CTL escape in variable Gag proteins associated with rapid disease progression

Denis Chopera, PhD

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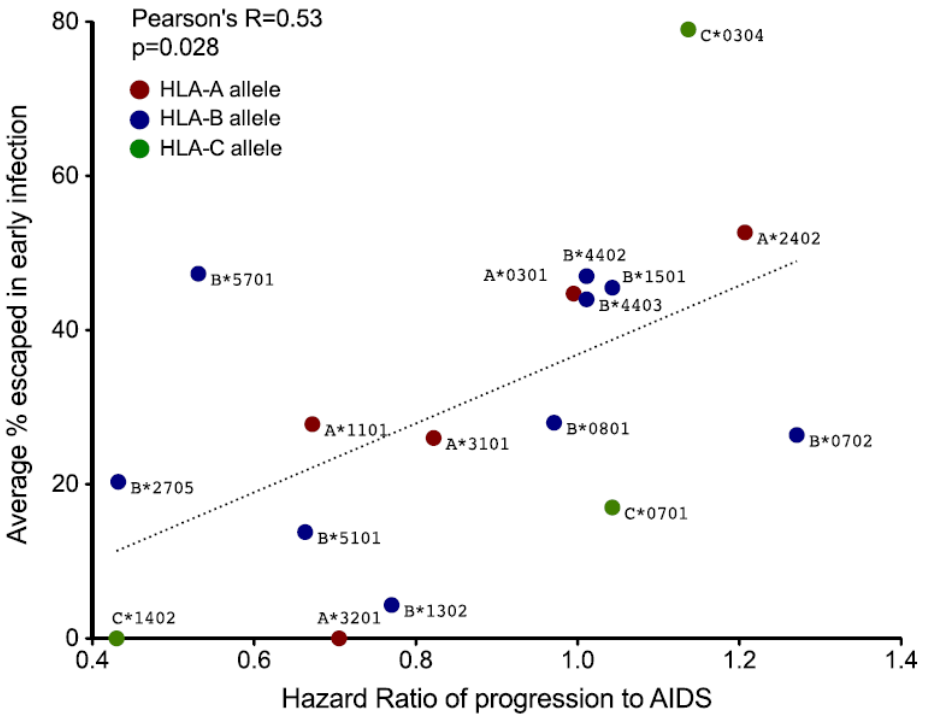
Background

- Specific HLA-driven viral evolution in Gag in acute and chronic infection known to affect disease progression (e.g. T242N, R264K)
- Most studies assessing the impact of CTL escape on disease progression have focused on specific HLA alleles and epitopes
- A recent study in subtype B reported that hazardous HLA alleles predominantly select for escape mutations in acute infection while protective alleles select for escape mutations in chronic infection
- The extent to which CTL escape mutations in acute/early subtype C infection influence long term disease outcome has not been well studied

Early CTL escape in subtype B associated with HLA hazard



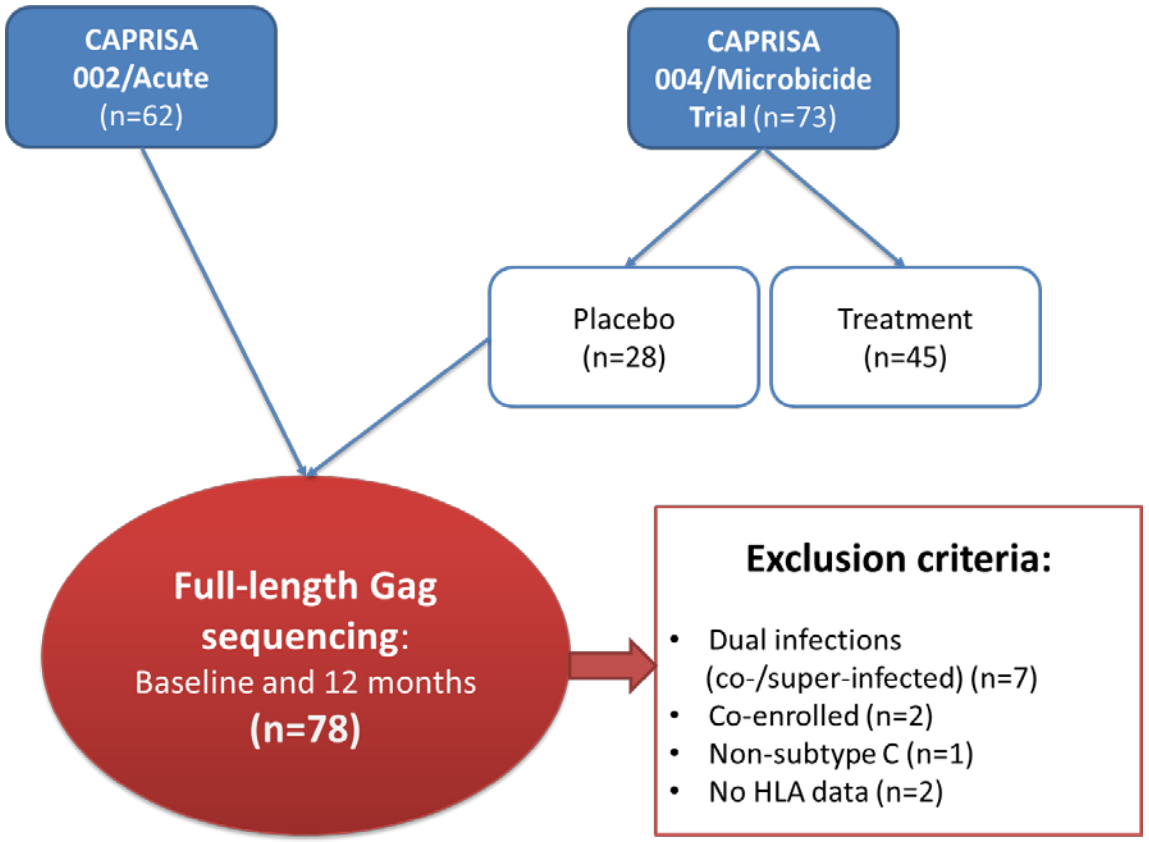
Martin E., Carlson J. et al., 2014

What is the impact of early CTL escape in Gag on long-term disease progression in subtype C infection?

Aim

To comprehensively assess the impact of acute/early HLA-associated escape on disease progression over the first five years of infection

Study design



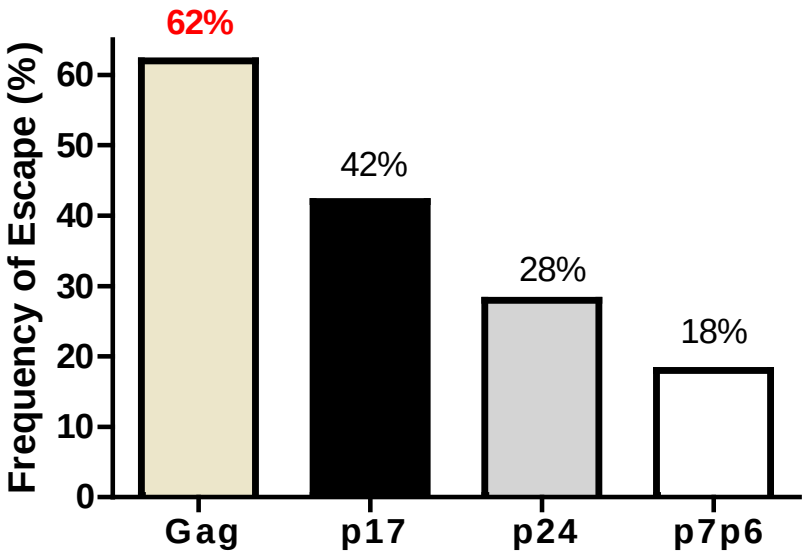
Definition of Escape:

- Mutation towards an HLA-adapted AA
- Mutation away from a non-adapted AA

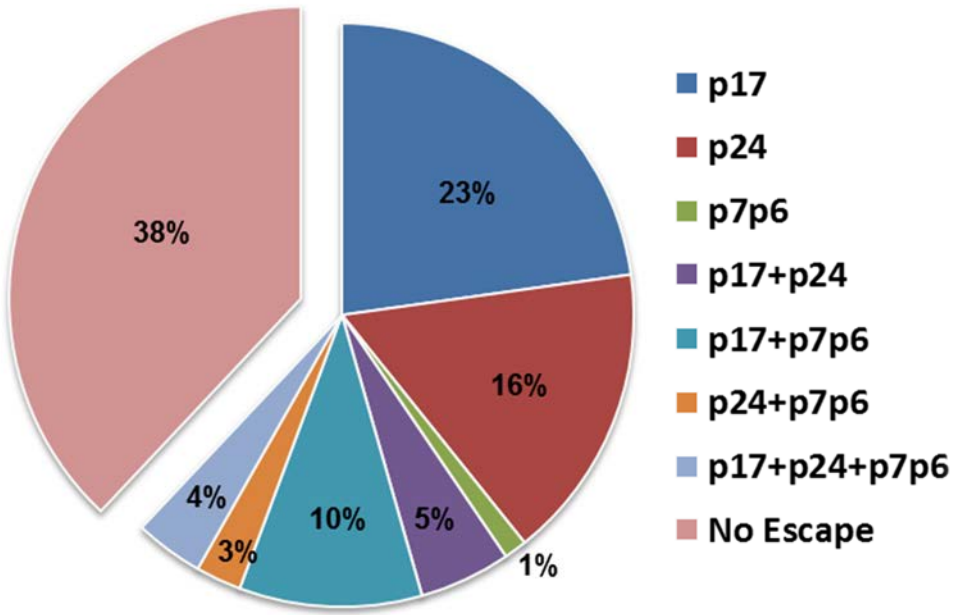
[Carlson et al (2012) and unpublished]

High frequency of escape in acute/early infection

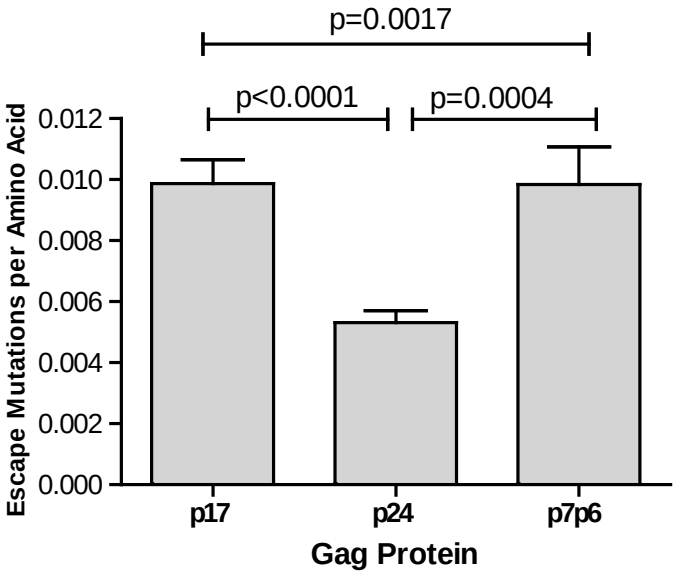
Frequency of Gag escape

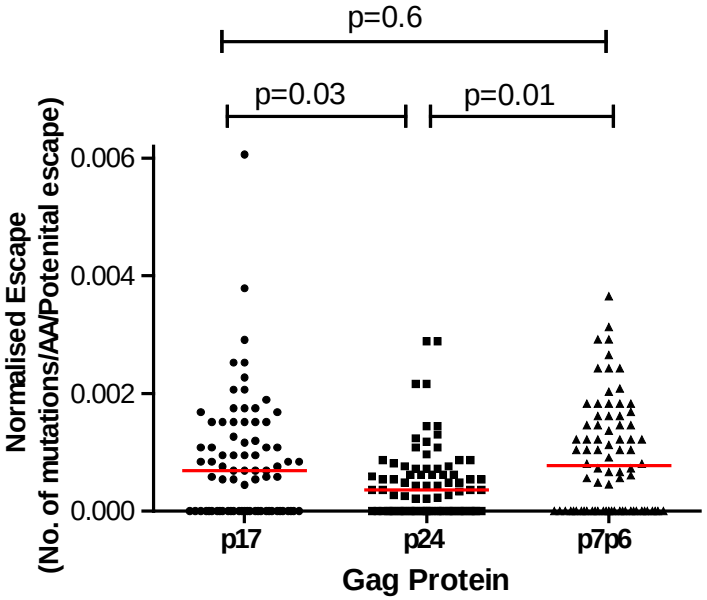


Distribution of escape in Gag



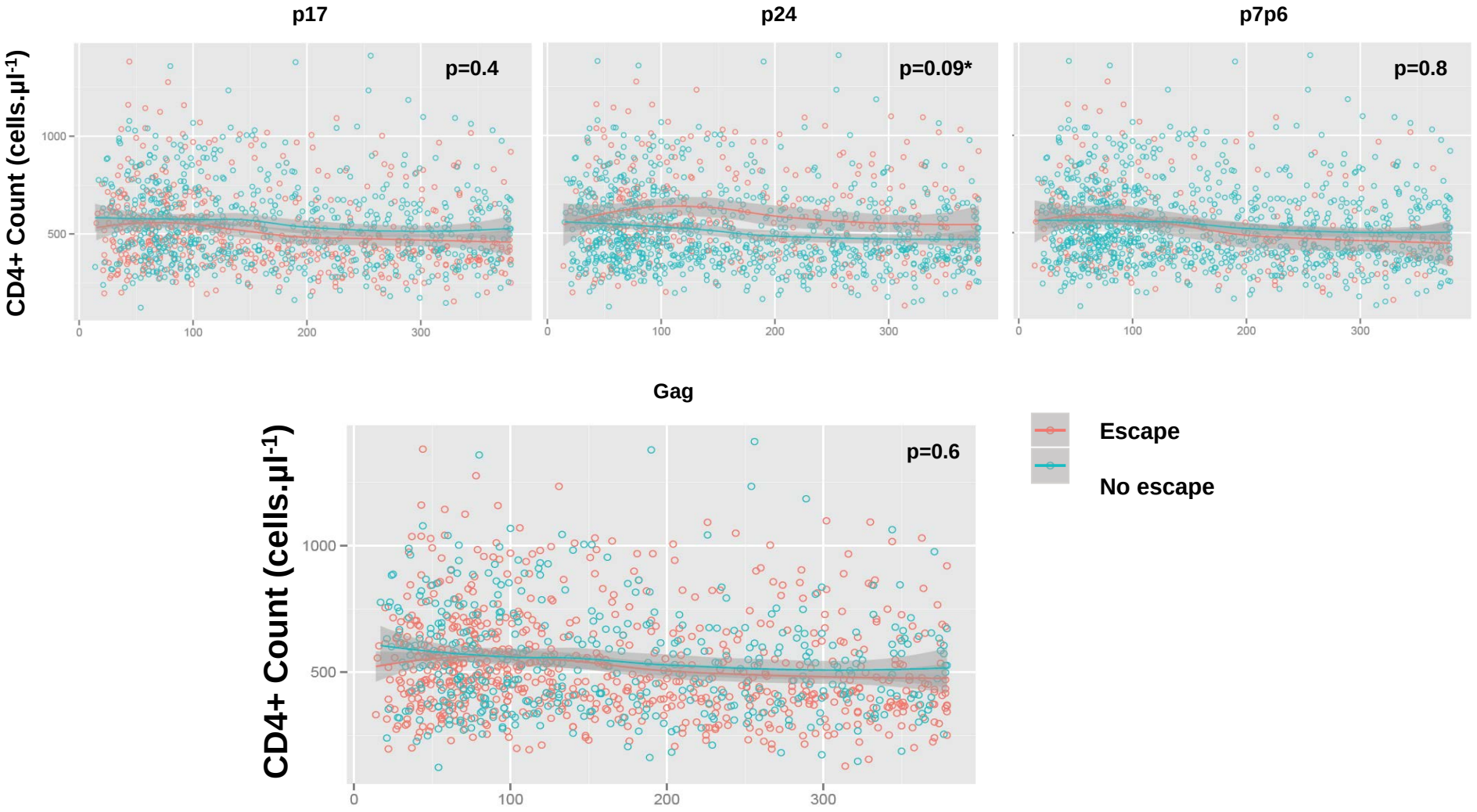
Early escape predominantly occurs in p17 and p7p6





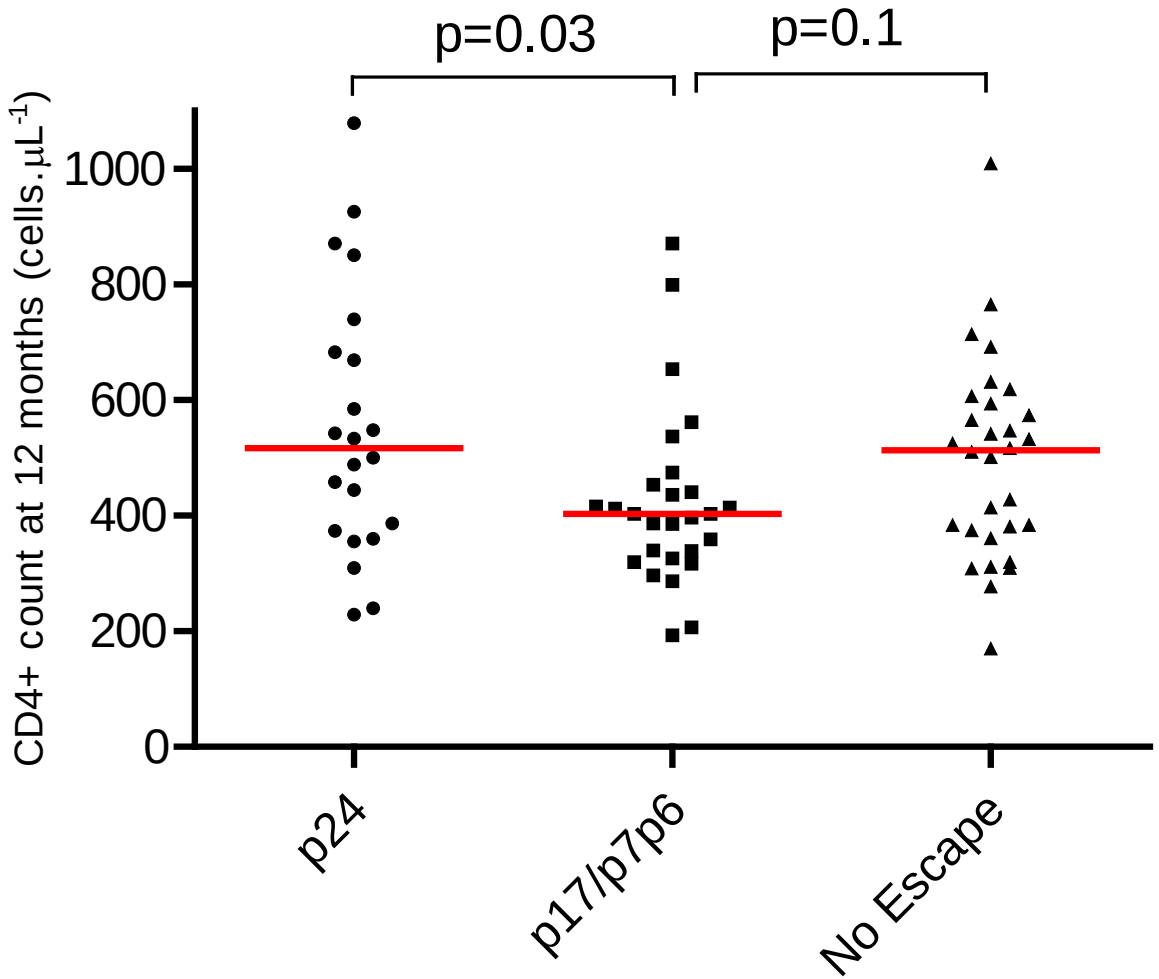
First year of infection:

Early escape does not appear to affect disease progression



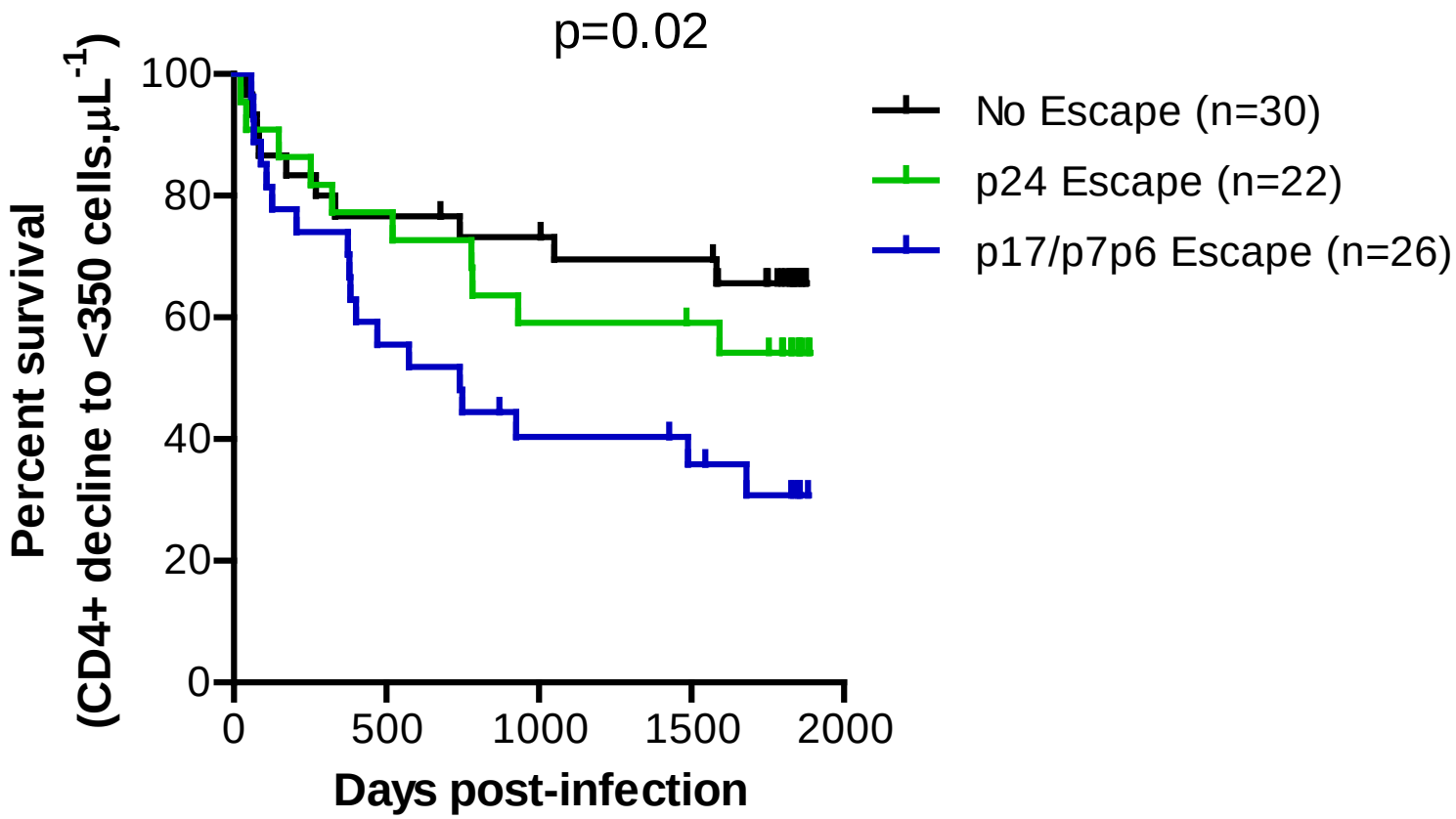
One year post-infection:

Escape in variable regions associated with lower CD4+ counts



Five year post infection:

Escape in variable regions associated with rapid CD4+ decline



Summary

- We observed a high frequency of acute/early CTL escape (62%)
- Early escape predominantly occurred in variable Gag regions (p17 and p7p6)
- Individuals showing escape in p24 had a higher CD4+ count at 12 months post infection than those who escaped in variable Gag proteins
- Early escape in Gag is associated with increased CD4+ decline over the first five years of infection
- CD4+ decline is more rapid in individuals who developed escape in variable Gag proteins alone

Conclusion

Early/acute CTL escape is associated with rapid disease progression and this is more pronounced in variable Gag regions

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