Increasing Neutralisation resistance in HIV-1 Clade C over the course of the southern African Epidemic.

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HIV-1 Transmission and Antigenic Drift

**Transmitted Virus Envelope Characteristics**
- Higher env content
- Enhanced fusion
- Shorter Loops (A,C but not B)
- Reduced glycosylation

**Antigenic Drift**
- Increased divergence and resistance.

(Parrish et al., 2013; Derdeyn ‘04, Chohan ‘05, Lui ‘08, Ping’13, Sagar’09, Gnanakaran’11, Bouvin-Pley 2013, 2014, Hraber ‘14, Bunnik ‘10)
Outline

1. What viral characteristics predict neutralisation sensitivity and serotype?
2. Are TF viruses genotypically different from chronic viruses?
3. Is the antigenic diversity of the HIV-1 epidemic changing over time?
Clade C Pseudovirus-Panel (n=200)

- Classification
  - TF n=152: ≤3 amino acid mismatches from consensus generated from ≥5 SGAs
  - nTF n=34: >3 amino acid mismatches from consensus
  - ND n=14
  - Chronic: External sequence dataset >2 years post infection (n=113)
Neutralization properties

- 30 South African serum samples from chronic infection
- > 3 years of infection and/or CD4 200-400 cells/µl
- Collected 2011-2013
- Within Clade-Coverage
  - 13% of serum able to neutralise >90% of viruses
  - 83% of serum able to neutralise >50% of viruses
Virus relatedness does not predict neutralization serotype

**Approach:** Comparison of serum dendogram topology (hierarchical clustering of neutralization susceptibilities) and phylogenetic topology using permutation approach and Mantel test.

- Polyclonal serum recognise conserved neutralization determinants across the southern African clade C epidemic.
Limited regional differences in virus susceptibility

Approach: Compared country matched (ZA serum against ZA viruses) to mismatched (ZA serum against BW, MW, TZ and ZM viruses) responses;

- Responses of country matched and mismatched viruses were similar.
- Confirming that neutralisation determinants are largely shared between southern African countries.
Env pseudovirus characteristics correlate with neutralization sensitivity

- Negative correlation of neutralisation sensitivity with: V1V2 hyper variable loop length. (Spearmans’ rank correlation test)
- Weak positive correlation of neutralisation sensitivity and overall V1V2 net charge (Kendalls rank correlation tau)
TF viruses are genotypically different from chronic viruses.

**Approach:** Compared TF viruses to chronic dataset (> 2 years from infection).

- TF viruses have significant shorter loop length and reduced glycosylation.
- As loop length is correlated with resistance, this implies that TF viruses may be expected to be more neutralization sensitive than chronics.

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**One sided Mann-Whitney**

![V1V2 loop length](image)  
![V1V2 Glycan Density](image)
Reduced V1V2 Loop Lengths in acute Clade C & A

Acute and Early V1V2 loop length compared to chronics per clade C, B CRF01_AE and A

One sided Mann-Whitney

- Reduced V1V2 loop length in early samples observed for Clade C and A, but not for B and CRF01_AE
Reduced branch lengths in samples collected from early in the epidemic (Korber et al.)
Changing antigenic diversity of the HIV-1 Clade C epidemic

Divergence (branch length from midpoint root) correlated positively to year

Neutralisation sensitivity correlated negatively to divergence.

Kendall's rank correlation tau test

- Increasing divergence over time, together with increased resistance with divergence implies indirectly that viruses are becoming more neutralization resistant over the course of the epidemic (Korber et al)
Conclusion

1. Common neutralization determinants across the southern African epidemic exist, suggesting that it will be possible to develop vaccines that provide regional coverage.

2. TF clade C viruses are genotypically distinct from chronic viruses, containing compact variable loops with reduced glycosylation.

3. There is antigenic drift over the course of the epidemic which implies that vaccines may need to be adapted over time to track viral divergence.

This panel of Clade C transmitted founder viruses provides reagents that are current and biologically more relevant than cross-sectional collections, supporting the rationale for development of acute PSV registry with which to evaluate vaccine responses and inform vaccine design.
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