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We aimed to investigate whether the character of the immunodominant HIV-Gag peptide (variable or conserved) targeted by CD8+ T cells in early HIV infection would influence the quality and quantity of T cell responses, and whether this would affect the rate of disease progression. Treatment-naïve HIV-infected study subjects within the OPTIONS cohort at the University of California, San Francisco, were monitored from an estimated 44 days postinfection for up to 6 years. CD8+ T cells responses targeting HLA-matched HIV-Gag-epitopes were identified and characterized by multicolor flow cytometry. The autologous HIV gag sequences were obtained. We demonstrate that patients targeting a conserved HIV-Gag-epitope in early infection maintained their epitope-specific CD8+ T cell response throughout the study period. Patients targeting a variable epitope showed decreased immune responses over time, although there was no limitation of the functional profile, and they were likely to target additional variable epitopes. Maintained immune responses to conserved epitopes were associated with no or limited sequence evolution within the targeted epitope. Patients with immune responses targeting conserved epitopes had a significantly lower median viral load over time compared to patients with responses targeting a variable epitope (0.63 log10 difference). Furthermore, the rate of CD4+ T cell decline was slower for subjects targeting a conserved epitope (0.85% per month) compared to subjects targeting a variable epitope (1.85% per month). Previous studies have shown that targeting of antigens based on specific HLA types is associated with a better disease course. In this study we show that categorizing epitopes based on their variability is associated with clinical outcome.

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