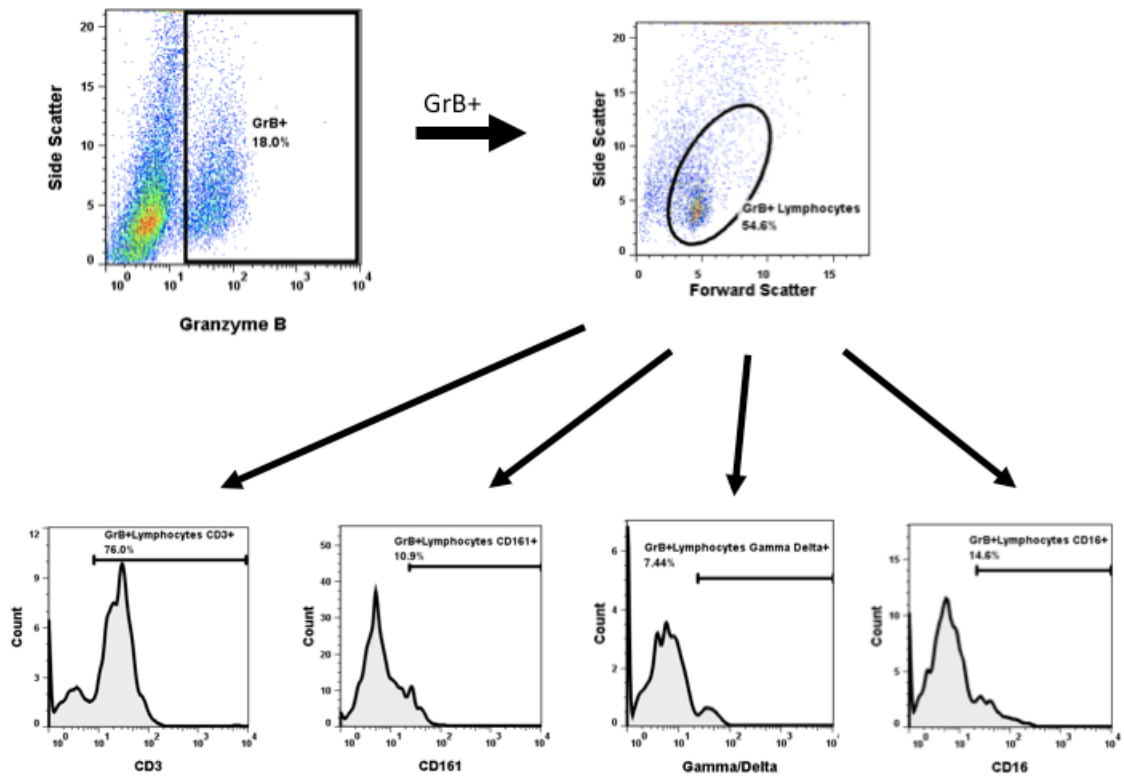**Figure S1. Gating Strategy for CMV-stimulated Teff and Treg.** The graph shows a typical representation of the Teff or Treg gating strategy. The **left** panel shows the lymphocyte gate in the forward/side scatter. The events in the lymphocyte gate are analyzed for CD3 and CD4 expression as shown in the **middle** panel. For convenience, CD3+CD4- events are used in substitution of CD3+CD8+. The **right** panel indicates total (upper and right rectangles) and double positive (upper right square) MIP-1b and TNFa expression
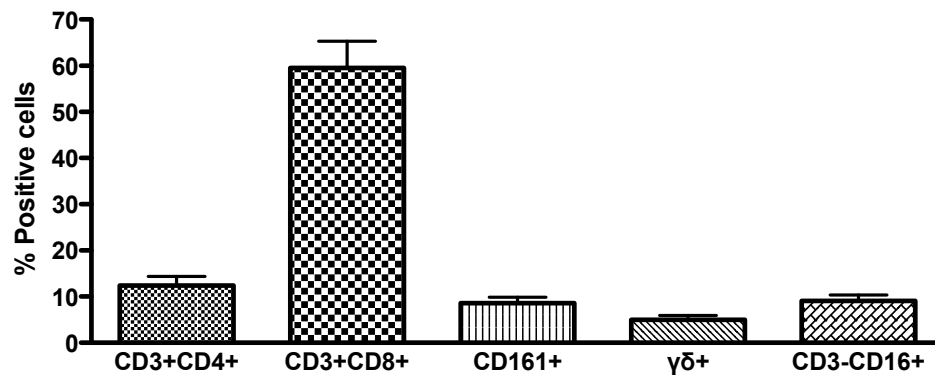
A

B

Figure S2. Distribution of lymphocytes responsible for CMV-specific GrB production. PBMC from 11 HIV-infected CMV-seropositive donors were infected with a low-passage live CMV clinical isolate, such that T cell epitopes were presented by CMV-

infected monocytes both in the context of HLA Class I and Class II. **Panel A** shows the gating strategy. Lymphocytes were identified by size and granularity (A1). Next, we identified the GrB+ lymphocytes (A2). Finally, we measured the proportions of different cell populations, including CD3+CD4+, CD3+CD8+, CD16+, CD161+ and $\gamma\delta$+ events among the GrB+ lymphocytes. **Panel B** shows means and SEM of the proportions of the different CMV-specific GrB+ lymphocytes.
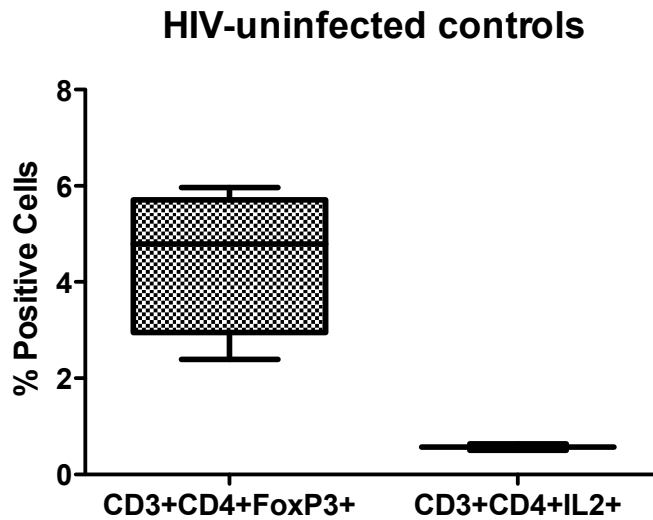
Figure S3. Examples of CD4+ subset frequencies in mock-stimulated PBMC from HIV-uninfected controls. Data were derived from 4 sets of PBMC from HIV-uninfected donors used as assay controls. Cells were incubated for 4 days under the same conditions as the cells obtained from HIV+ study subjects. Bars represent medians, 10th and 90th percentiles of CD4+FoxP3+ and CD4+IL2+%. The median frequency of CD4+FoxP3+% in mock-stimulated PBMC of HIV-infected subjects was 19.74% in CMV EOD cases and 7.05% in non-EOD controls, whereas healthy individuals had a median of 4.79%. Similarly, median CD4+IL2+% was 26.79% in CMV EOD, 7.50% in non-EOD and 0.59% in healthy individuals.

Table S1. GrB and IFNγ ELISPOT responses in **cases with CMV retinitis** and their CMV-seropositive matched controls without EOD.

Parameter	Cases			OR	p Value
	N	*Median (Q1-Q3) SFC/10^6 PBMC*	*N pos (%)*		
GrB	**22**	**210 (15- 375)**	**15 (68)**	**3.63**	**0.04**
IFNγ	22	1 (0- 7)	3 (14)	0.35	0.20

Table S2. GrB and IFNγ ELISPOT responses in **cases with non-retinitis CMV-EOD** and their CMV-seropositive matched controls without EOD.

Parameter	Cases			OR	p Value
	N	*Median (Q1-Q3) SFC/10^6 PBMC*	*N pos (%)*		
GrB	**12**	**78 (40- 295)**	**7 (58)**	**3.45**	**0.08**
IFNγ	11	0 (0- 29)	3 (27)	0.68	0.67