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Intrahost evolution of HIV-2 p24 correlates with progression to AIDS

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Research question:
Does intrahost evolution of HIV-2 p24 associate with disease outcomes?

Background:
- HIV-2 infection will progress to AIDS in most patients without treatment
- HIV-2 progresses to AIDS at half the rate of HIV-1 infection
- Gag-specific cytotoxic lymphocyte (CTL) responses have been linked to long-term non-progression of HIV-2 infection

Methods:
- We included **12** ART-naïve HIV-2 infected adults
- All had longitudinal CD4% and clinical staging data
- Gag amplicons of 735 nucleotides were amplified, cloned and sequenced from 25 longitudinally collected blood plasma samples
- Sequences were analysed by Bayesian phylogenetics

Results:
- 371 heterochronous HIV-2 *p24* sequences were included in the final analysis
- CD4+ T cell data was used to stratify patients into faster and slower disease progressor groups (**FIG.1**)
- Faster progressors had lower CD4% levels at the midpoint of follow-up, and faster CD4% change rates
- The time to AIDS was approximately twice as long among slower progressors than faster progressors

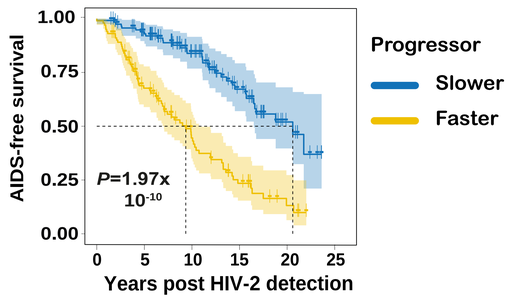


Figure 1: Kaplan-Meier curves for time to AIDS for progressor groups. Median time to AIDS was 9.4 years among faster progressors (yellow) and 20.6 years in slower progressors (blue) (logrank P<0.001).

- *p24* evolved under negative selection in both progressor groups
- Site-specific selection pressure was overwhelmingly negative (**FIG. 2**)

1) HIV-2 p24 intrahost evolution is highly constrained, with a low nonsynoymous evolutionary rate

2) Higher evolutionary rates are associated with lower CD4% in follow-up, and shorter time to AIDS

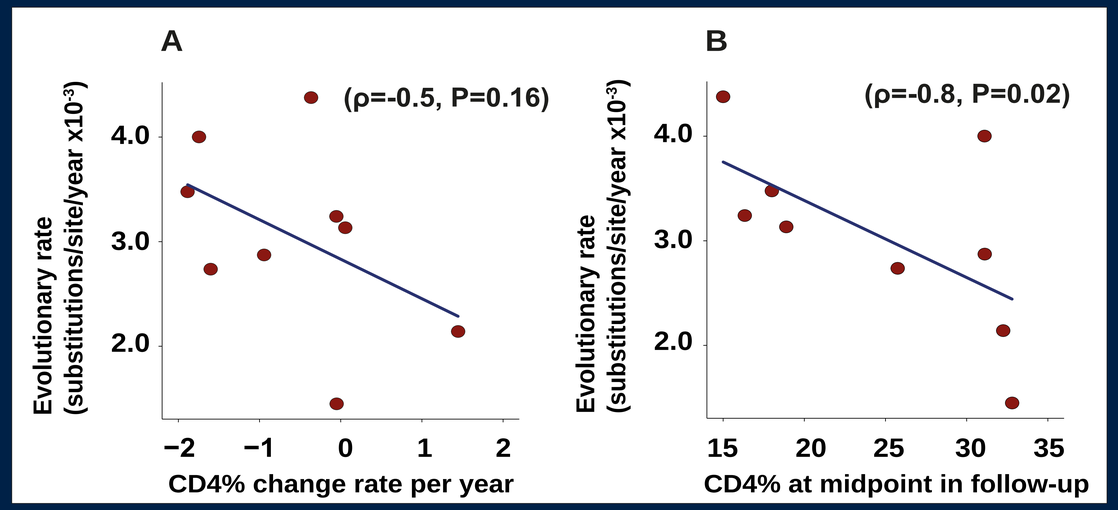
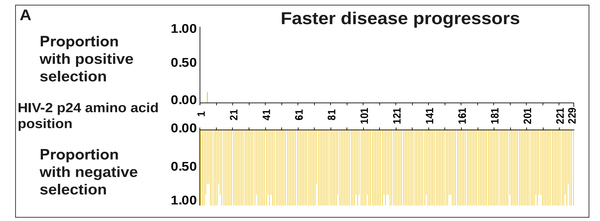


Figure 4: Correlation of evolutionary rates with CD4% rate of change and midpoint CD4%.



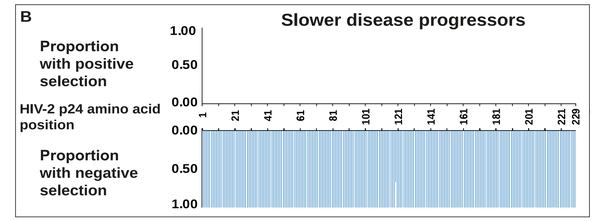


Figure 2: Per-site selection pressures in HIV-2 p24 by progressor groups. Prominent negative selection. Faster progressors (yellow) and slower (blue). X-axis shows the amino acid position in HIV-2 p24.

- Synonymous and nonsynonymous substitution rates were higher in faster than slower progressors ($4.5x10^{-3}$ vs. $1.6x10^{-3}$ and $5.9x10^{-4}$ vs. $2.7x10^{-4}$ substitution/site/year, P<0.001)
- Synonymous substitution rates were an order of magnitude higher than nonsynonymous substitution rates (**FIG. 3**)
- Viral evolutionary rates correlated negatively with CD4% level but not CD4% rate of change (**FIG. 4**)

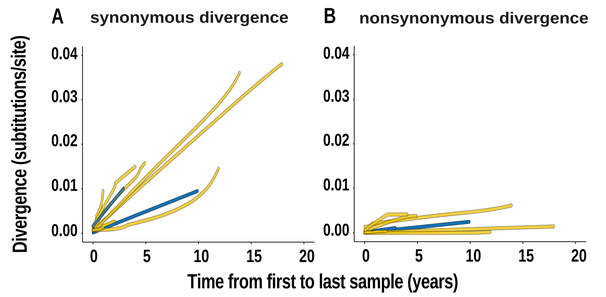


Figure 3: HIV-2 synonymous and nonsynonymous divergence over time by progressor groups. The accumulated divergence (y-axis) from the first sample for each patient indicated by time = 0 (x-axis). Faster progressors (yellow) and slower (blue).

Discussion:
- Negative selection is the main mode of evolution in HIV-2 *p24*
- Despite the association of Gag-specific CTL responses with long-term non-progression we found no evidence of positive selection in known CTL epitopes
- These results suggest that viral replicative capacity and immune activation drive progression to AIDS in HIV-2 infection

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