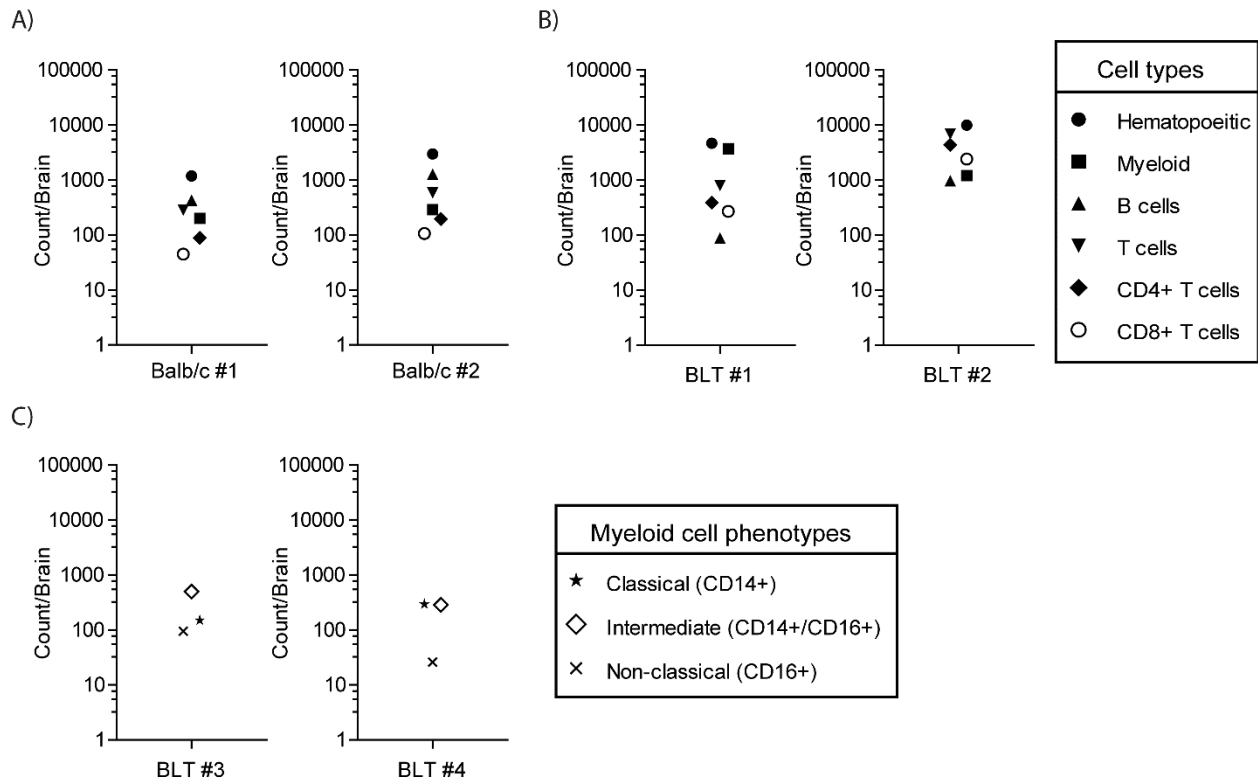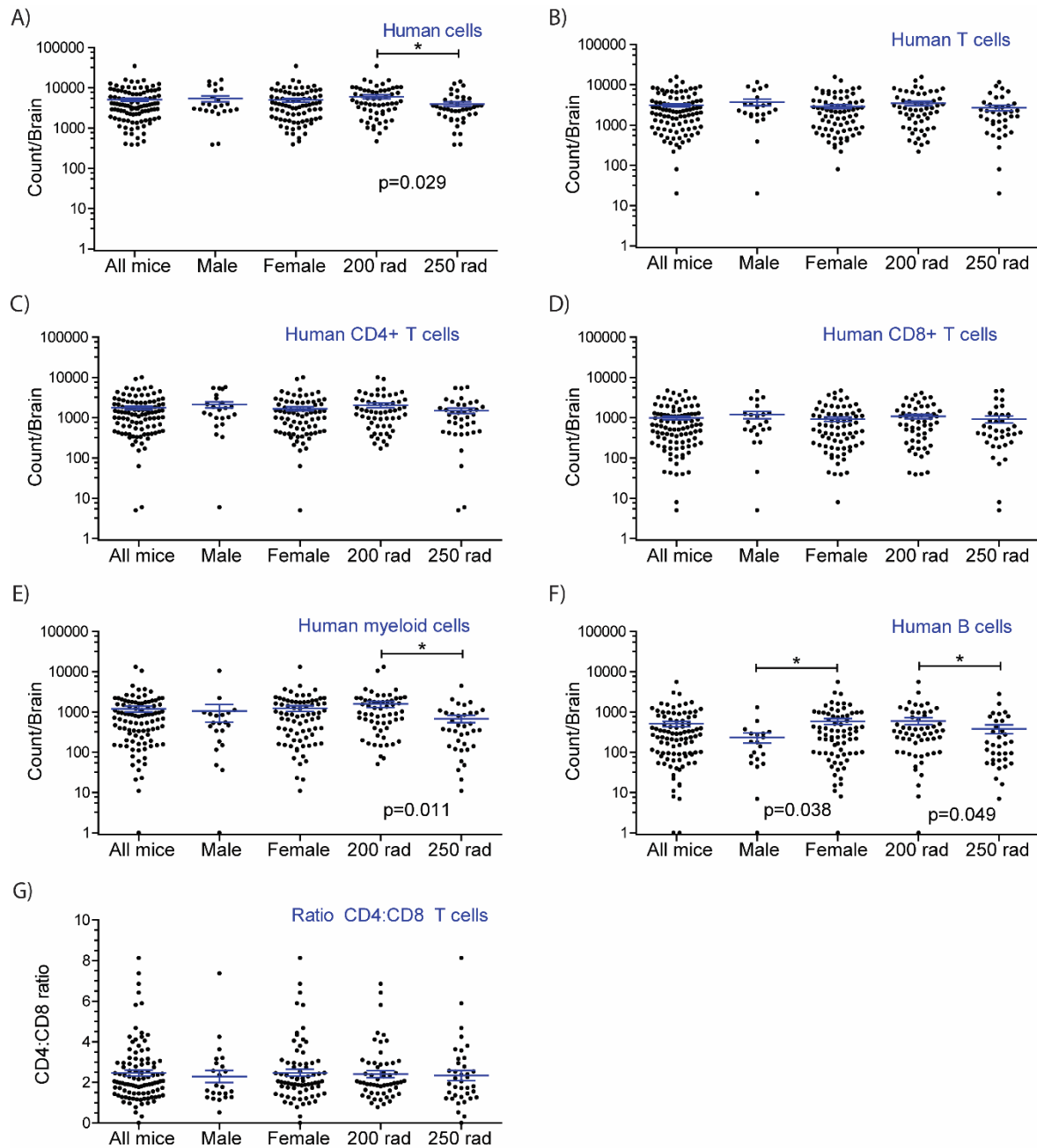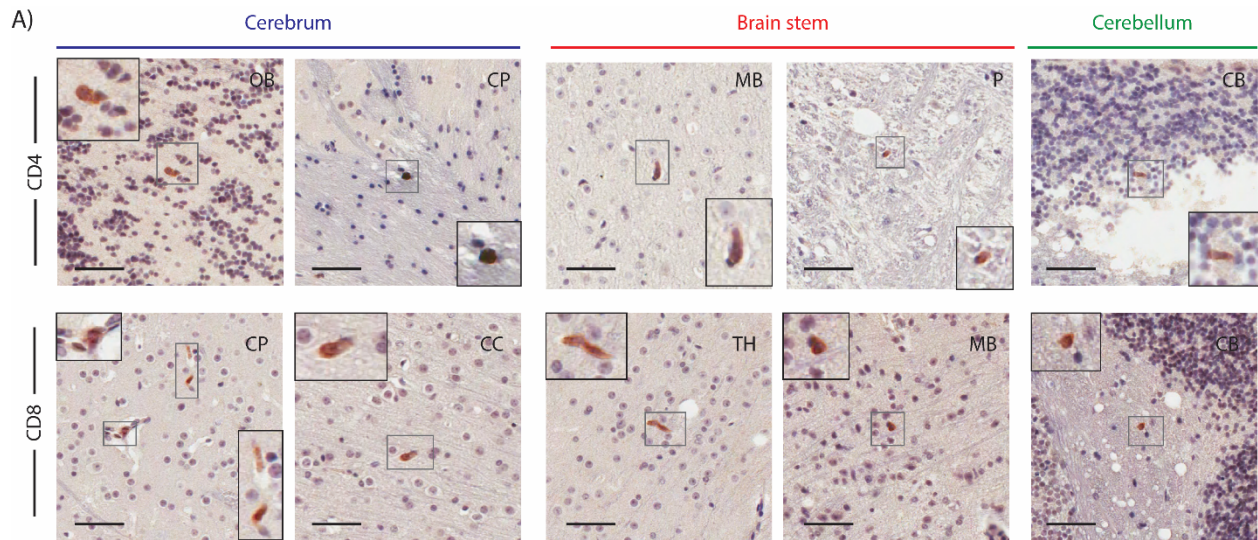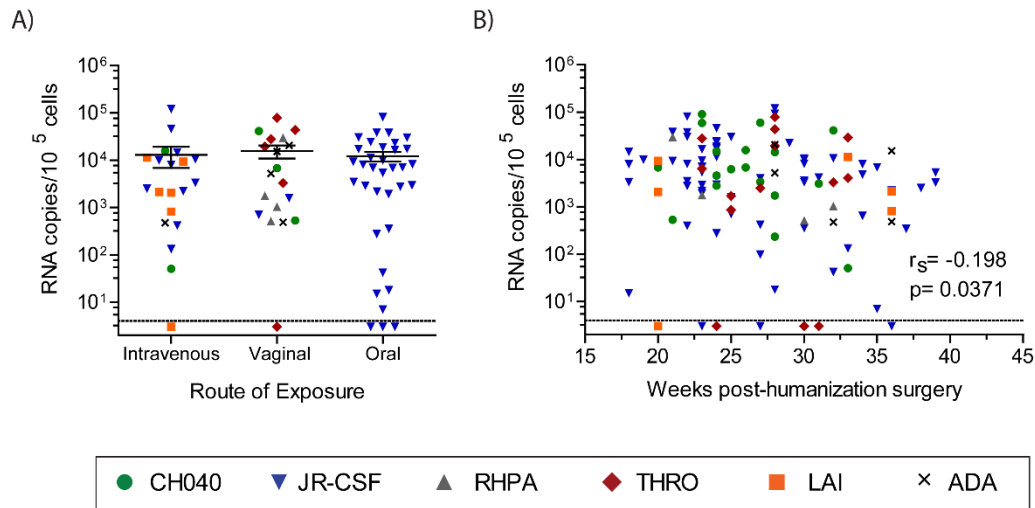**Supplemental Figures:**

Supplemental Figure 1: Quantitation of flow cytometry from Figure 1. The total numbers of hematopoietic cells (filled circles) including myeloid cells (filled squares), B cells (filled upwards triangles), T cells (filled downwards triangles), CD4+ T cells (filled diamonds), and CD8+ T cells (open circles) were quantified for (A) Balb/c mice # 1 and 2 and (B) BLT mice #1 and #2. (C) The numbers of human myeloid cells expressing a classical (stars), intermediate (open diamonds) or non-classical (x marks) phenotype were quantified for BLT mice #3 and #4.
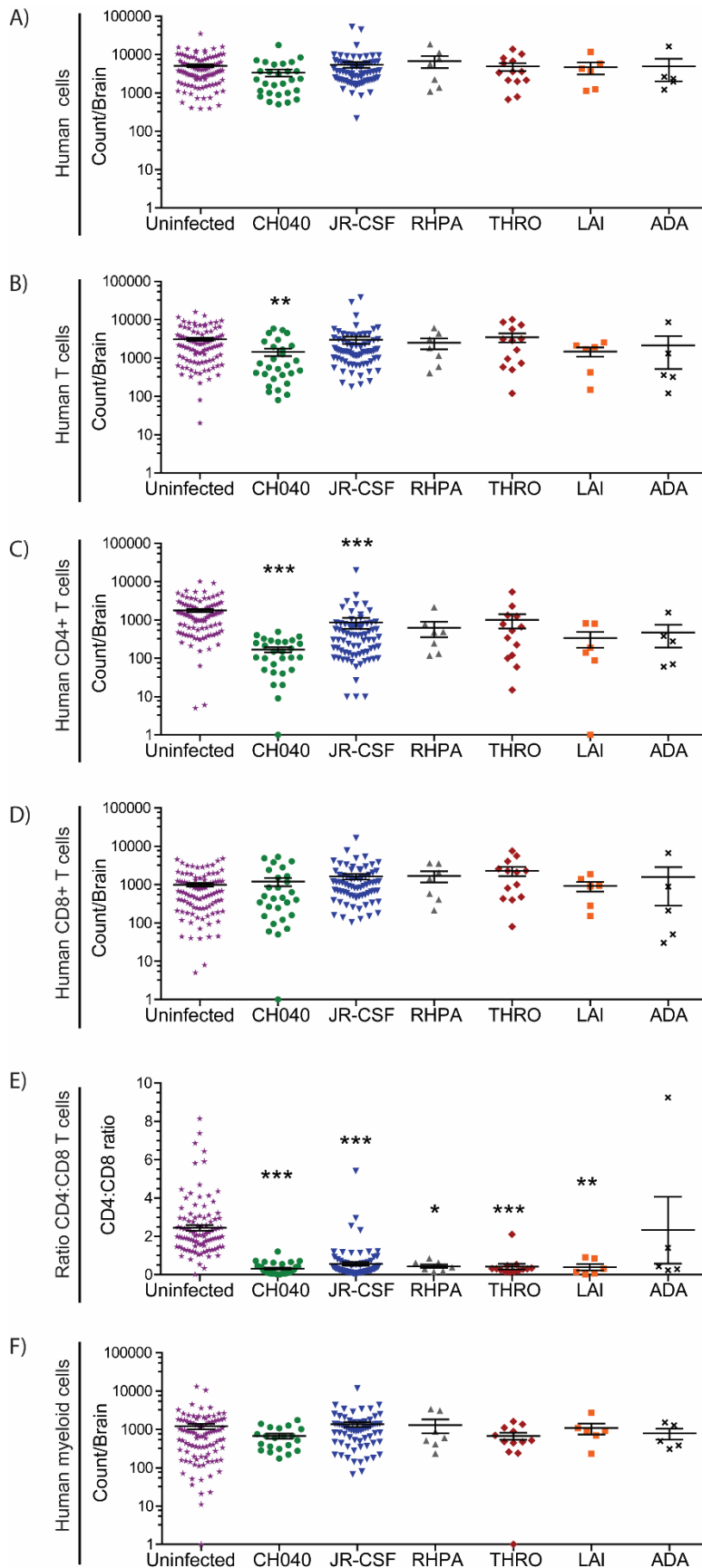
Supplemental Figure 2: Effect of sex and irradiation on the levels of human immune cells in the brains of BLT mice. Total numbers of human (A) hematopoietic cells, (B) T cells, (C) CD4+ T cells, (D) CD8+ T cells, (E) myeloid cells, (F) B cells and (G) the CD4:CD8 T cell ratio in the brains of BLT mice (n=104) according to sex (male, n=23; female, n=81) and level of pre-conditioning (200 rad, n=60; 250 rad, n=41). A Mann-Whitney test was used to compare males versus females and 200 rad versus 250 rad. Significant p-values are indicated as follows: * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001.

Supplemental Figure 3: Human T cell subsets are distributed throughout the brain of BLT mice. (A) Brain sections from the cerebellum (CB), cerebral cortex, (CC), caudate putamen (CP), midbrain (MB), olfactory bulb (OB), pons (P) and thalamus (TH) of BLT mice were stained with antibodies directed against human CD4 (top panels) and CD8 (bottom panels). Positive cells appear brown. Scale bars represent 50 um. Inset images show a 2x-magnification of the original image.

Supplemental Figure 4: Effect of exposure route or weeks post-humanization on virus levels in BLT brains. (A) HIV-RNA levels were measured in the brains of HIV-infected BLT mice (y-axis) and grouped by route of exposure (intravenous n=20, vaginal n=19, and oral n=35). A Kruskal-Wallis test with Dunn's post-test was used to compare virus levels between groups of mice (all p>0.05). (B) HIV-RNA levels in the brains of mice systemically infected with HIV-1 (n=18 CH040, 65 JR-CSF, 4 RHPA, 14 THRO, 6 LAI and 5 ADA) were plotted by weeks post-humanization surgery and analyzed using a Spearman rank correlation test (r_s and p-values are listed on the graph). Mice infected with HIV-1 CH040 (green circles), JR-CSF (blue downwards triangles), RHPA (gray upwards triangles), THRO (red diamonds), LAI (orange squares) and ADA (black x) are shown with the same symbol.

Supplemental Figure 5: Comparative analysis of human immune cells present in the brains of uninfected or HIV-infected BLT mice. Total numbers of human (A) hematopoietic cells, (B) T cells, (C) CD4+ T cells, (D) CD8+ T cells, E) the CD4:CD8 T cell ratio, and the numbers of (F) myeloid cells in the brains of uninfected BLT mice (purple stars, n=104) and BLT mice infected with HIV-1: CH040 (green circles, n=28) JR-CSF (blue downward triangles, n=73), RHPA (gray upward triangles, n=7), THRO (red diamonds, n=13), LAI (orange squares, n=6) and ADA (black x, n=5) were determined by flow cytometric analysis and compared using a Kruskal-Wallis test with Dunn's multiple comparisons. The asterisks note significant differences (p<0.05) between uninfected and HIV-infected BLT mice. P-values are indicated as follows: * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001.
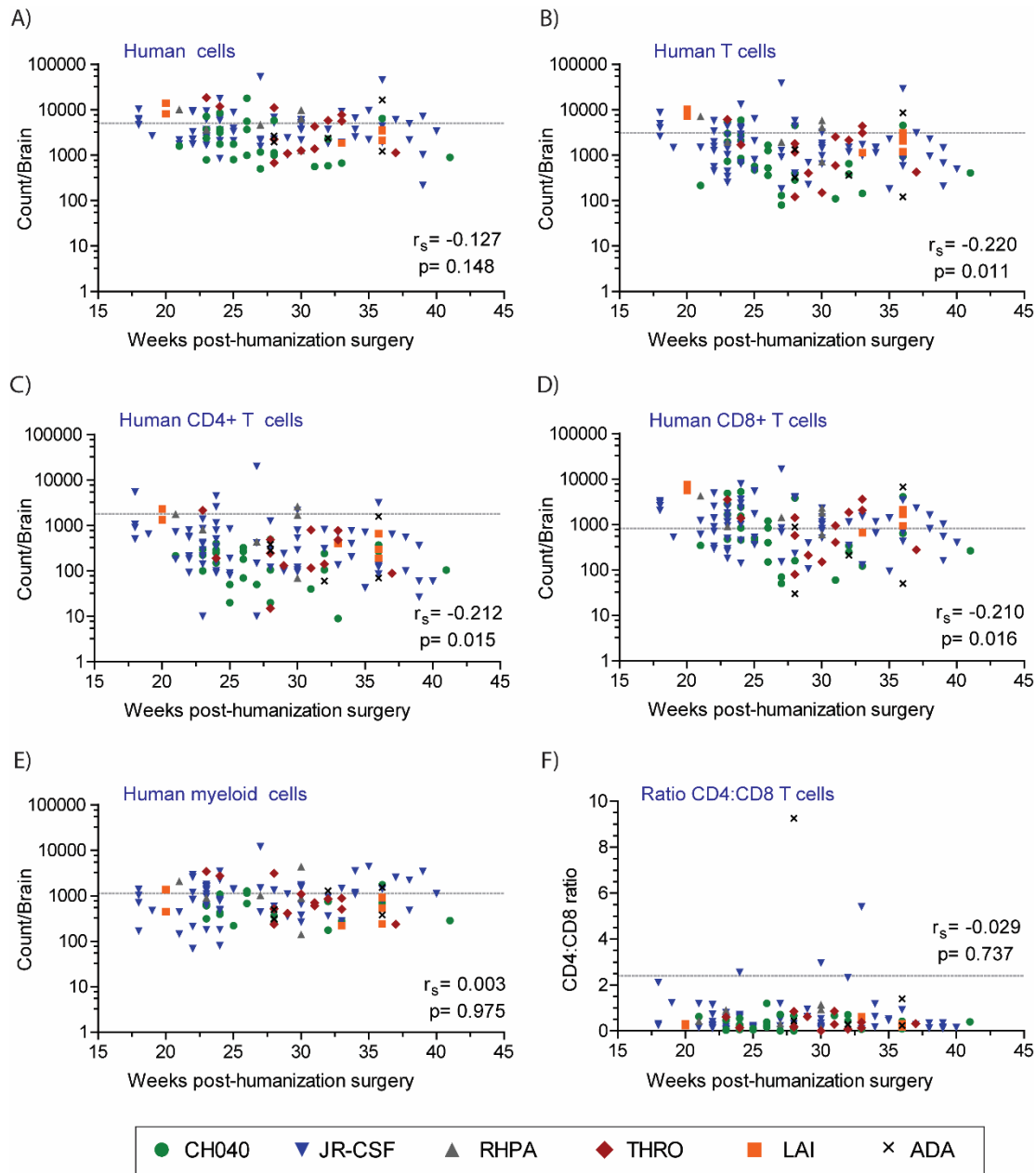
Supplemental Figure 6: Analysis of human immune cells present in the brains of HIV-1 infected BLT mice over time post-humanization. Scatter plots indicate weeks post-humanization surgery (x-axis) and on the y-axis the total numbers of human (A) hematopoietic cells, (B) T cells, (C) CD4+ T cells, (D) CD8+ T cells, (E) myeloid cells and (F) the CD4:CD8 T cell ratio in the brains of BLT mice infected with HIV-1: CH040 (green circles, n=28) JR-CSF (blue downward triangles, n=73), RHPA (gray upward triangles, n=7), THRO (red diamonds, n=13), LAI (orange squares, n=6) and ADA (black x, n=5). The correlation over time for each parameter was assessed using a Spearman rank correlation test and the r_s and p-values are shown on each graph. The dashed gray lines represent the mean values for uninfected animals.
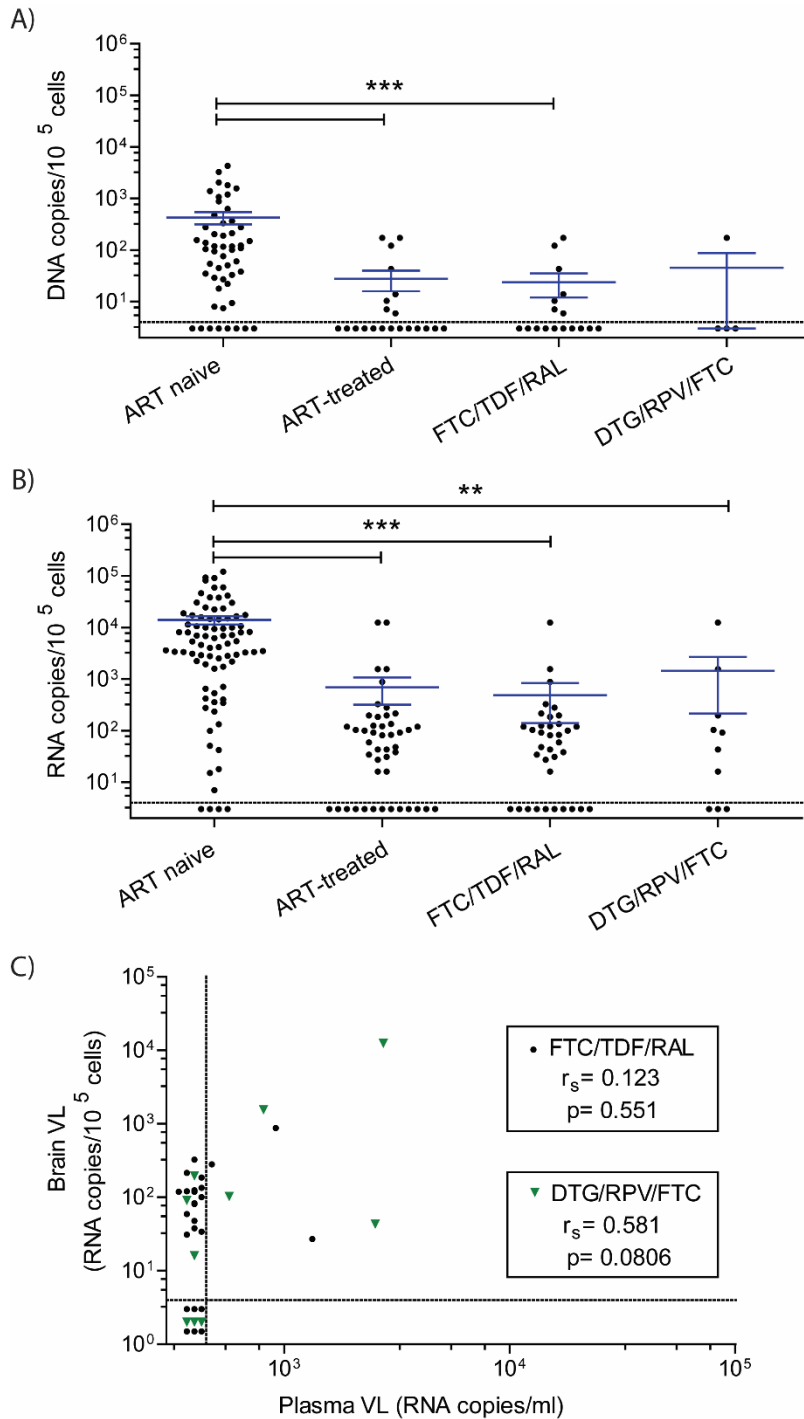
Supplemental Figure 7: ART effectively reduced viral burden in the brain and periphery of HIV-infected BLT mice. (A) HIV-DNA and (B) HIV-RNA levels were measured in the brain of HIV-infected ART-naïve (n=110) and ART-treated BLT mice (n=47). ART-treated BLT mice were administered either FTC/TDF/RAL (n=37) or DTG/RPV/FTC (n=10). A Kruskal-Wallis test with Dunn's multiple comparisons was used to compare data in A and B and p-values are indicated as follows: * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$. (C) A scatter plot depicts the HIV-RNA levels in the peripheral blood plasma (x-axis) and the brain (y-axis) of HIV-infected BLT mice treated with FTC/TDF/RAL (black circles, n=26) or DTG/RPV/FTC (green downward triangles, n=10) at the time of analysis. A Spearman rank test was used to analyze data in C (r_s and p-values are listed on the graph). In A-C, dashed horizontal lines represent the lower LOD for cell-associated DNA/RNA (~4 copies). In C, a dashed vertical line represents the lower LOD for plasma VL (~688 RNA copies/ml plasma).