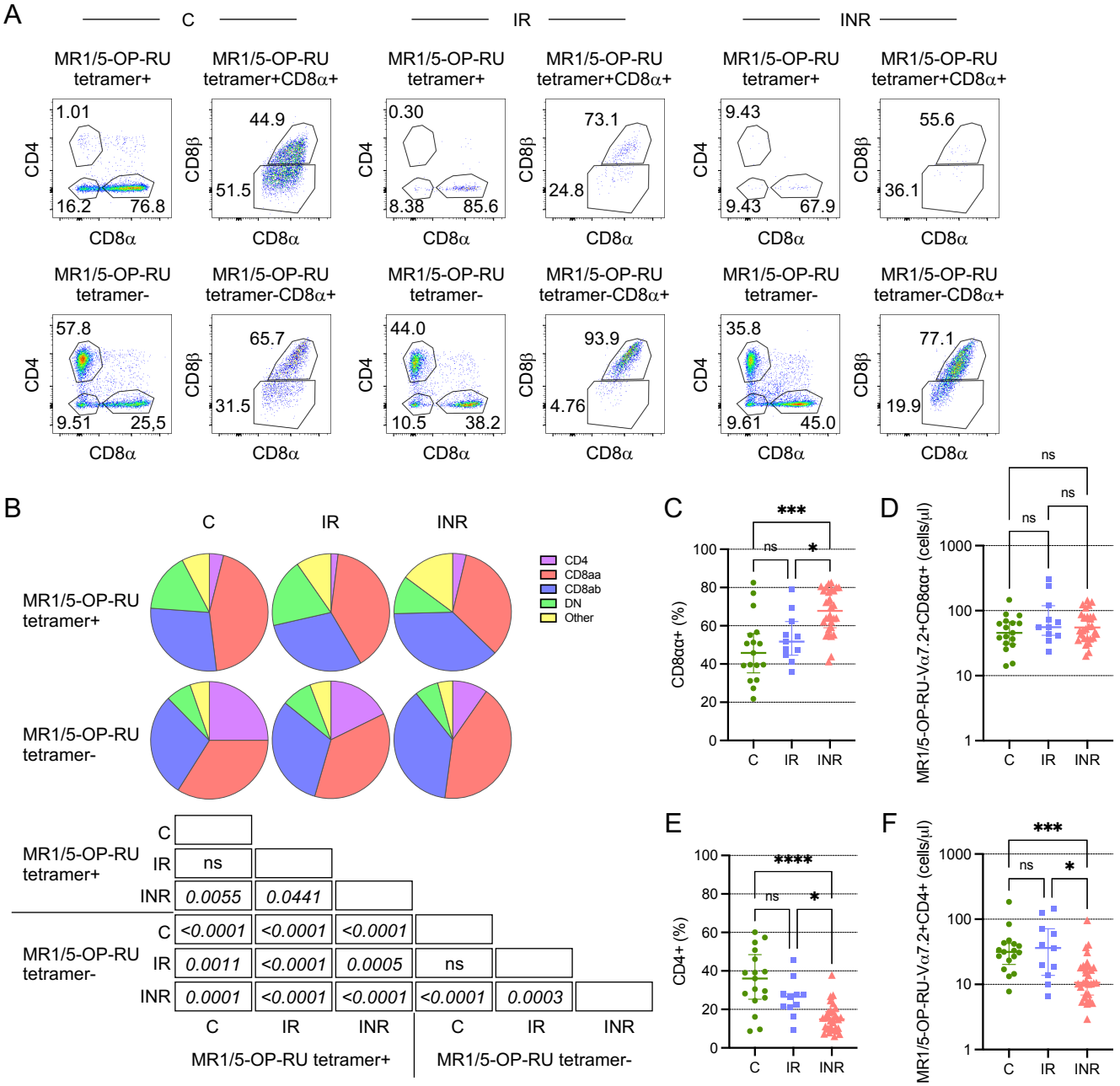

Supplementary Figure 3. Reduced CD4+ cells in MAIT cells from INR drives the proportional increase in CD8+ MAIT cell subpopulations. Cryopreserved peripheral blood mononuclear cells (PBMCs) from Cleveland Immune Failure (CLIF) study control (C, n=17), immune responder (IR, n=11), and immune non-responder (INR, n=30) donors were thawed, labeled with MR1/5-OP-RU tetramers, and stained with surface antibodies. (**A**) Representative pseudocolor plots showing, for MR1/5-OP-RU tetramer$^+$Vα7.2$^+$ T cells (top row) or for MR1/5-OP-RU tetramer$^-$ Vα7.2$^+$ T cells (bottom row), CD4 and CD8α staining on total cells (left plots for each donor group) and CD8α and CD8β staining on CD8α^+ cells (right plots for each donor group).

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Numbers on plots indicate the percent of cells in the indicated gate. (**B**) Pie charts showing the proportion of MR1/5-OP-RU tetramer$^+$ Vα7.2$^+$ CD3$^+$ T cells (top row) and MR1/5-OP-RU tetramer$^-$ Vα7.2$^+$ CD3$^+$ T cells in each of the indicated subsets. Analysis of the cell subset distribution is shown in the matrix and was performed using the SPICE permutation test with 10,000 iterations. (**C**) Proportion of MR1/5-OP-RU tetramer$^-$ Vα7.2$^+$ CD3$^+$ T cells that are CD8$\alpha\alpha^+$. Lines and error bars indicate the median ± IQR. (**D**) Number of CD8$\alpha\alpha^+$ MR1/5-OP-RU tetramer$^-$ Vα7.2$^+$ CD3$^+$ T cells per μL of peripheral blood. Lines and error bars indicate the median ± IQR. (**E**) Proportion of MR1/5-OP-RU tetramer$^-$ Vα7.2$^+$ CD3$^+$ T cells that are CD4$^+$. Lines and error bars indicate the median ± IQR. (**F**) Number of CD4$^+$ MR1/5-OP-RU tetramer$^-$ Vα7.2$^+$ CD3$^+$ T cells per μL of peripheral blood. Lines and error bars indicate the median ± IQR. Statistics for **C-F** were calculated using Kruskal-Wallis test with Dunn's correction for multiple comparisons. ns, not significant; *P<0.05; ***P<0.001; ****P<0.0001.

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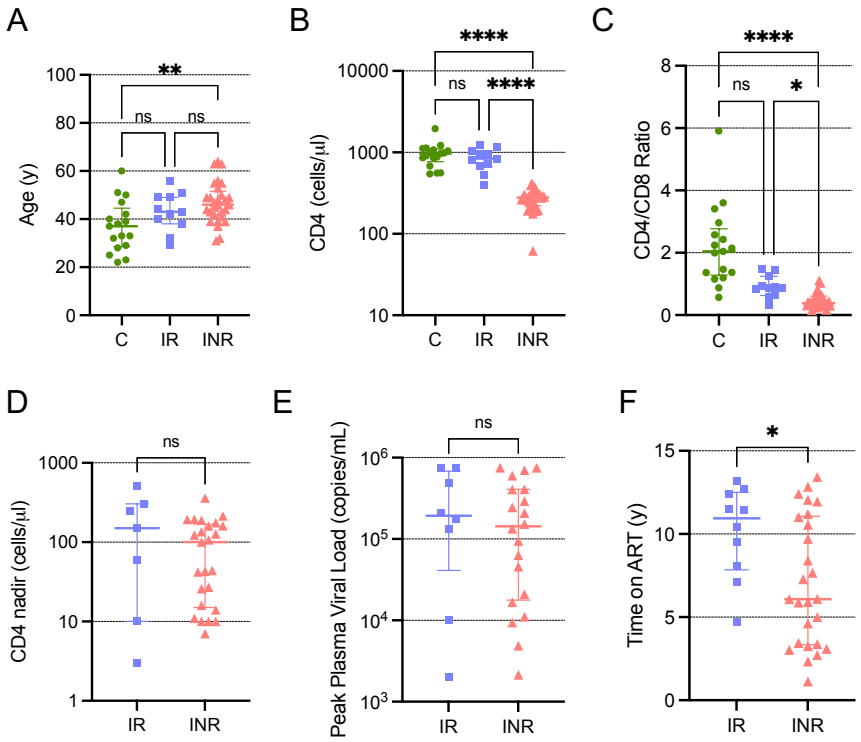

Supplementary Figure 4. Clinical comparison of Cleveland Immune Failure study donors. (**A**) Age of Cleveland Immune Failure (CLIF) study control (C, n=17), immune responder (IR, n=11), and immune non-responder (INR, n=29) donors. Lines and error bars indicate the median ± IQR. (**B,C**) Number of CD4$^+$ T cells per µL of peripheral blood (**B**) and CD4/CD8 T cell ratio (**C**) from C (n=17), IR (n=11) and INR (n=30) donors. Lines and error bars indicate the median ± IQR. (**D**) Nadir CD4 T cells per µL of peripheral blood from IR (n=7) and INR (n=25) donors. Lines and error bars indicate the median ± IQR. (**E**) Peak plasma HIV-1 RNA (viral load) copies per µL of peripheral blood from IR (n=8) and INR (n=20) donors. Lines and error bars indicate the median ± IQR. (**F**) Time on antiretroviral therapy (ART) for IR (n=10) and INR (n=26) donors. Lines and error bars indicate the median ± IQR. Statistics for **A-C** were calculated using Kruskal-Wallis test with Dunn's correction for multiple comparisons. Statistics for **D-F** were calculated using Mann-Whitney U test. ns, not significant; *P<0.05; **P<0.01; ****P<0.0001.

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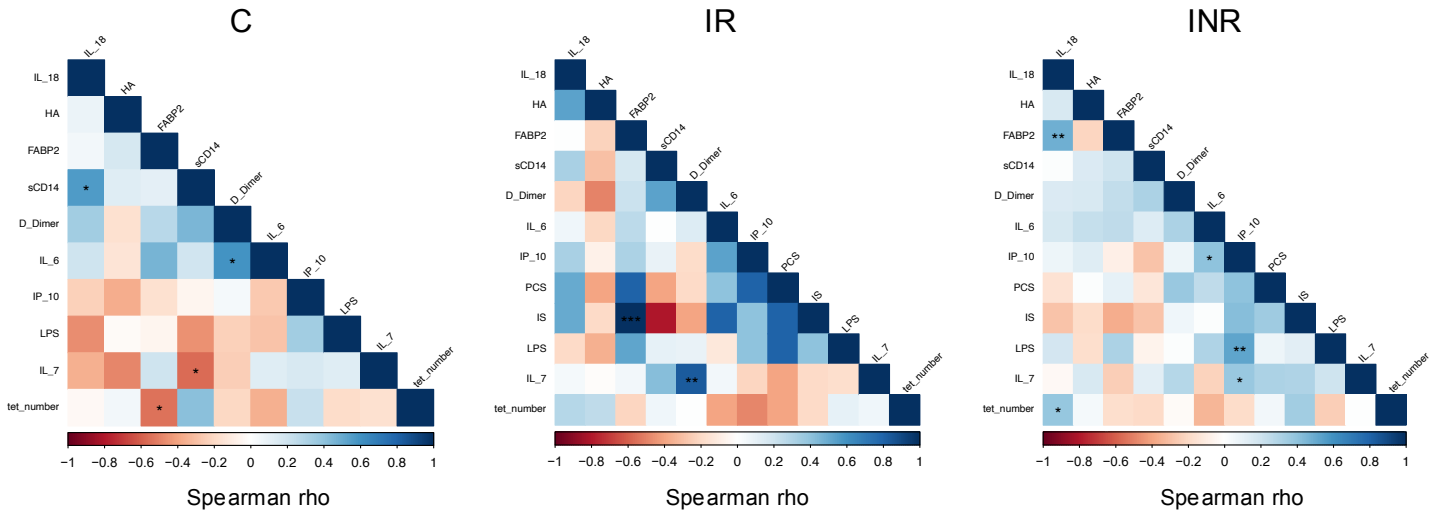

Supplementary Figure 5. Associations of soluble markers of inflammation with MAIT cell numbers and with each other within each donor group. Correlograms of MAIT cell numbers (tet_number) and soluble plasma analytes for Cleveland Immune Failure (CLIF) study control (C, n=16-17), immune responder (IR, n=4-11), and immune non-responder (INR, n=18-30) donors. Neither p-cresol sulfate (PCS) nor indoxyl sulfate (IS) were measured in plasmas of C donors. Statistics were calculated using Spearman correlation. *P<0.05; **P<0.01.

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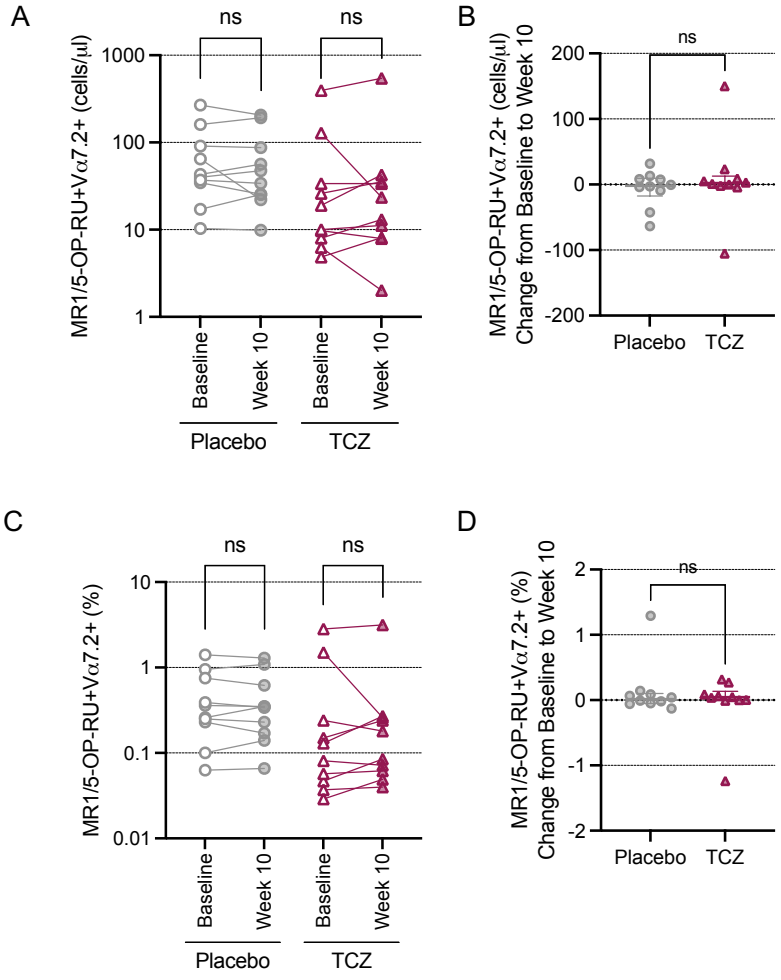

Supplementary Figure 6. There is no change in the number of MR1/5-OP-RU+ cells following inhibition of IL-6 signals *in vivo*. Cryopreserved PBMCs from NCT02049437, from baseline and at week 10 following monthly administrations (at week 0, week 4, and week 8) of tocilizumab (TCZ, n=10) or placebo control (n=10), were thawed, labeled with MR1/5-OP-RU tetramers, and stained with surface antibodies. (**A**) Number of MR1/5-OP-RU tetramer$^+$Vα7.2$^+$ CD3$^+$ T cells per μL of peripheral blood at baseline or week 10 of placebo or TCZ administration. Lines and error bars indicate the median ± IQR. (**B**) Change in the number of MR1/5-OP-RU tetramer$^+$Vα7.2$^+$ CD3$^+$ T cells per μL of peripheral blood from baseline to week 10.
(C) Proportion of CD3$^+$ T cells that are MR1/5-OP-RU$^+$Vα7.2$^+$ at baseline or week 10 of placebo or TCZ administration. Lines and error bars indicate the median ± IQR. **(D)** Change in the proportion of CD3$^+$ T cells that are MR1/5-OP-RU$^+$Vα7.2$^+$ from baseline to week 10. Statistics for **A,C** were calculated using Wilcoxon matched-pairs signed rank test and statistics for **B,D** were calculated using Mann-Whitney U test. ns, not significant.

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