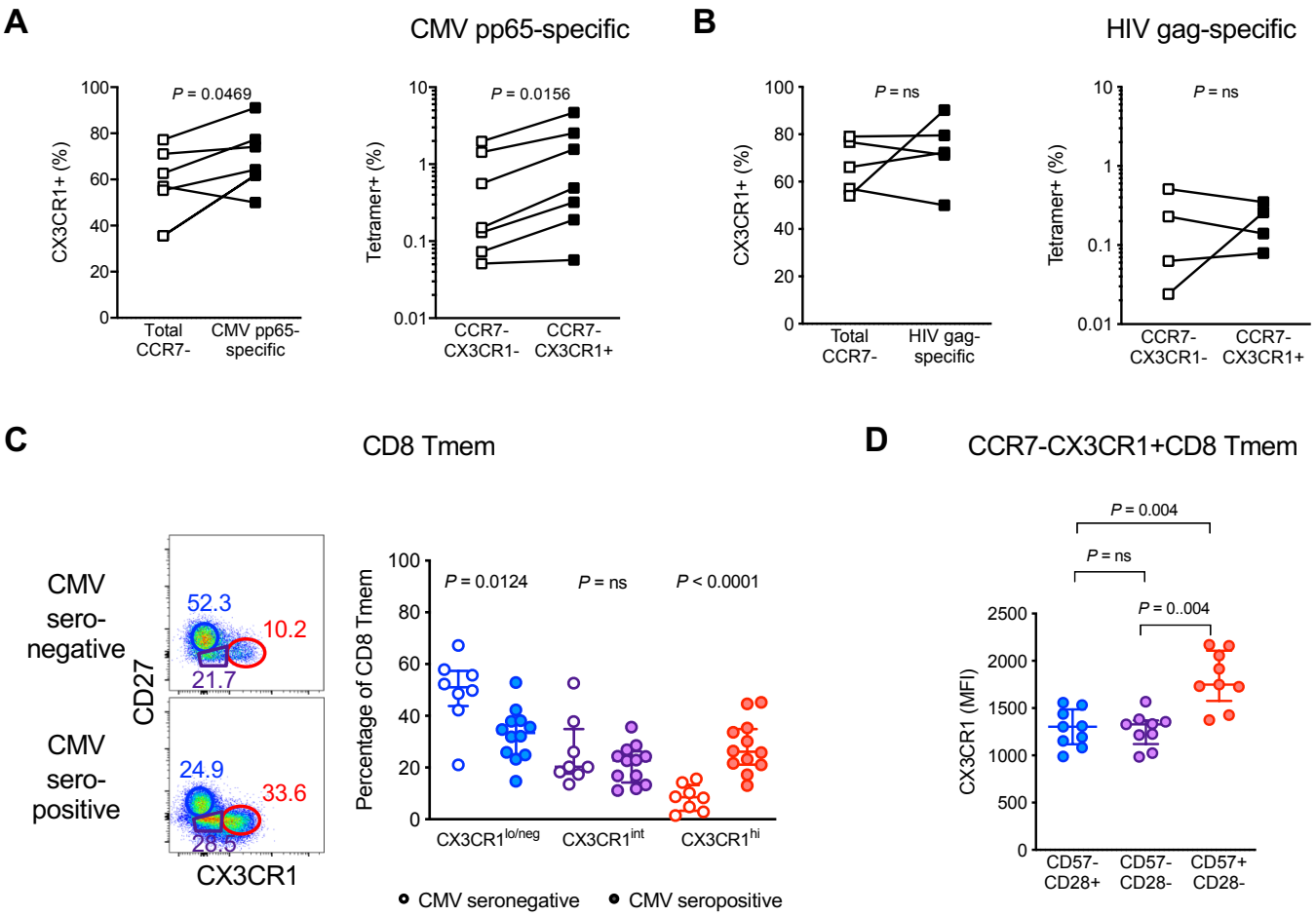

Figure S1. CX3CR1+CD57+CD28- CD8 Tmem and CX3CR1^{hi} CD8 Tmem are substantially the same population.

Proportion of total CCR7- CD8 Tmem or virus-specific CD8 Tmem that are CX3CR1+ (*left*) and percentage of CCR7-CX3CR1- and CCR7-CX3CR1+ CD8 Tmem that are virus-specific (*right*) for CMV pp65-specific (A) or HIV gag-specific CD8 Tmem (B) in CMV+ PLWH (n=4-7). (C) Representative staining and quantification of CD27+CX3CR1$^{lo/neg}$, CD27-CX3CR1^{int}, and CD27-CX3CR1^{hi} CD8 Tmem subpopulation in CMV- (n=8) and CMV+ (n=12) PLWH. Data represent median ± IQR. Significance determined by Mann-Whitney test. (D) CX3CR1 expression on indicated CD8 Tmem subsets in CMV+ PLWH (n=9). Data represent median ± IQR. Significance determined by Kruskal-Wallis test with Dunn's correction for multiple comparisons.

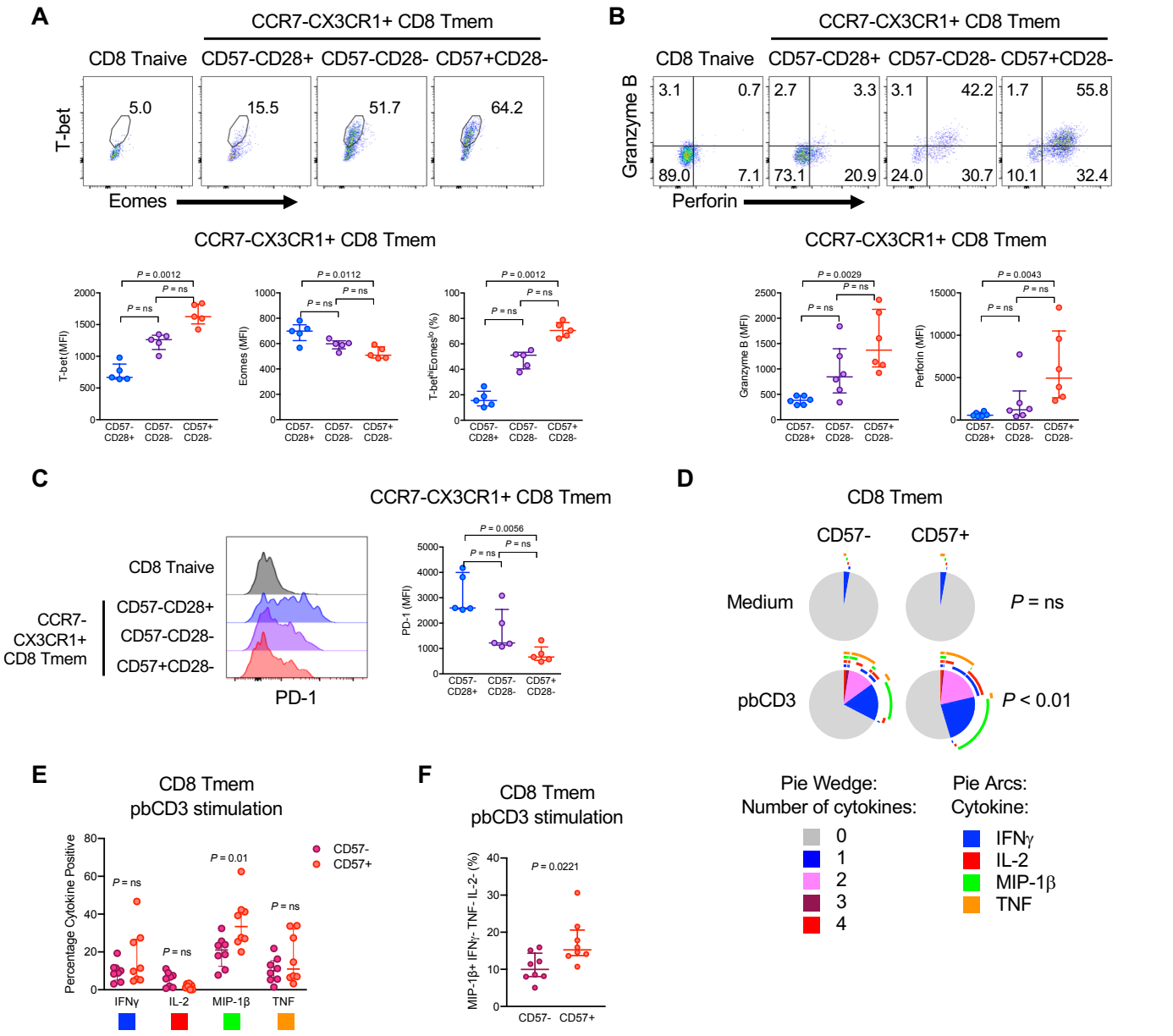

Figure S2. CX3CR1+CD57+ CD8 Tmem have a pro-cytolytic effector phenotype.
Intracellular expression of T-bet and Eomes (A), and granzyme B and perforin (B), and surface expression of PD-1 (C) in naïve CD8 T cells and in subsets of CCR7-CX3CR1+ CD8 Tmem stratified by CD57 and CD28 from CMV+ PLWH (n=5). Data represent median ± IQR. Significance determined by Kruskal-Wallis test with Dunn's correction for multiple comparisons. (D) Pie graphs showing cumulative intracellular cytokine expression in CD57+ and CD57- CD8 Tmem from CMV+ PLWH (n=6) after *in vitro* stimulation for 6h with medium control or with plate-bound anti-CD3 (pbCD3). Pie chart comparisons were performed using SPICE software (NIH). (E) Percentage of CD57- and CD57+ CD8 Tmem from CMV+ PLWH (n=8) that synthesize the indicated cytokines after *in vitro* stimulation for 6h with pbCD3. Data represent median ± IQR. Significance determined by Mann-Whitney test. (F) Percentage of CD57- and CD57+ CD8 Tmem from CMV+ PLWH (n=8) that are MIP-1β+IFNγ-TNF-IL-2- after *in vitro* stimulation for 6h with pbCD3. Data represent median ± IQR. Significance determined by Mann-Whitney test.

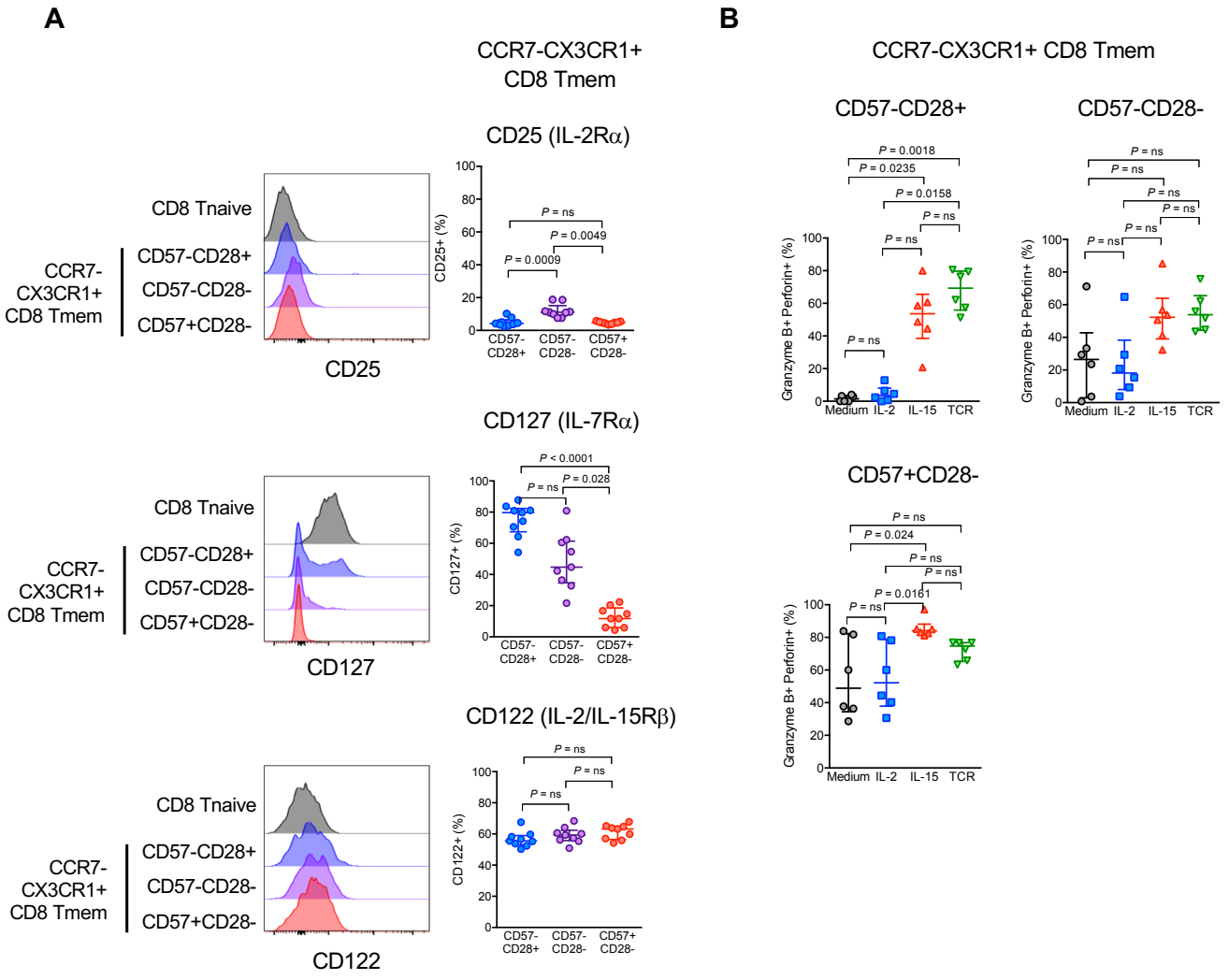

Figure S3. IL-15 promotes granzyme B and perforin expression in CX3CR1+ CD8 Tmem subpopulations. (A) Expression of IL-2Rα (CD25), IL-7Rα (CD127), and IL-2/IL-15Rβ (CD122) in naïve CD8 T cells and in subsets of CCR7-CX3CR1+ CD8 Tmem stratified by CD57 and CD28 expression from CMV+ PLWH (n=8). Data represent median ± IQR. Significance determined by Kruskal-Wallis test with Dunn's correction for multiple comparisons. (B) Granzyme B and perforin co-expression in subsets of CCR7-CX3CR1+ CD8 Tmem stratified by CD57 and CD28 expression 48h after indicated stimulation in CMV+ PLWH (n=6). Data represent median ± IQR. Significance determined by Kruskal-Wallis test with Dunn's correction for multiple comparisons.

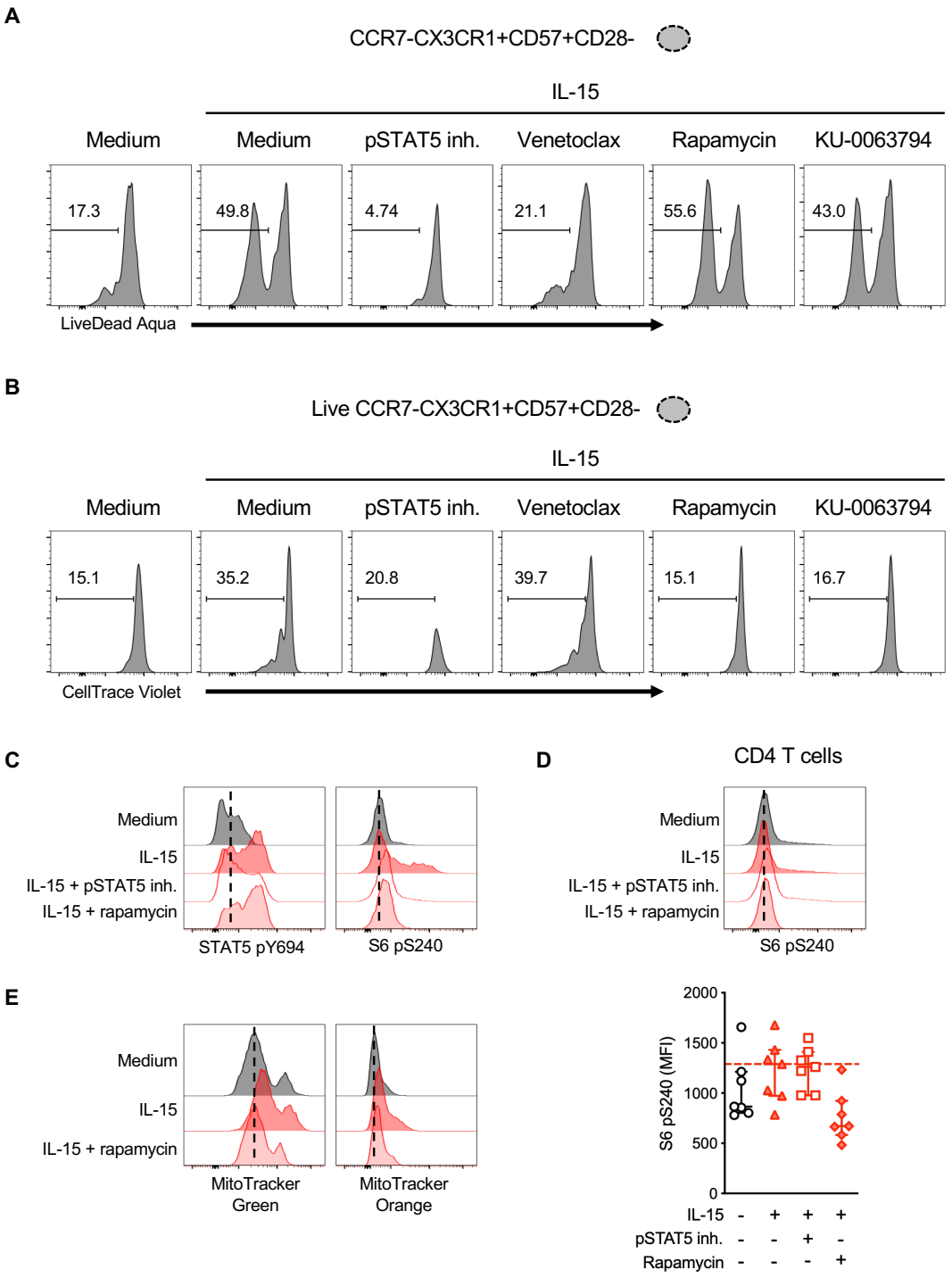

Figure S4. IL-15 promotes viability and proliferation of CCR7-CX3CR1+CD57+CD28- CD8 Tmem via STAT-5 activity.

Representative histograms showing labeling with Live/Dead Aqua (A) or CellTrace Violet (B) in sorted CCR7-CX3CR1+CD57+CD28- CD8 Tmem from CMV+ PLWH. Histograms in (B) are gated on viable cells shown in (A). (C) Representative histograms of STAT5 pY694 and S6 pS240 expression 45min after stimulation with medium control or IL-15 with or without indicated inhibitors in gated CD57+ CD8 T cells from CMV+ PLWH (n=9). (D) Representative histograms and quantitation of ribosomal S6 pS240 expression 45 min after stimulation with medium control or IL-15 with or without indicated inhibitors in CD4 T cells from CMV+ PLWH (n=9). Data represent median ± IQR. Significance determined by Kruskal-Wallis test with Dunn's correction for multiple comparisons. (E) Representative histograms of MitoTracker Green and MitoTracker Orange labeling in gated CD57+ CD8 T cells from CMV+ PLWH (n=9) following 4 days stimulation with IL-15 with or without rapamycin.

	HIV-uninfected	HIV-infected	*P*-value
n (female, %)	27 (29.6%)	51 (13.7%)	ns[1]
Age (y)[2]	34.5 (28-47.5)	57 (45-61)	< 0.0001[3]
Race/Ethnicity:			
Asian (n, %)	4 (14.8%)	0 (0%)	0.0123[1]
Black (n, %)	1 (4.7%)	26 (51.0%)	< 0.0001[1]
Hispanic (n, %)	1 (4.7%)	3 (5.9%)	ns[1]
White (n, %)	20 (74.1%)	21 (41.2%)	0.0084[1]
Unknown/Other (n, %)	1 (4.7%)	1 (2.0%)	ns[1]
CMV serostatus:			
Positive (n, %)	9 (33.3%)	42 (82.4%)	< 0.0001[1]
Negative (n, %)	10 (37.0%)	9 (17.6%)	
Unknown/Untested (n, %)	8 (29.6%)	0 (0 %)	

Table S1. Participant Characteristics, stratified by HIV infection status.
[1]Fisher's Exact Test
[2]Median ± IQR
[3]Mann-Whitney test
ns, not significant

	CMV-seronegative	CMV-seropositive	*P*-value
n (female, %)	9 (11.1%)	42 (14.3%)	ns[1]
Age (y)[2]	60 (54-61)	55.5 (45.25-61)	ns[3]
Race/Ethnicity:			
Asian (n, %)	0 (0%)	0 (0%)	ns[1]
Black (n, %)	4 (44.4%)	22 (52.4%)	ns[1]
Hispanic (n, %)	1 (2.4%)	2 (4.8%)	ns[1]
White (n, %)	4 (44.4%)	17 (40.5%)	ns[1]
Unknown/Other (n, %)	0 (0%)	1 (2.4%)	ns[1]
Estimated Period of Untreated Infection (y)[2]	0.22 (0.06-2.94)	1.16 (0.16-4.83)	ns[3]
Time on ART (y)[2]	13.79 (12.55-16.93)	10.96 (5.58-16.83)	ns[3]
ART Regimen[4]:			
NRTI (n, %)	7 (77.8%)	37 (84.1%)	ns[1]
NNRTI (n, %)	6 (66.7%)	13 (31.0%)	ns[1]
PI (n, %)	2 (22.2%)	13 (31.0%)	ns[1]
INSTI (n, %)	4 (44.4%)	18 (42.9%)	ns[1]
PK Enhancer (n, %)	1 (11.1%)	7 (16.7%)	ns[1]
CD4 T cells (cells per μl)[2]	513 (336-1010)	717 (503.25-847)	ns[3]
CD8 T cells (cells per μl)[2]	504 (451-783)	789.5 (583-1067)	ns[3]
CD4/CD8 ratio[2]	1.81 (0.67-2.20)	0.81 (0.60-1.04)	ns[3]
CD4 nadir (cells per μl)[2]	210 (5-260)	159 (62-320)	ns[3]

Table S2. Characteristics of HIV-infected participants, stratified by CMV serostatus.

[1]Fisher's Exact Test

[2]Median ± IQR

[3]Mann-Whitney test

[4]NRTI, Nucleoside reverse transcriptase inhibitor; NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; INSTI, Integrase strand transfer inhibitor; PK, Pharmacokinetic

ns, not significant