MRC Human Immunology Unit, University of Oxford, Oxford, UK. The IFN-γ enzyme-linked immunospot (ELI-Spot) assay is often used to map HIV-specific CD8 T-cell responses. We compared overlapping 15-mer pools with optimized CD8 epitopes to screen ELISpot responses in HIV-infected individuals. The 15-mer pools detected responses to previously undefined epitopes, but often missed low-level responses to predefined epitopes, particularly when the epitope was central in the 15-mer, rather than at the N-terminus or C-terminus. These factors should be considered in the monitoring of HIV vaccine trials.