



HIV reservoir establishment during hyperacute clade C infection



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Background

Little is known about the establishment of HIV reservoir at the earliest stages of infection. Here, we analyzed clade C HIV-1 reservoir seeding in women identified with hyperacute infections in Durban, South Africa through twice-weekly screening of high-risk individuals.

Methods

Patients. The FRESH cohort was launched in 2013 in KZN South Africa. It enrolls high risk HIV negative women aged 18 to 23 to be followed for 24 months and offers twice-weekly HIV-1 RNA testing during year 1, then 3-monthly during year 2. This study longitudinally examined the establishment and longitudinal evolution of HIV-1 viral DNA reservoirs in four participants who tested HIV+ (n=4).

Table 1. Patient characteristics

	FRESH ID	HLA-A	HLA-A	HLA-B	HLA-B	HLA-C	HLA-C	Earliest PBMC (this study)	Peak Viremia
Patient 1	127-33-0897-461	03.01	29.02	44.03	58.02	66.02	07.01	Fiebig II	2.6x10 ⁸
Patient 2	127-33-0397-268	01.01	66.01	39.10	81.01	12.03	18	Fiebig II	7.7x10 ⁷
Patient 3	127-33-0911-442	68.02	74	15.03	07.02	02.10	18	Fiebig V	1.39
Patient 4	127-33-0262-198	23.01	30.01	15.10	58.01	03.02	18.01	Fiebig V	5.7x10 ⁷

Figure 1. Sampling time points

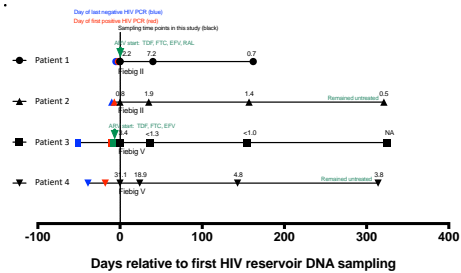
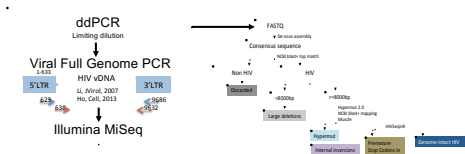


Figure 2. HIV reservoir quantification and genotyping



Results

Figure 3. A total of 287 HIV genomes were sampled from these four patients over all sampling time points (each horizontal line represents one viral genome). Navy blue lines represent intact HIV genomes; other colors represent defective HIV genomes.

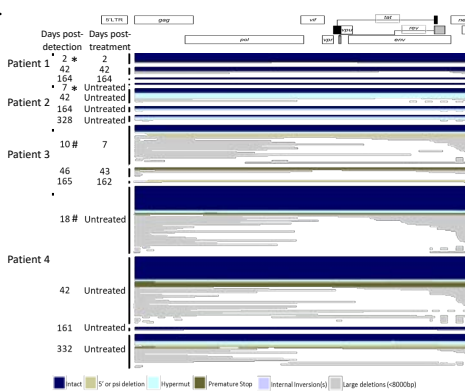


Figure 4. Fiebig II versus Fiebig V. Immediately post detection at study baseline, HIV reservoir sizes in patients at Fiebig II (0.8, 22 intact genomes per million PBMC) was lower than V (3.4, 31.1). (a) Intact genomes were observed at higher frequencies in Fiebig II than V. (b) No APOBEC 3G/3F-hypermutated HIV DNA was detected at Fiebig II, while 5% and 4% were detected at V.

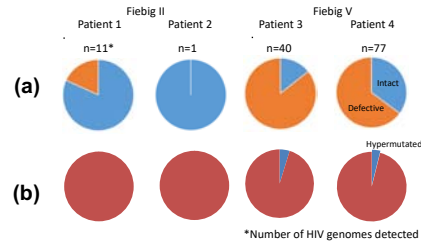


Figure 5. HIV reservoir sizes shows a general trend of decrease over time in all four patients (genome-intact HIV, orange line). HIV reservoir sizes by ddPCR (intact + defective genomes, blue line) are included for comparison.

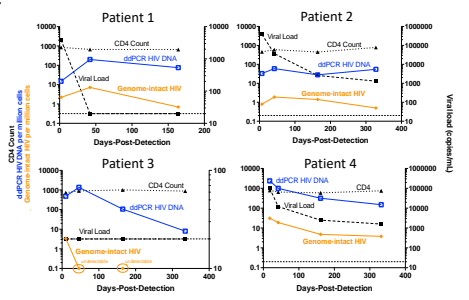
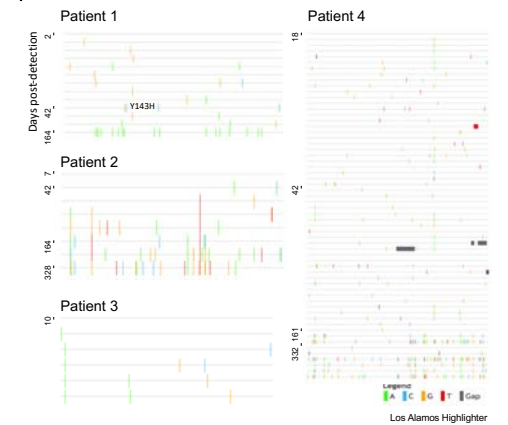


Figure 6. Single base substitutions were responsible for 87-100% of genetic variations in early reservoirs (genome-intact HIV only). This diversity increased overtime in untreated patients (median pairwise distance 0 to 18 and 4 to 39), but decreased in treated patients (3 to undetectable, 3 to 6 to 0). Y143H, an integrase inhibitor resistance associated mutation, was detected from patient 1 at 42-days post-detection, suggesting early-seeding of a drug resistant variant.



Conclusions

Early HIV reservoirs in PBMC were small and had high levels of sequence homogeneity. Single-base substitutions were the major source of genetic diversity, and early treatment limited diversification.