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Gag-protease-mediated Replication Capacity Differs According to HIV-1 Subtype

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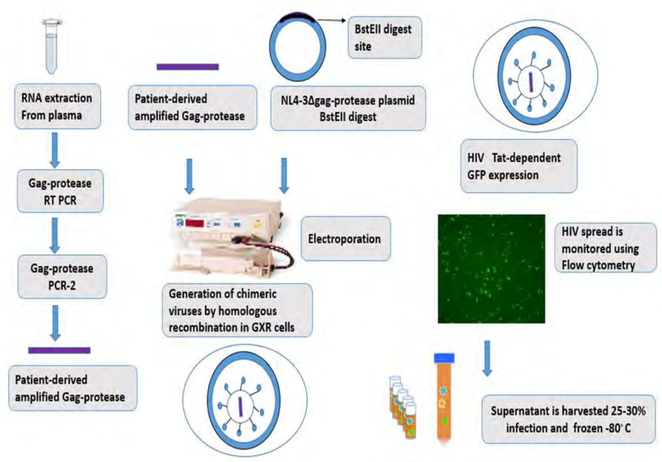
Background

- The global HIV-1 epidemic is characterized by extraordinary genetic heterogeneity with diverse subtypes prevalent in distinct geographical areas.
- In East Africa, subtypes A, C, D and their recombinants co-exist and subtype-specific differences in disease progression and epidemic spread have been noted. However, the underlying mechanisms for these differences are unknown.
- In the present study we aimed to determine whether there were subtype-specific replication capacity differences in recombinant viruses possessing *gag-protease* genes.
- We hypothesized that Gag-protease recombinant viruses derived from subjects who are infected with HIV-1 subtypes A, C, D and recombinants will show differences in replication capacity.

Materials and Methods

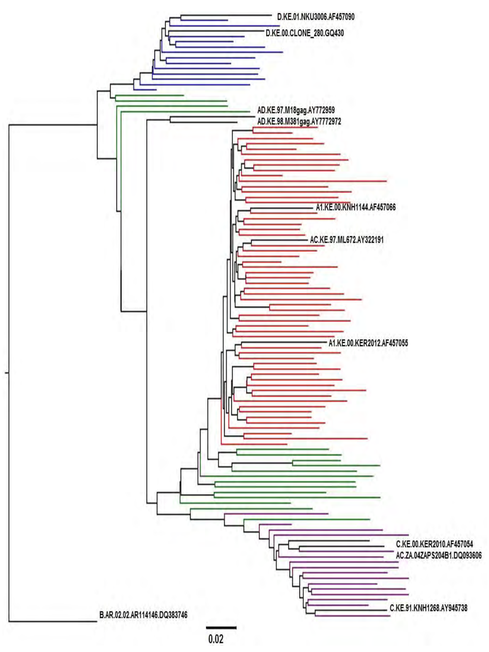
- *Gag-protease* was amplified from plasma of 103 study participants from the Majengo sex worker cohort- based in Nairobi, Kenya, and recombinant viruses were generated by homologous recombination. Virus replication capacity was measured by an HIV-1 inducible reporter gene assay.
- Informed consent was obtained from participants and ethical clearance from the relevant ethical review boards.
- CD4 counts (flow cytometry) and viral load measurements (NucliSENS) were performed.

Fig 1: Summary of the viral replication fitness assay



Results

Fig 2: Phylogenetic analysis showing the various subtypes in the cohort



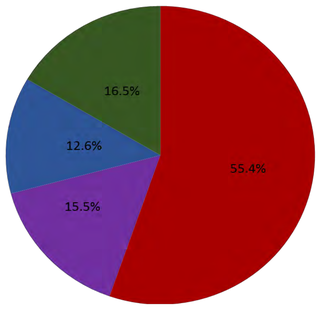


Fig 3: Wide range of replication capacity in the cohort

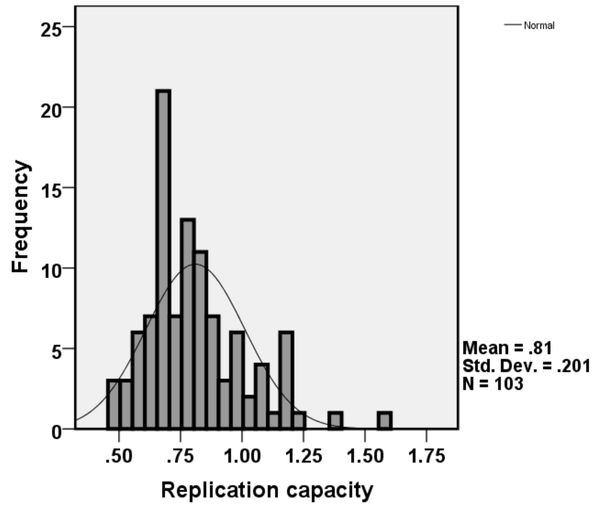


Fig 4: Significant differences in replication capacity among subtypes

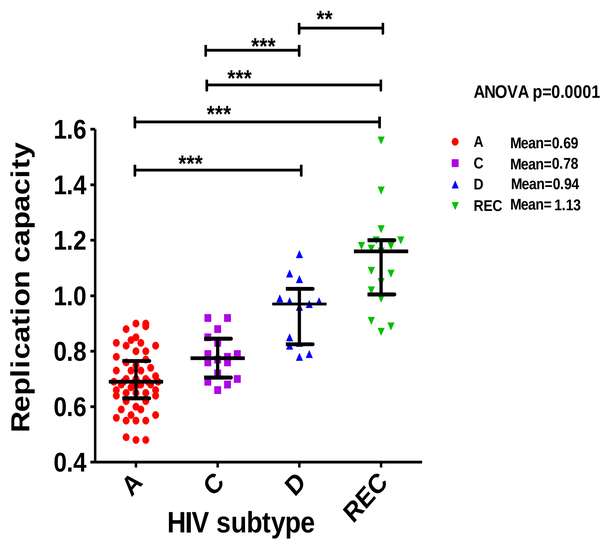


Table 1: Amino acid variants significantly associated with altered replication capacity

Codon	Amino acid	Consensus	With amino acid	Without amino acid	n=with amino acid	n=without amino acid	p-value	q-value
75	I	L	0.65	0.70	13	40	0.07	0.04
107	L	I	0.64	0.69	9	43	0.007	0.03
125	S	S	0.70	0.65	37	15	0.02	0.03
126	S	S	0.69	0.62	47	8	0.01	0.03
315	N	N	0.67	0.71	18	36	0.05	0.04
499	S	S	0.70	0.62	48	6	0.03	0.04

- The polymorphism 107L and consensus amino acid 315N were significantly more frequent in subtype A (Chi square test; $p=10^{-8}$ and p=0.01, respectively) and were associated with reduced replication capacity .

Conclusion

These data show a hierarchy of Gag-protease driven replicative fitness where subtypes A/C are less fit than D, which is also less fit than inter-subtype recombinants. The data are consistent with reported differences in subtype-specific differences in rate of disease progression. The data also suggest that the more fit viruses are less dominant in the East African epidemic. We identified amino acids that may contribute to these differences. Further studies to better understand the mechanisms underlying subtype-specific differences in replication capacity are warranted. Furthermore, these data may have implications for the differences observed in the rate of disease progression and for the uneven spread and expansion of HIV-1 subtypes in the global epidemic.

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