Supplemental Figures

**SI Figure 1:** CD127/PD1 co-expression analysis of enriched HBV-specific CD8+ T cells according to different phases of chronic HBV infection, patients who resolved a chronic HBV infection as well as of HCV-specific CD8+ T cells obtained from chronically HCV-infected patients. Each dot represents one virus-specific CD8+ T-cell population: HBeAg+ CHB, n=5; HBeAg- CHB/NUC treated HBeAg- CHB, n=30 and HBeAg- cHBV infection, n=20; crHBV, n=4; cHCV: n=12. Bar charts show the median value with IQR. Statistical analysis was performed via Kruskal-Wallis test including Dunn's multiple comparisons test (B). (*: p<0.05; **: p<0.01; ***: p<0.001)
**SI Figure 2:** Flow cytometric analyses of TOX expression of HBV core epitope-specific CD8+ T cells obtained from chronically HBV-infected patients. (A) Representative flow cytometry dot plots show circulating peptide/HLA-A*01:01 and peptide/HLA-A*11:01 tetramer-enriched HBV core$_{30}$- and HBV core$_{141}$-specific CD8+ T cells (black) and bulk CD8+ T cells (grey). The frequency of HBV core epitope-specific CD8+ T cells within the total CD8+ T-cell population is indicated. (B) Representative flow cytometric histograms of the TOX expression in HBV core epitope-specific CD8+ T cells including the gating and statistical graph summarizing the frequencies of TOX-expressing HBV core epitope-specific CD8+ T cells are displayed (black: HBV core$_{18}$, core$_{30}$- or core$_{141}$- specific CD8+ T cells; grey: bulk CD8+ T cells). Each dot represents one HBV core epitope-specific CD8+ T-cell population: HBV core$_{18}$, n=28; HBV core$_{30}$, n=5; HBV core$_{141}$, n=3. Bar charts indicate the median value with IQR. Statistical analyses were performed via Kruskal-Wallis test including Dunn’s multiple comparisons test (B).
**SI Figure 3:** Functional analyses of HBV-specific CD8+ T cells of chronically HBV-infected patients. (A) Representative dot plots showing cytokine production and degranulation by *in vitro* HBV peptide-expanded CD8+ T cells after PMA and ionomycin re-stimulation and without re-stimulation (gated on bulk CD8+ T cells). (B) AST and ALT values of patients with therapy-mediated versus endogenous viral control are depicted. Each dot represents one HBV-specific CD8+ T-cell population: NUC-treated HBeAg- CHB, n=15-24 and HBeAg- cHBV infection, n=12-20. Bar charts show the median value with IQR. Statistical analysis was performed via Wilcoxon test (B). (*: p<0.05; **: p<0.01).
SI Figure 4: (A) Subset definition of CD8+ T-cell differentiation stages is illustrated in the representative flow cytometry dot plots of virus-specific CD8+ T cells from chronically HBV-infected patients and healthy controls (black: TOX+ virus-specific CD8+ T cells; grey: corresponding bulk CD8+ T cells) (upper row). The frequency of virus-specific CD8+ T cells within the CD45RA/CCR7-defined differentiation stages is depicted in the lower row. (B) Co-expression analysis of TOX and EOMES or T-bet in virus-specific CD8+ T-cell populations. Representative flow cytometric histograms including gating of the individual markers are displayed (black: virus-specific CD8+ T cells; grey: bulk CD8+ T cells). (C) Expression levels of PD1, CD39, CD38, KLRG1, CD57, CD127, TCF1, EOMES and T-bet are plotted on the t-SNE plot. (D) Functionality of in vitro expanded CMV-, EBV- and FLU-specific CD8+ T cells obtained from healthy controls was assessed in terms of cytokine production (IFN-γ and TNF) and degranulation (CD107a) after peptide-specific re-stimulation for additional 5h. Representative dot plots showing cytokine production and degranulation by in vitro EBV peptide-expanded CD8+ T cells after PMA and ionomycin or peptide re-stimulation or without re-stimulation (gated on bulk CD8+ T cells). Frequencies of IFN-γ+, TNF+ or CD107a+ cells within the CD8+ T-cell population are depicted. Corresponding correlation analyses were performed with the frequency of TOX+ virus-specific CD8+ T cells at day 0 (ex vivo) and the ratio of cytokine producing (IFN-γ+ or TNF+) or degranulating CD107a+ CD8+ T cells divided by the frequency of HBV-specific CD8+ T cells after 14 days in vitro expansion as estimate for effector function in addition to proliferation. Each dot represents one virus-specific CD8+ T-cell population: HBV: HBeAg+ CHB, n=5; HBeAg- CHB/NUC treated HBeAg- CHB, n=30 and HBeAg- cHBV infection, n=20; healthy controls analyzing for CMV-, EBV- and FLU-specific CD8+ T cells: n=35-46. Bar charts show the median value with IQR. Statistical analyses were performed by Friedman test including Dunn’s multiple comparisons test (A), Ordinary one-way ANOVA including Tukey’s multiple comparisons test (B: T-betHigh) Kruskal-Wallis test including Dunn’s multiple comparisons test (B: Eomes, T-betHigh), and Spearman r correlation (D). (*: p<0.05; **: p<0.01; ***: p<0.001 ****: p<0.0001).