



HLA B57/5801 escape mutations in HIV-1 Gag do not influence the clinical course of infection

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Introduction:

There is evidence for a critical role of cytotoxic T lymphocytes (CTL) in controlling HIV replication during infection. HLA B57 and the closely related HLA B5801 are strongly associated with long-term non-progressive (LTNP) HIV-1 infection. Although the HLA B57/B5801 restricted CTL responses have been studied extensively, the mechanism behind the HLA B57/5801 mediated protection remains unclear. Recently described mutations in the HLA-B57/5801 Gag epitope TSTLQEQIGW (T242N and G248X) were associated with viral escape and loss of viral fitness. In our present study, we wanted to analyze whether the HLA B57/5801 restricted CTL responses enforce a strong selective pressure on HIV-1, resulting in viral escape mutants with reduced viral fitness.

Methods:

Biological virus clones were isolated from cryopreserved PBMC samples that were obtained longitudinally in the course of infection of six HLA B57/5801 individuals. Three of the six individuals showed progression whereas the other three individuals showed no or slow progression. To study viral evolution, regions of the Gag gene, including the TSTLQEQIGW epitope, were sequenced and analyzed.

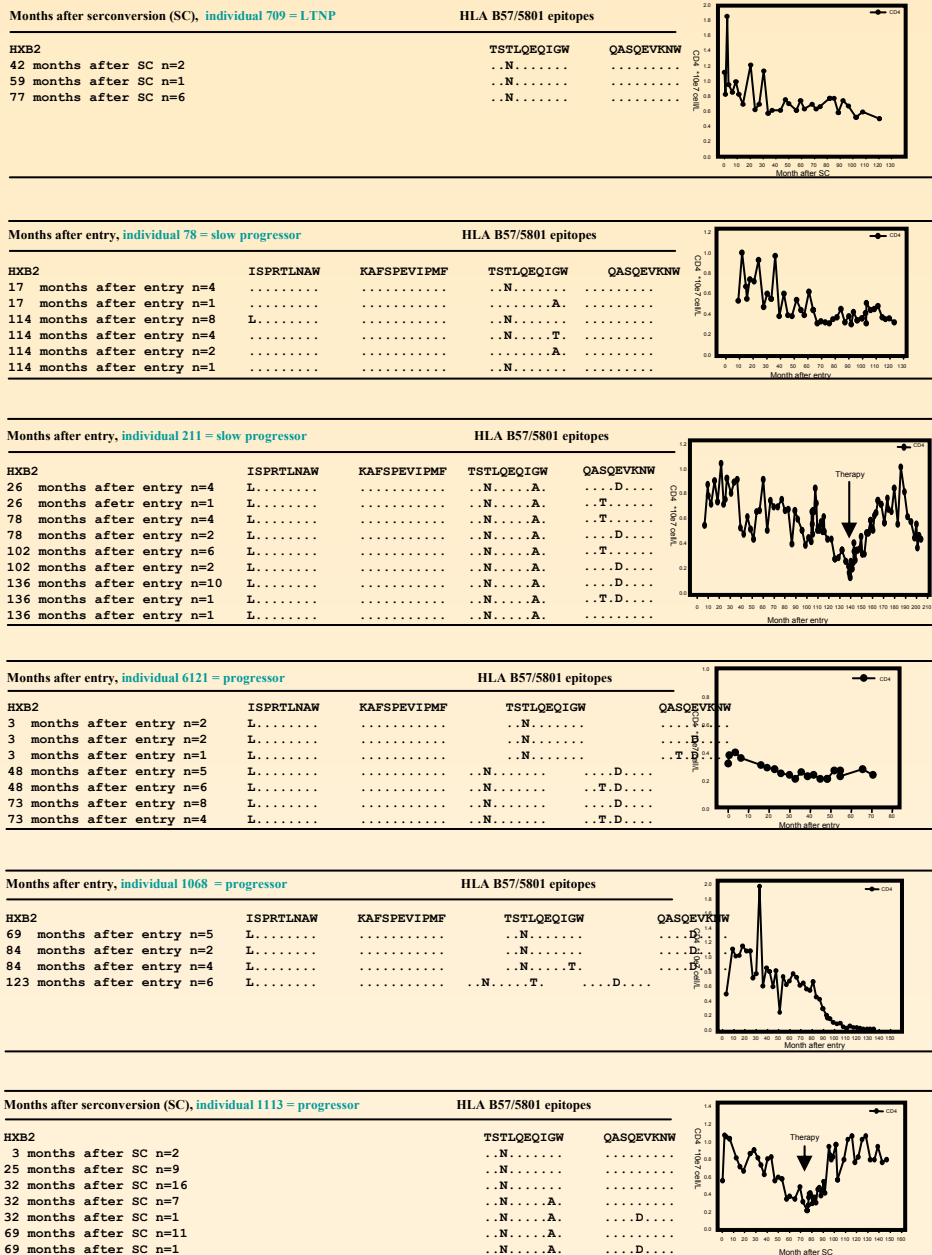


Figure II

The figure shows the sequence of a region of Gag containing the four HLA B57/5801 epitopes present in the Gag gene (with the exception of individuals 1113 and 709, here two of the four epitopes are shown) and de CD4 count of the three progressors as well as the 3 LTNP/slow progressors. The sequences of the epitopes are compared to the consensus epitope sequences of HXB2 at various timepoints throughout HIV-1 infection started at the point of seroconversion or entry into the Amsterdam Cohort studies.

Results:

None of the six individuals show mutations in the KF11 epitope. In both the IW9 and the QW9 epitopes there are mutations that have not been described before, whether these mutations are escape mutations induced by HLA B57/5801 specific CTL response is not yet known. The mutations T242N and G248X in TSTLQEQIGW have been described previously and associated with CTL escape. These mutations were present in all longitudinally obtained HIV-1 clones from all six individuals, irrespective of their clinical course of infection.

Conclusion:

In this study we show that viral evolution associated with an HLA B57/5801 directed immune response is present in both typical progressors as well as slow progressors. Because the escape mutations are observed in both progressors as well as slow progressors the clinical relevance of these mutations can be questioned.

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Figure I Procedure of clonal virus isolation

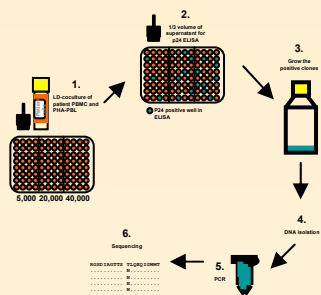


Table I Characteristics of HIV-1 infected individuals

Individual	LTNP	Slow progressor	Progressor
709	LTNP		
78		Slow progressor	
211		Slow progressor	
6121			Progressor
1068			Progressor
1113			Progressor