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Limited evidence for alterations in Gag-mediated HIV replication capacity over the course of the North American epidemic (1979-present)

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Background

The extent to which HIV replication capacity (RC) has changed over the epidemic's course, and the influence of HLA-associated immune pressure as its driving force remains unknown. We performed a comparative study of immune escape and RC in historic (1979-1989) and modern Gag subtype B sequences from North America.

Methods

Using phylogenetically-informed methods, we identified HLA-associated Gag polymorphisms in a historic cohort (N=239; 1979-1989). We also generated recombinant NL4-3 viruses encoding clonal plasma RNA Gag from 80 historic and 58 modern (2002-2008) sequences. Viral RC was measured using a GFP reporter T-cell assay and results were normalized to NL4-3 controls.

Results

95% of HLA-associated polymorphisms identified in the historic cohort were consistent with published modern escape pathways. Overall, the prevalence of HLA-associated polymorphisms in the general population increased a median 1.3-fold between historic and modern sequences; however in many cases this was influenced by differences in HLA allele frequencies between HIV-infected populations examined. Of note, the prevalence of the B*27-associated R264K escape mutation increased from 0.4 to 1.3% in the general population over time despite B*27 allele frequency remaining constant at 2.5%. Modestly lower viral RC was observed for Gag recombinant viruses constructed from pre-1985 sequences (median 0.86 [IQR 0.78-0.97], N=24) compared to those from 1985-1989 (median 0.98 [IQR 0.87-1.05], N=56) and 2002-2008 (median 0.96 [IQR 0.83-0.1.10], N=58) (p=0.049). In both historic and modern cohorts, host expression of HLA-B*27 was associated with lower RC (p=0.007). Gag codons associated with lower RC, including S67A, were identified in an exploratory analysis.

Conclusion

Gag-mediated viral RC may have increased modestly since the beginning of the North American epidemic, despite limited evidence for HLA-driven viral sequence evolution during this time. Although mechanisms driving RC differences remain unclear, results do not support rapid and substantial accumulation of HLA-driven escape mutations in circulating North American HIV-1 sequences.

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