

## Supplemental Figures:

**Figure S1: Analysis of HIV-1-specific CD8 T<sub>SCM</sub> in carriers of protective HLA class I alleles.** (A): Relative proportions and absolute counts of HIV-1-specific CD8 T cells in 6 untreated progressors (UP, n=10 responses), 14 untreated controllers (UC, n=27 responses), and 20 ART treated patients (ART, n=28 responses). (B): Proportions of HIV-1-specific CD8 T cells restricted by either protective (HLA-B\*27/57) or non-protective (non-HLA-B\*27/57) HLA class I alleles in 14 controllers (UC) and in 20 ART treated patients (ART). (C): Proportions of HIV-1-specific CD8 T cell subsets in responses restricted by either protective or non-protective HLA-I alleles in 14 controller patients. (D): Proportions of HIV-1-specific CD8 T cell subsets in responses restricted by either protective or non-protective HLA-I alleles in 20 ART treated patients. Statistical comparisons in (A-D) were performed using Kruskal-Wallis test followed by post-hoc analysis with Dunn's test for multiple comparisons.

**Figure S2: Relative proportions and absolute counts of total CD8 T<sub>SCM</sub> cells in HIV-1-infected patients.** (A): Pie charts reflecting the subset distribution of total CD8 T cells in 14 UP, 16 UC, 31 ART-treated patients, and 18 HIV-1-negative donors. Statistical comparisons among pie charts were performed by  $\chi^2$  test in SPICE 5.3. \*: Statistically different from all other cohorts ( $P \leq 0.026$ ); \*\*: Statistically different from all other cohorts ( $P \leq 0.0005$ ). (B-C): Relative proportions of indicated CD8 T cell subsets (B) and of CD8 T<sub>SCM</sub> cells (C) in indicated study cohorts. (D-E): Absolute counts of indicated CD8 T cell subsets (D) and of CD8 T<sub>SCM</sub> cells (E) in indicated study cohorts. Statistical comparisons in (B-E) were performed using Kruskal-Wallis tests followed by post-hoc analysis with Dunn's test for multiple comparisons.

**Figure S3: Relative proportions and absolute counts of total CD4 T<sub>SCM</sub> cells in HIV-1-infected patients.** (A): Pie charts reflecting the subset distribution of total CD4 T cells in 14 UP, 16 UC, 25 ART-treated patients, and 13 HIV-1-negative donors. Statistical comparisons among pie charts were performed by  $\chi^2$  test in SPICE 5.3. \*: Statistically different from all other cohorts ( $P \leq 0.042$ ). (B-C): Relative proportions of indicated CD4 T cell subsets (B) and of CD4 T<sub>SCM</sub> cells (C) in indicated study cohorts. (D-E): Absolute counts of indicated CD4 T cell subsets (D) and of CD4 T<sub>SCM</sub> cells (E) in indicated study cohorts. Statistical comparisons in (B-E) were

performed using Kruskal-Wallis tests followed by post-hoc analysis with Dunn's test for multiple comparisons.

**Figure S4: Relative proportions and absolute counts of CD4 T<sub>SCM</sub> cells in ART-treated HIV-1-infected patients.** (A): Pie charts reflecting the subset distribution of total CD4 T cells in 14 untreated progressors and in 25 patients treated with ART for 0.2 to 2 years (n=10), 3 to 7 years (n=24), or 8 to 14 years (n=15). (B-C): Relative proportions of indicated CD4 T cell subsets (B) and of CD4 T<sub>SCM</sub> cells (C) in indicated study cohorts stratified according to treatment duration. (D-E): Absolute frequencies of indicated CD4 T cell subsets (D) and of CD4 T<sub>SCM</sub> cells (E) in indicated study cohorts. Statistical comparisons in (B-E) were performed using Kruskal-Wallis tests followed by post-hoc analysis with Dunn's test for multiple comparisons.

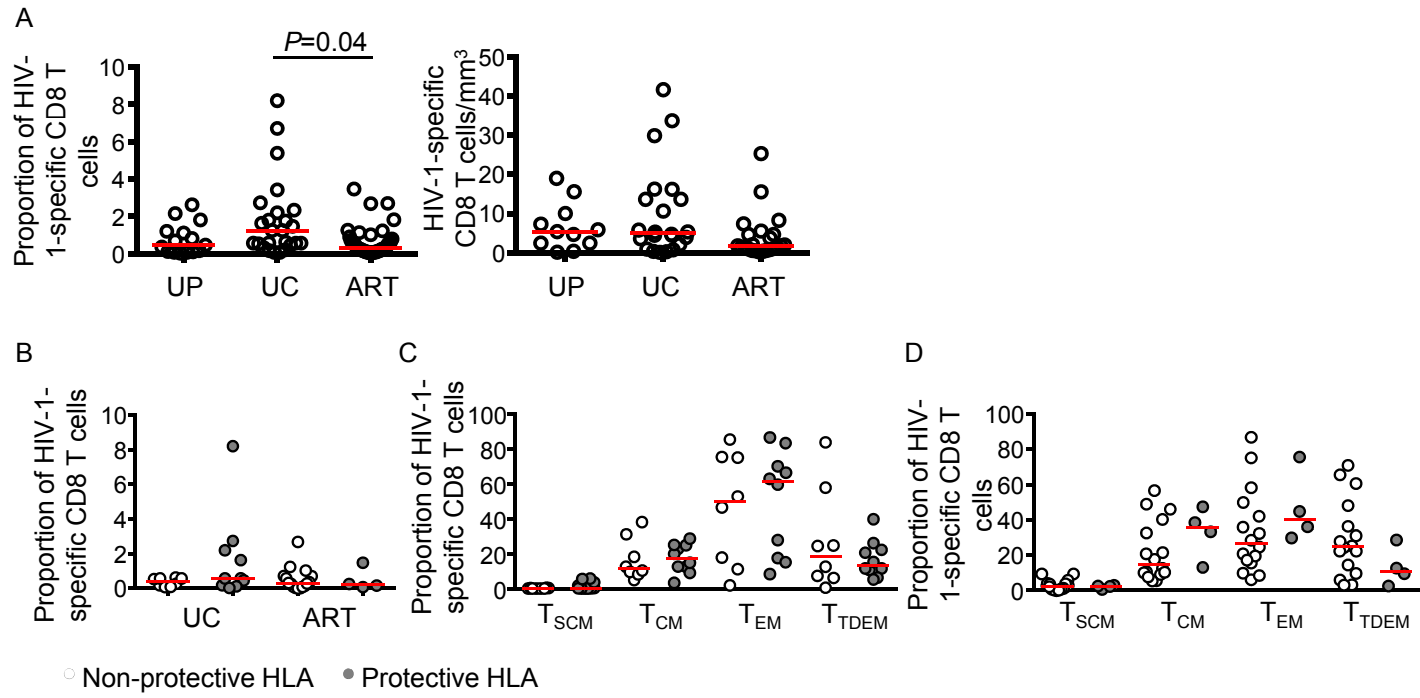
**Figure S5: Correlations between CD4 or CD8 T cell subsets and duration of antiretroviral therapy.** (A-B): Data show associations between absolute counts of indicated HIV-1-specific CD8 T cell subsets from 21 patients (A, n=53 responses) or of total CD8 T cells from 42 patients (B) and corresponding years of antiretroviral therapy. (C-D): Associations between proportion of CD4 T cell subsets (C, n=68) or number of CD4 T cells (D, n=68) and corresponding years of antiretroviral therapy. Data from all study patients and all available time points were cumulatively analyzed using Generalized Estimating Equations (GEE) adjusted for repeated measures of the same patients.

**Figure S6: Associations between CD8 T cell activation and markers of clinical HIV-1 disease progression.** (A-B): Proportions of HIV-1-specific (A; UP, n=4; UC, n=9; ART 0.2-2y n=2; ART 3-7y n=9; ART 8-14y n=7) and total (B; UP, n=3; UC, n=11; ART 0.2-2y n=11; ART 3-7y n=20; ART 8-14y n=11) CD38/HLA-DR<sup>+</sup> CD8 T cells in indicated study cohorts. Statistical comparisons were performed using Kruskal-Wallis tests or Friedman's tests (for paired comparisons) followed by post-hoc analysis with Dunn's test for multiple comparisons. (C): Associations between proportions of HIV-1-specific CD38/HLA-DR<sup>+</sup> CD8 T cells and HIV-1 viral loads or CD4 T cell counts in untreated progressors and controllers (n=12). (D): Associations between proportions of CD38/HLA-DR<sup>+</sup> CD8 T cells and HIV-1 viral loads or CD4 T cell counts in untreated progressors and controllers (n=14). (E): Associations between

proportions of CD38/HLA-DR<sup>+</sup> CD8 T<sub>SCM</sub> cells and HIV-1 viral loads or CD4 T cell counts in untreated progressors and controllers (n=14). **(F-G)**: Associations between CD4 T cell counts and the proportions of HIV-1-specific (F, n=12) and total (G, n=19) CD38/HLA-DR<sup>+</sup> CD8 T cells in ART-treated patients. **(H)**: Associations between CD4 T cell counts and proportions of CD38/HLA-DR<sup>+</sup> CD8 T<sub>SCM</sub> cells in ART-treated patients (n=19). Spearman's rank correlation coefficients are shown.

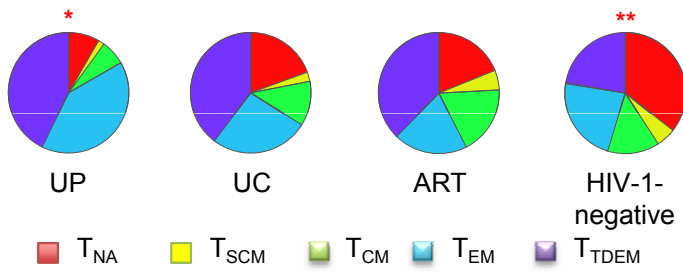
**Figure S7: Proportions of virus-specific cytokine producing CD8 T cell subsets. (A)**: Proportions of IFN- $\gamma$ -producing CD8 T cells in CEF-specific CD8 T cells of HIV-1-infected patients (n=15 responses) and in HIV-1-specific CD8 T cells of indicated study cohorts (UP n=12, UC n=25, ART n=29 responses). **(B)**: Proportions of IFN- $\gamma$ <sup>+</sup>/IL-2<sup>+</sup> co-producing CEF- (n=15) or HIV-1-specific CD8 T cells of indicated study cohorts (UP n=12, UC n=25, ART n=29 responses). **(C)**: Pie charts reflecting the cell subset distribution of IFN- $\gamma$  producing virus-specific CD8 T cells in indicated study cohorts (UP n=12, UC n=25, ART n=29 responses). Statistical comparisons among pie charts were performed by  $\chi^2$  test in SPICE 5.3. \*: Statistically different from all other cohorts ( $P \leq 0.034$ ); **(D)**: Relative proportions of indicated CD8 T cell subsets within total IFN- $\gamma$ -producing, virus-specific CD8 T cells. Statistical comparisons in (A, B, and D) were performed using Kruskal-Wallis tests followed by post-hoc analysis using Dunn's test for multiple comparisons.

Supplementary Figure 1



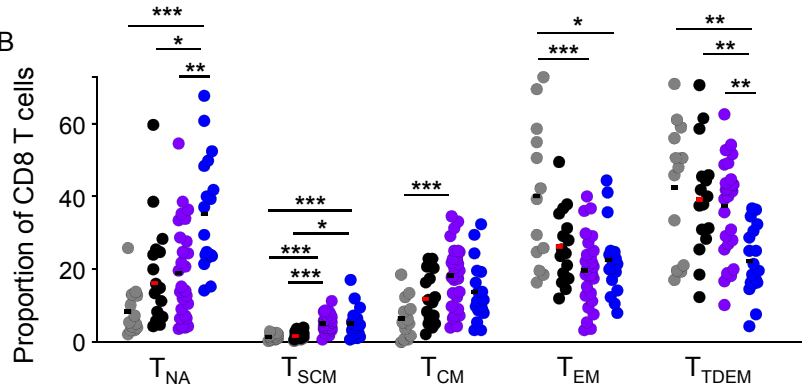
Supplementary Figure 2

A

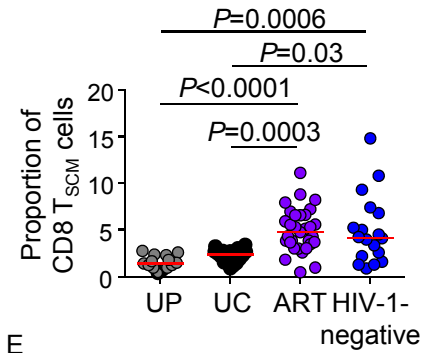


\*  $P \leq 0.03$   
 \*\*  $P \leq 0.0094$   
 \*\*\*  $P \leq 0.0006$

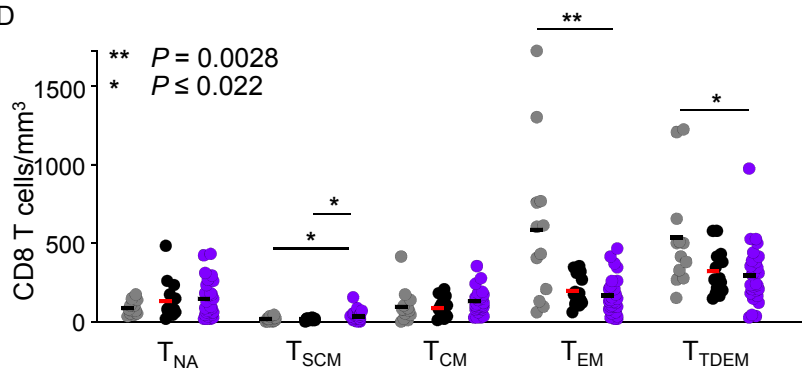
B



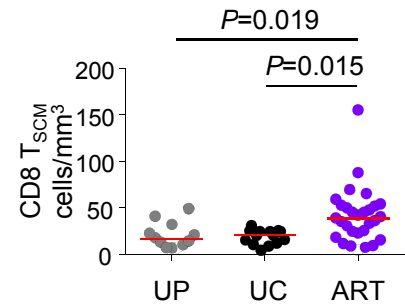
C



D

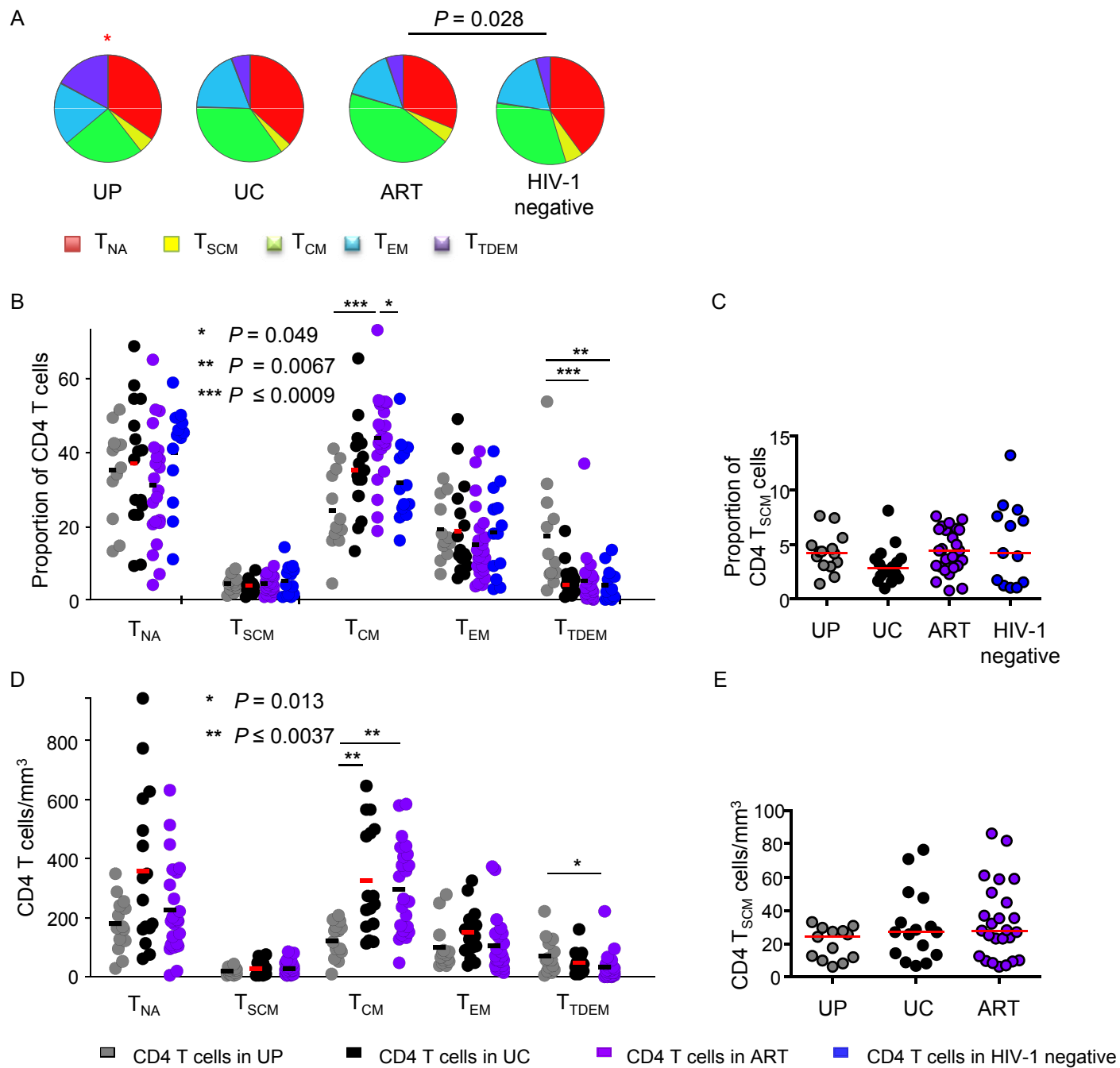


E



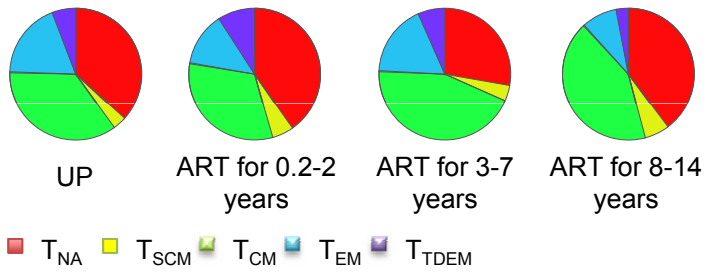
■ CD8 T cells in UP ■ CD8 T cells in UC ■ CD8 T cells in ART ■ CD8 T cells in HIV-1 negative

Supplementary Figure 3

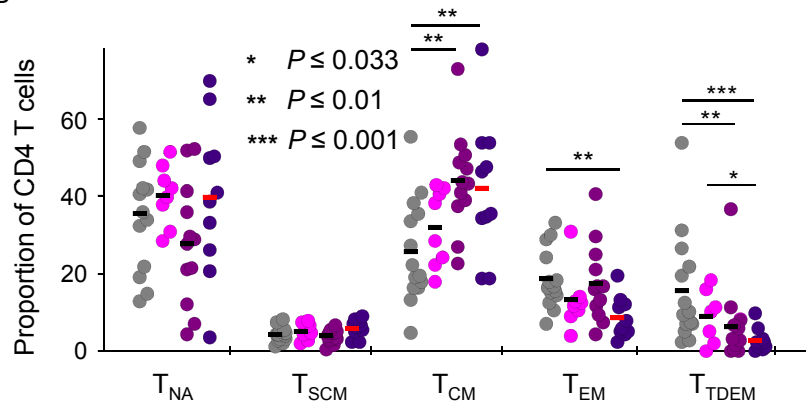


Supplementary Figure 4

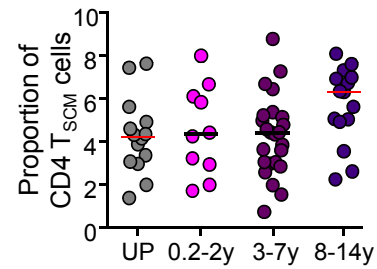
A



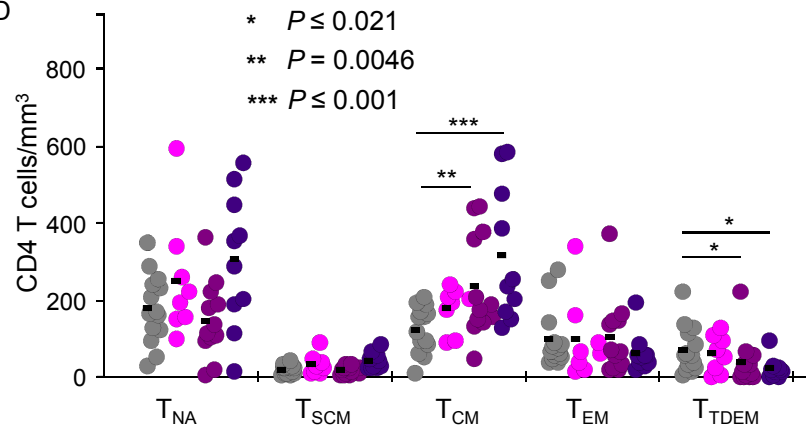
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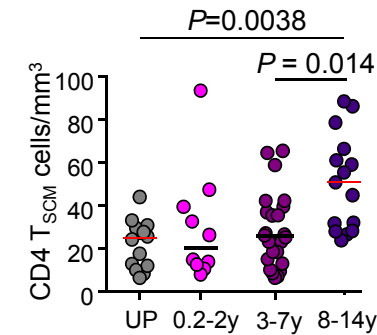
C



D

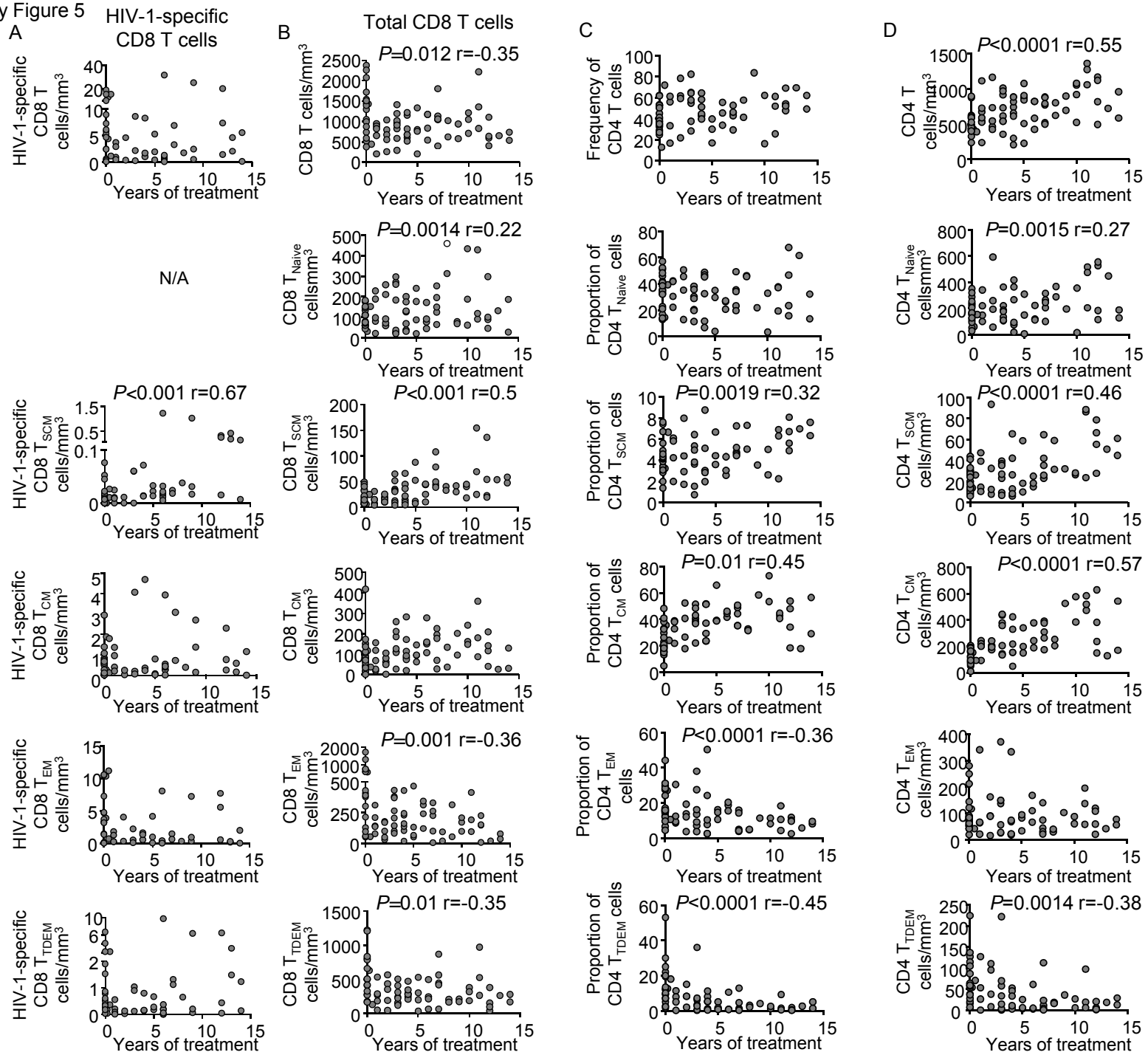


E



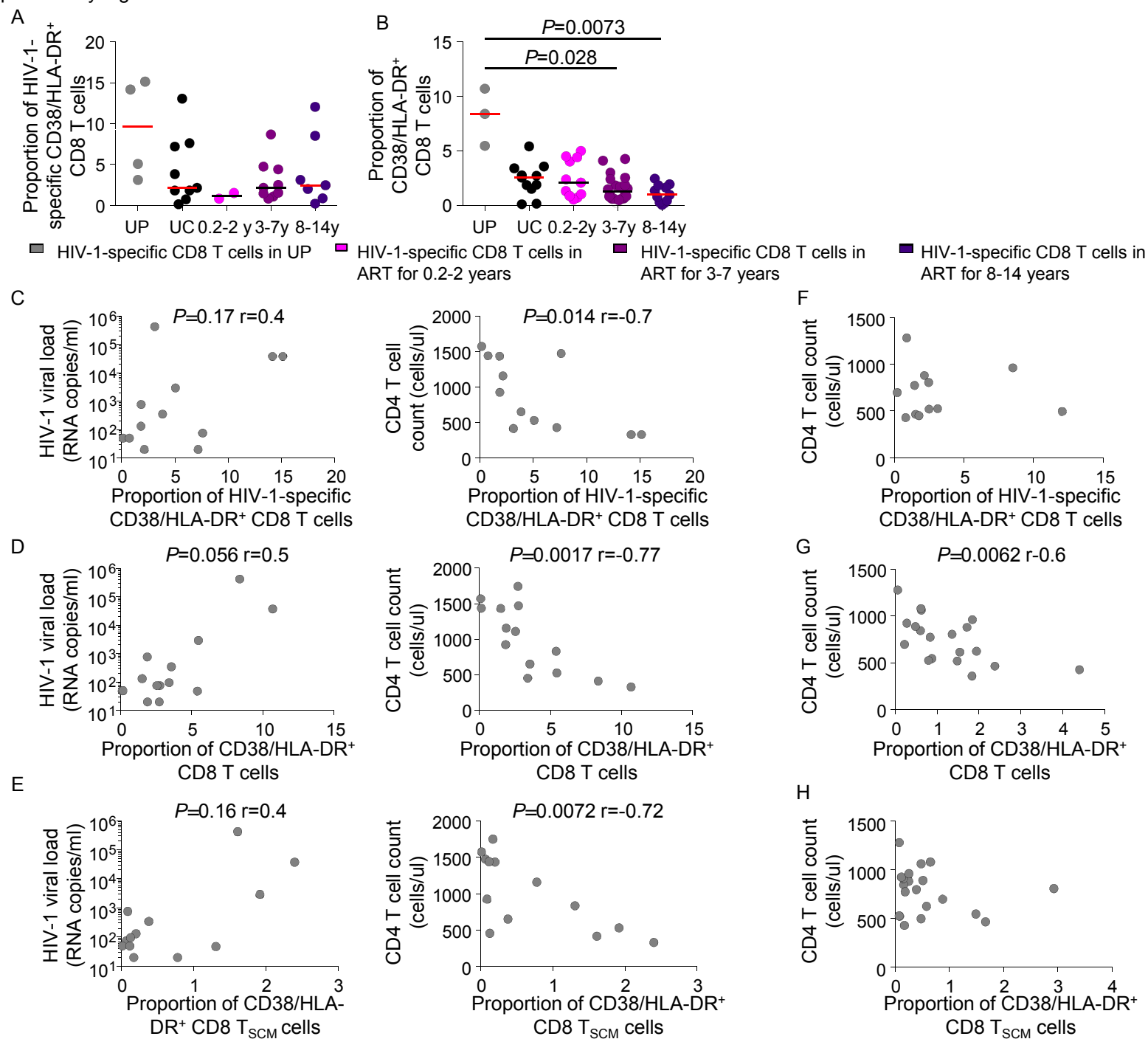
■ CD4 T cells in UP   ■ CD4 T cells in ART for 0.2-2 years   ■ CD4 T cells in ART for 3-7 years   ■ CD4 T cells in ART for 8-14 years

Supplementary Figure 5





Supplementary Figure 6



Supplementary Figure 7

