29th Annual Canadian Conference on HIV / AIDS Research

29e Congrés annuel canadien de recherche sure le VIH/sida

Characterization of Gag mutations in long term non progressors infected by HIV-1 non-B subtypes

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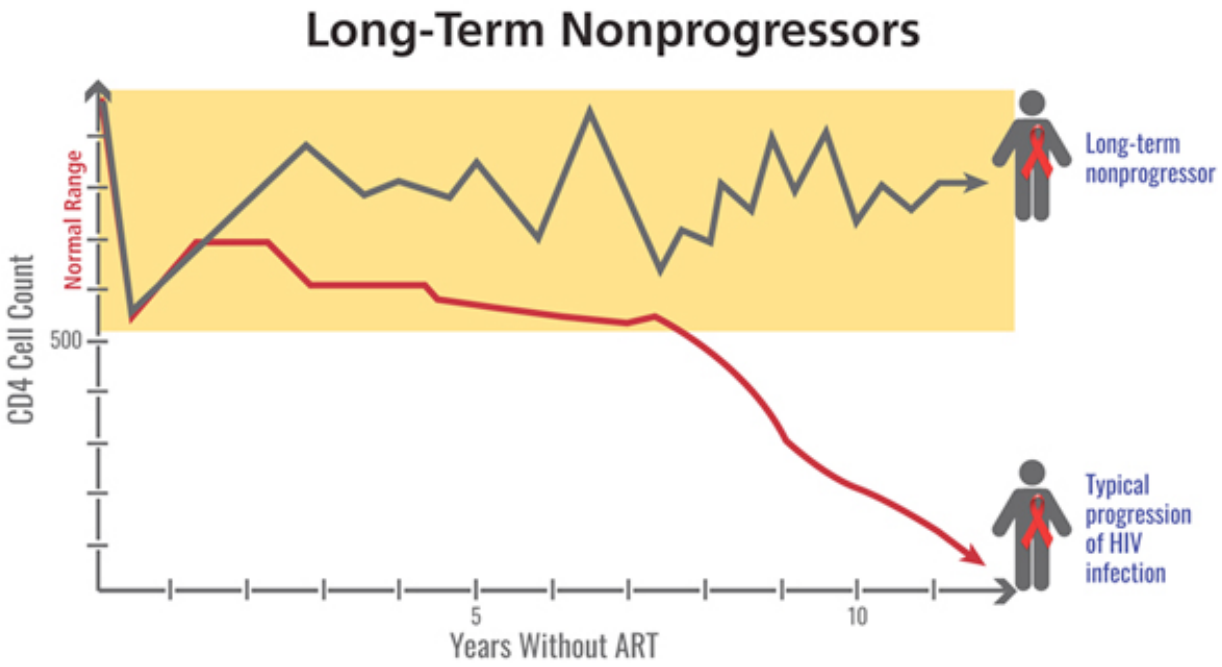
CONFLICT OF INTEREST DISCLOSURE

I have no conflicts of interest to declare

BACKGROUND: LONG TERM NON PROGRESSORS



- In the absence of ART, people living with HIV will typically develop AIDS within 10 years of infection.
- A small subset (<10%) of people living with HIV, known as Long term non progressors (LTNPs), maintain normal CD4 T-cell counts and remain asymptomatic for a decade or longer. Many LTNP also naturally control viremia to relatively low levels.

Factors associated with HIV slow disease progression in the absence of therapy remain incompletely understood.

https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/423/long-term-nonprogressors

Grabar S et al., AIDS 2009

RATIONALE

- Protective HLA alleles and robust $CD8^+$ T cell responses contribute to immune-mediated HIV control.
- Selection of viral escape mutations in targeted epitopes due to adaptation to immune pressure can result in loss of HIV control.
- Some escape mutations reduce viral protein function and/or replication capacity, and such fitness costs likely constrain the extent to which HIV can adapt to host immunity.
- A better understanding of viral adaptation pathways and associated fitness costs across HIV-1 subtypes may inform vaccine development and cure research efforts.

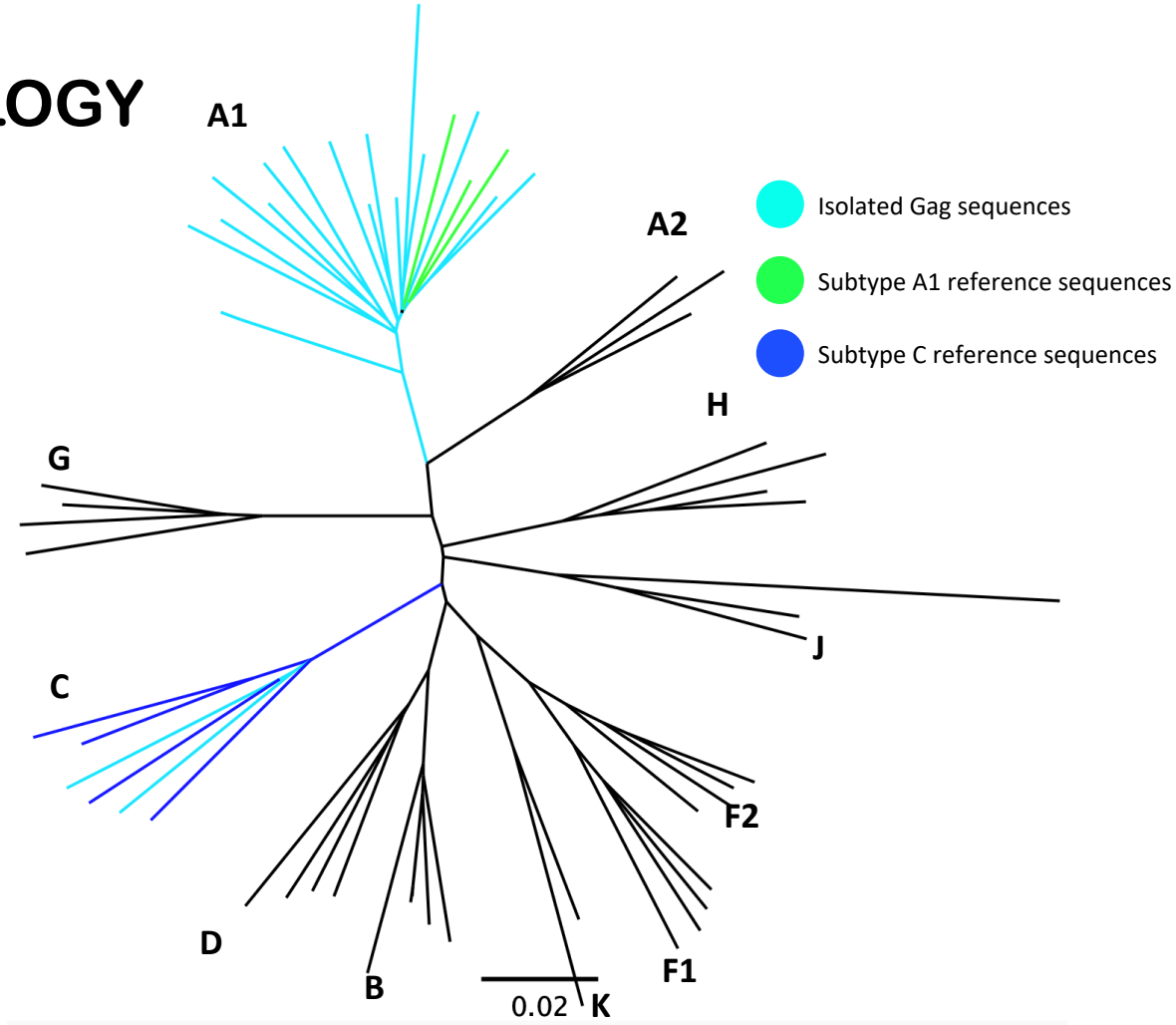
METHODOLOGY

Plasma HIV-1 RNA was isolated from 20 ART-naive LTNPs in a Rwandan cohort

- Normal CD4 count for > 25 years (median 453 cells/mm^3)
- Median plasma viral load 3.61 Log_{10} HIV RNA copies/ml

⬇

- Gag Nested RT- PCR
- Sanger sequencing
- Phylogenetic inference and HIV subtype classification
- Known HLA-driven mutations in Gag were identified by sequence alignment to consensus reference strains.

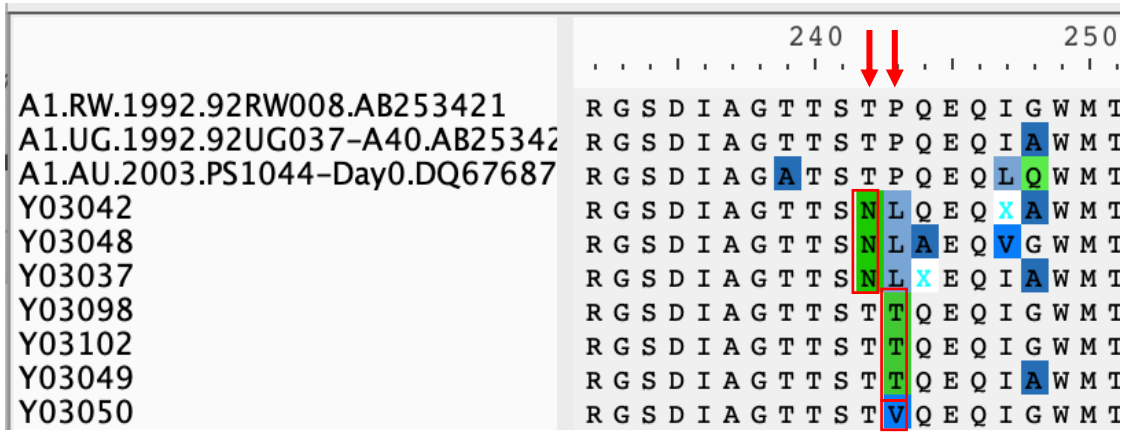


Phylogeny inferred from HIV subtype reference and study sequences.

Viral subtypes are indicated by letters. 90% of isolated Gag sequences were subtype A1.

RESULTS

Amino acid alignment showing T242N, P243T and P243V variations in the Gag TW10 epitope



Selection of known HLA-driven Gag mutations observed in the dataset

HLA TYPE	HLA B*57/58							B*44
EPITOPE	KF11	TW10			QW9	IW9		AW11
MUTATION	A163G	T242N	P243T	P243V	E312D	L147M	L147V	S310T
N (%)	6 (30%)	3 (15%)	3 (15%)	1 (5%)	8 (40%)	1 (5%)	2 (10%)	12 (60%)

- Many of the identified mutations were previously shown to reduce *in vitro* HIV replication capacity, suggesting that viral attenuation is common in this group.

CONCLUSIONS

- Reduced viral fitness associated with Gag sequence variation may contribute to long term non progression in this group.

- Our future work will confirm this hypothesis by measuring the replication capacity of selected Gag clones.

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