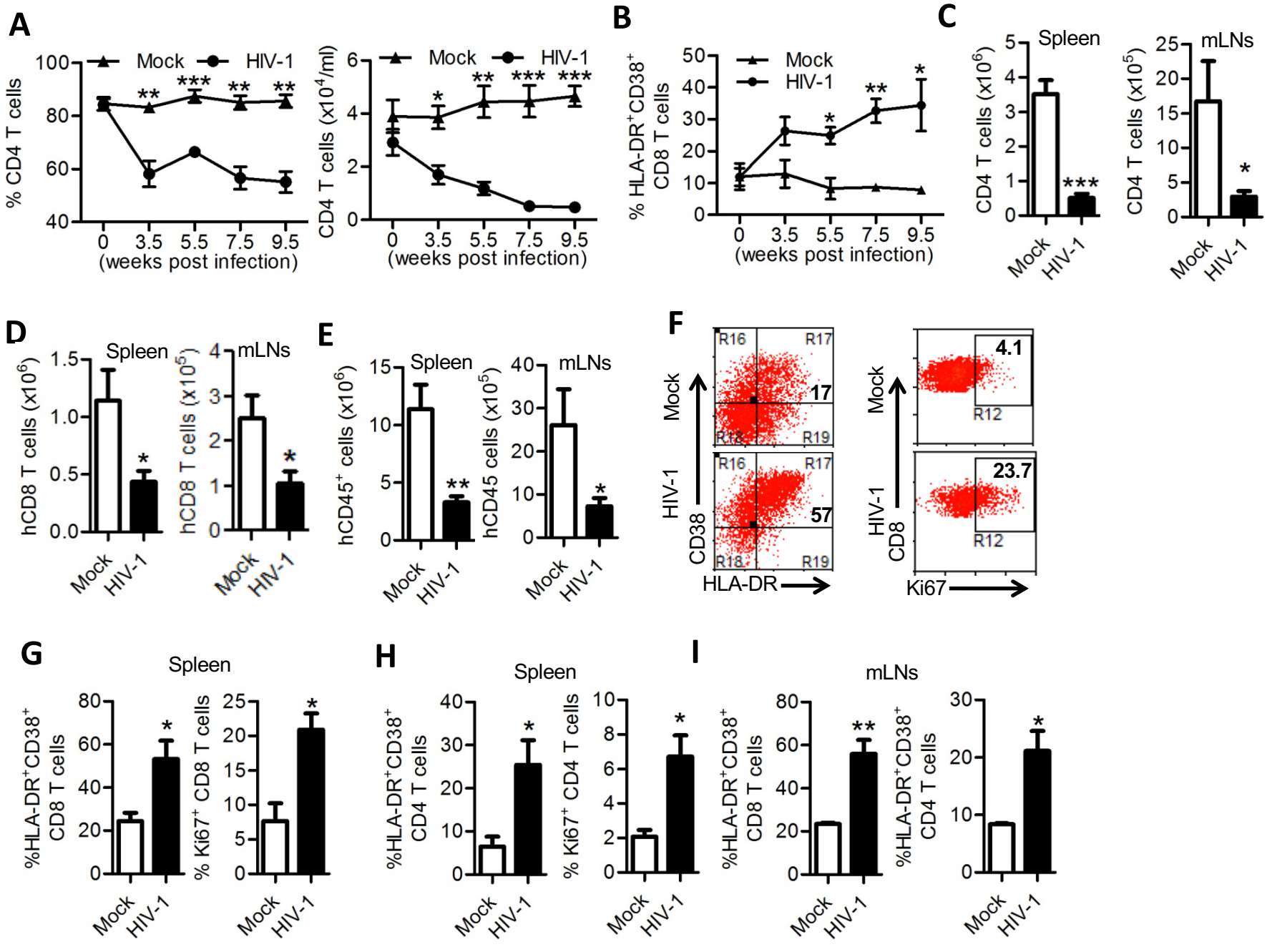

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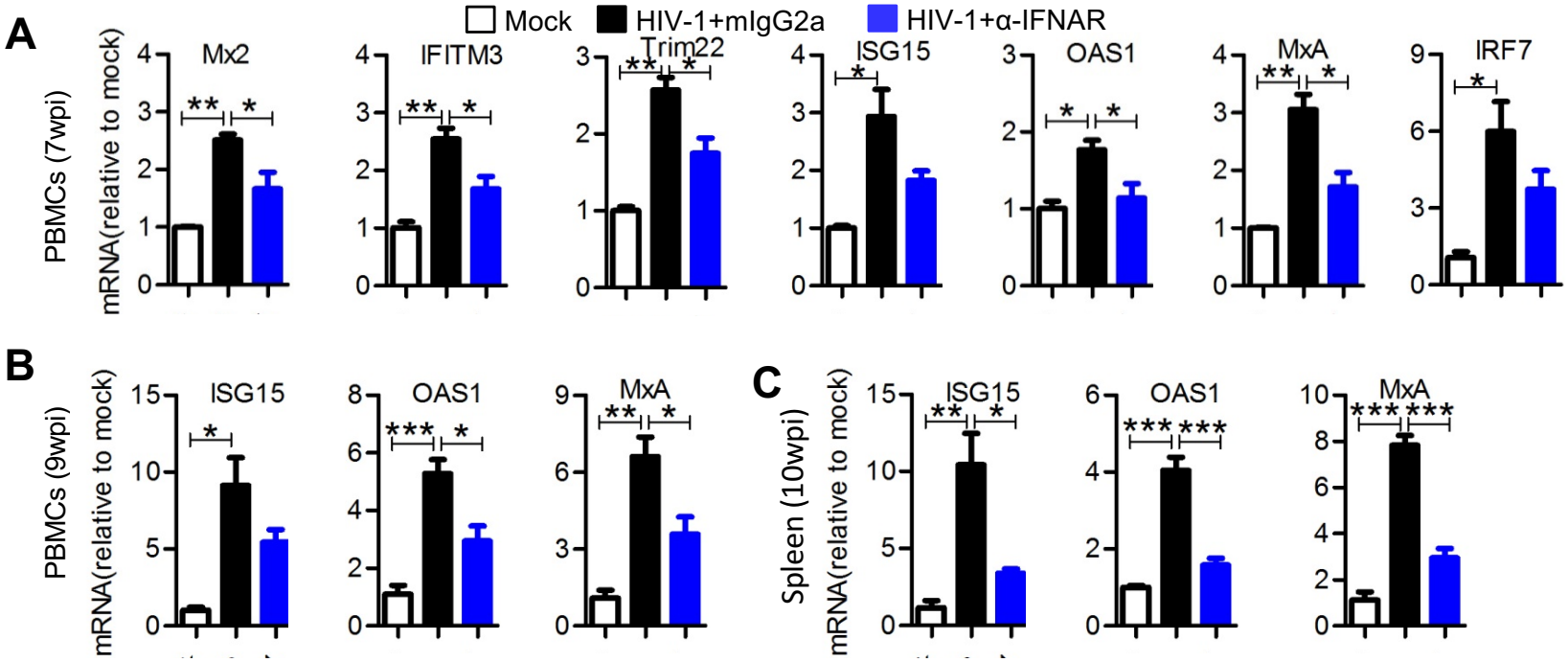
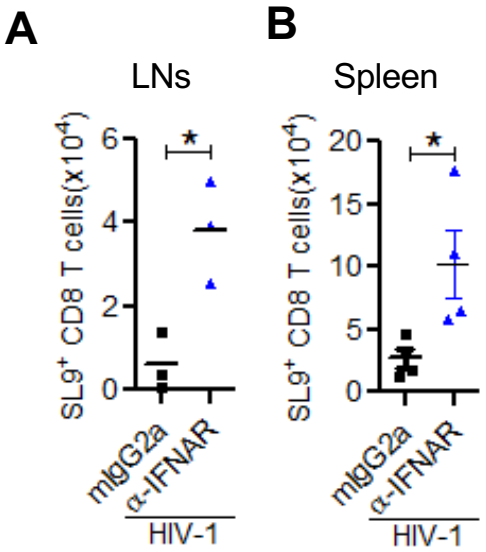
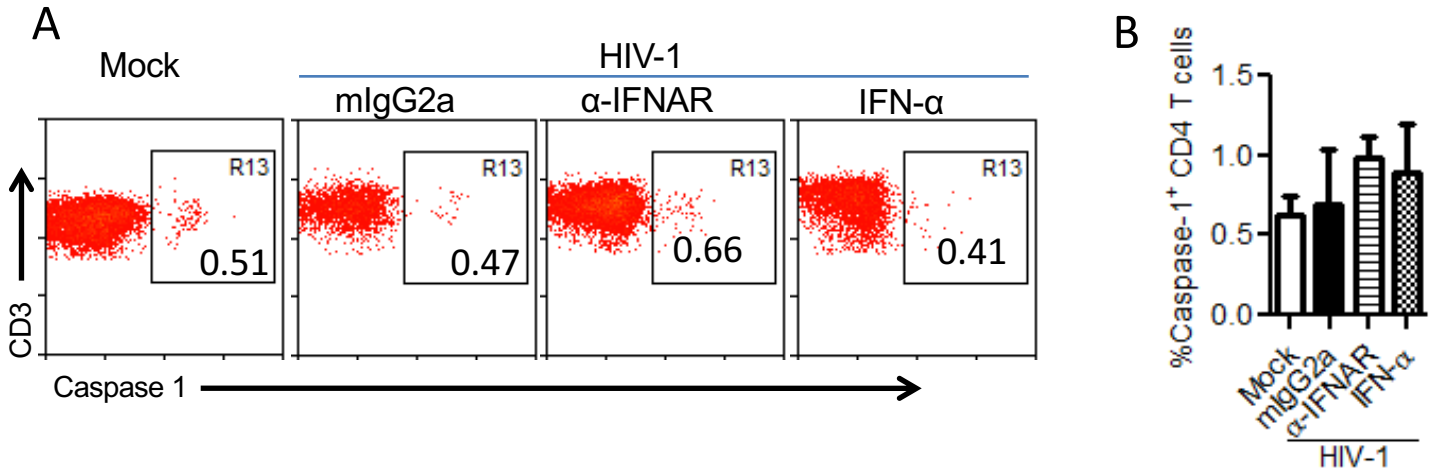
Supplementary Figure 1. HIV-1 persistent infection leads to human T cell depletion and hyper-immune activation. Humanized mice were infected with HIV-1 and analyzed at indicated weeks post-infection (wpi). (A) Percentage of CD4 T cells in total T cells and number of CD4 T cells in peripheral blood during HIV-1 infection at indicated time points. (B) Percentage of HLA-DR+/CD38+ CD8 T cells in peripheral blood at indicated time points. (C-E) Number of human CD4 T cells (C), CD8 T cells (D) and total human $CD45^+$ cells (E) in spleen and mLNs at termination (10.5wpi). (F) Representative FACS plot show expression of CD38/HLA-DR and Ki67 on CD8 T cells. (G-H) Summarized data show expression of CD38/HLA-DR and Ki67 on CD8 T cells and CD4 T cell in the spleen at termination (10.5wpi). (I) Summarized data show expression of CD38/HLA-DR on CD8 and CD4 T cell in the mesenteric lymph nodes (mLNs) at termination(10.5wpi). Shown are representative data of four independent experiments (mock, n=12; HIV-1, n=18 in total) with mean values ± s.e.m. from n=4 (mock) or n=5 (HIV-1) hu-mice per group. *P < 0.05, **P < 0.01, ***P < 0.001. Unpaired, two-tailed Student's t-test was performed to compare between groups at singular time point (A, B) or between two groups (C-I).



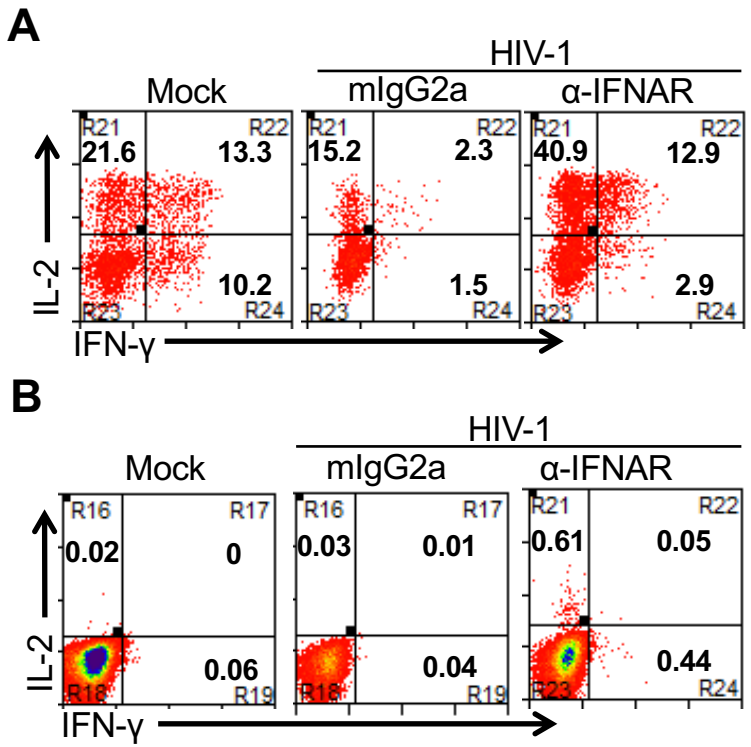
Supplementary Figure 2. IFNAR1 blockade reduces ISGs expression during persistent HIV-1 infection in humanized mice. Humanized mice infected with HIV-1 were treated with α-IFNAR1 mAb or isotype control(mIgG2a) twice a week from 6 to 10 wpi. (A, B) The relative mRNA level of indicated ISGs expression in PBMCs at week 7(A) and week 9 (B). Shown are representative data of three independent experiments (mock, n=7; HIV-1 + mIgG2a, n=11; HIV-1 + α-IFNAR1, n=12 in total) with mean values ± s.e.m. from n=3 (Mock) , n=5 (HIV-1 + mIgG2a) or n=5 (HIV-1 + α-IFNAR1) hu-mice per group. (C) The relative mRNA expression level of indicated ISGs and in spleen at termination (10.5wpi). Shown are combined data of two independent experiments (mock, n=6; HIV-1 + mIgG2a, n=9; HIV-1 + α-IFNAR1, n=9) with mean values ± s.e.m. *P < 0.05, **P < 0.01, ***P < 0.001.One-way analysis of variance (ANOVA) and Bonferroni's post hoc test was performed.



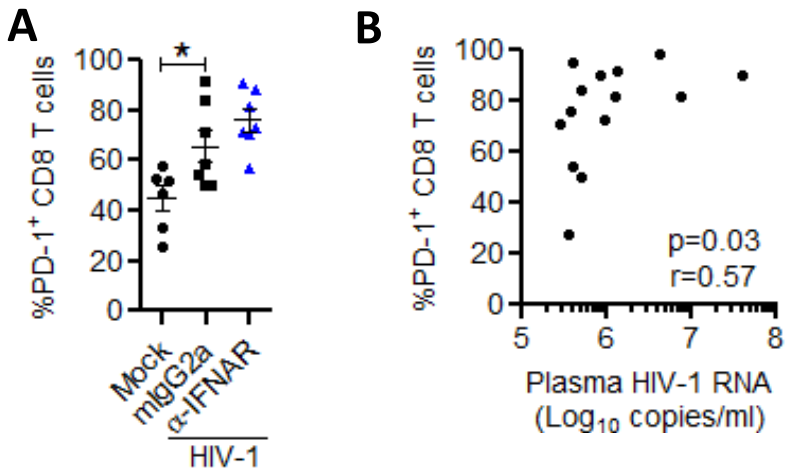
Supplementary Figure 3. IFNAR1 blockade rescues human HIV-specific CD8 T cell number during persistent HIV-1 infection in humanized mice. Humanized mice were treated as in figure 5C. Absolute number of CD8 T cells specific for the HLA-A2/SL-9 pentamer in LNs (mock, n=3; HIV-1 + mIgG2a, n=3; HIV-1 + α-IFNAR, n=3) and spleens (mock, n=3; HIV-1 + mIgG2a, n=4; HIV-1 + α-IFNAR1, n=4). *P < 0.05 by unpaired, two-tailed Student's t-test.



Supplementary Figure 4. Detection of activated caspase-1 in HIV-1 infected samples. Splenocytes from mock (n=2) or HIV-1 infected (n=4) humanized mice were cultured with IL-2 (20 u/ml) in vitro in the presence of control mIgG2a (10μg/ml), α-IFNAR (10μg/ml) or IFN- α (200u/ml) for 10 days. At day10, the cells were used for staining. Representative dot plots (A) and summarized data (B) show percentage of CD4 T cells with active caspase-1.



Supplementary Figure 5. IFNAR1 blockade during persistent HIV-1 infection rescues the function of human CD4 T cells. Humanized mice infected with HIV-1 were treated with α-IFNAR1 mAb or isotype control (mouse IgG2a) twice a week from 6-10 wpi. Mice were sacrificed at 10 wpi. (A) Splenocytes were stimulated *ex vivo* with PMA plus ionomycin for 4 hours followed by intracellular cytokine staining. Representative dot plots show percentages of IFN-γ and IL-2 producing CD4 T cells. (B) Splenocytes were stimulate *ex vivo* with peptide pool of HIV Gag protein for 8 hours (Brefeldin A was added at 3 hours) followed by intracellular cytokine staining. Representative dot plots show percentages of IFN-γ and IL-2 producing CD4 T cells.



Supplementary Figure 6. Detection of PD-1 expression on CD8 T cells after IFNAR1 blockade. Humanized mice infected with HIV-1 were treated with α-IFNAR1 mAb or isotype control (mouse IgG2a) twice a week from 6-10 wpi. Mice were sacrificed at 10 wpi. (A) Summarized data show PD-1 expressing CD8 T cells from the spleen (mock, n=6; HIV-1 + mIgG2a, n=7; HIV-1 + α-IFNAR1, n=7, combined data from 2 independent experiment with mean values ± s.e.m.). *P < 0.05, one-way analysis of variance (ANOVA) and Bonferroni's post hoc test was performed. (B) Correlation analysis between PD-1 expression on CD8 T cells and plasma HIV-1 RNA levels. Spearman rank correlation test was performed.