The Study of Clones in Subjects 1 and 2 from the Markam et al. paper, and Their Genetic Similarity as Time Progressed

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Outline

- Research Question
  - Hypothesis
- Explain the two subjects (1 and 2)
- Markham et al. Summary
- How was the information obtained and what databases
- Explanation of methods and results obtained from both subjects
- What the results say i.e (conclusion)
- Future studies

Research Question

- Question: Is the diversity of the clones for Subject 1 & 2 greater when separate, or when together ?
- Interested because I saw that they were genetically very similar in the 1st visit.

Table 2.1 Clustadist analysis of the sequences from Subject 1 and 2, visit 1.

Subject	Visit	S	Min Difference	Max Difference
Subject 1 & 2	1	30	0	14

Summary of Markham et al.

- Higher levels of both genetic diversity and divergence in the HIV-1 variants present in a given individual were associated with a greater decline in CD4 T cells

Subject 1 & 2

- **Subject 1=Rapid Progressor**
- **Subject 2 = Non-Progressor**

Photo provided by Markham et al.

Subject	No. of observations	CD4	Median intravisit nucleotide differences among clones	Virus copy number ($\times 10^3$)	Annual rate of CD4 T cell decline	in intravisit nucleotide differences per clone per year	(% nucleotides mutated from baseline consensus sequence per year)	Median dS/dN
Rapid Progressor								
Subject 4	4	1,028	0.90	6.8	−593	4.64	2.09	0.0
Subject 10	5	833	1.71	99.3	−363	3.16	1.00	0.2
Subject 11	4	753	2.27	62.2	−363	1.11	0.32	0.0
Subject 15	4	707	15.16	171.0	−362	−2.94	0.68	0.7
Subject 3	5	819	1.82	302.5	−294	0.53	0.74	1.0
Subject 1	3	464	5.64	307.6	−117	5.10	1.55	0.3
Moderate Progressor								
Subject 7	5	1,072	2.27	317.6	−392	−0.79	1.35	1.3
Subject 8	7	538	1.24	209.0	−92	1.68	1.16	0.5
Subject 14	9	523	1.00	50.9	−51	1.69	0.60	0.0
Subject 5	5	749	2.50	260.6	−41	0.06	0.50	1.4
Subject 9	8	489	9.49	265.0	−11	1.58	1.21	0.0
Subject 6	7	405	2.82	321.4	52	1.92	0.82	0.4
Nonprogressor								
Subject 2	5	715	1.64	21.6	30	1.32	0.49	1.8
Subject 12	6	772	2.80	5.1	44	0.62	0.13	0.9
Subject 13	5	671	0.87	1.7	53	0.53	0.28	3.5

Annual changes in CD4, intravisit nucleotide diversity, and percent nucleotide divergence from the first viruses sequenced after seroconversion reflect slopes of regression lines between individual visits. As slopes of CD4 T cell decline were quite variable between visits in the same subject, progressor categorization of subjects was based on the lowest level of CD4 T cell counts attained during the period of observation. Although subject 7 had a 392/year CD4 T cell decline, his CD4 T cell level never fell below 200 and therefore he was included in the moderate progressor group. His movement to the rapid progressor group would not have altered the statistical support for any of the conclusions reached.

Tools used

- GenBank; Nucleic acid data associated with Markham et al. paper
  - FASTA formatted sequence
- Biology Workbench
  - ClustalW tool; generates multiple sequence alignements
  - Clusdist tool; generate distance matrix where minimum and maximum values can be calculated

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Methods/Results

Subject 1, all visits

Table 1. Clustadist analysis of the sequences from Subject 1 all visits .

Subject	Visits	S	Min Difference	Max Difference
Subject 1	3	93	0	35

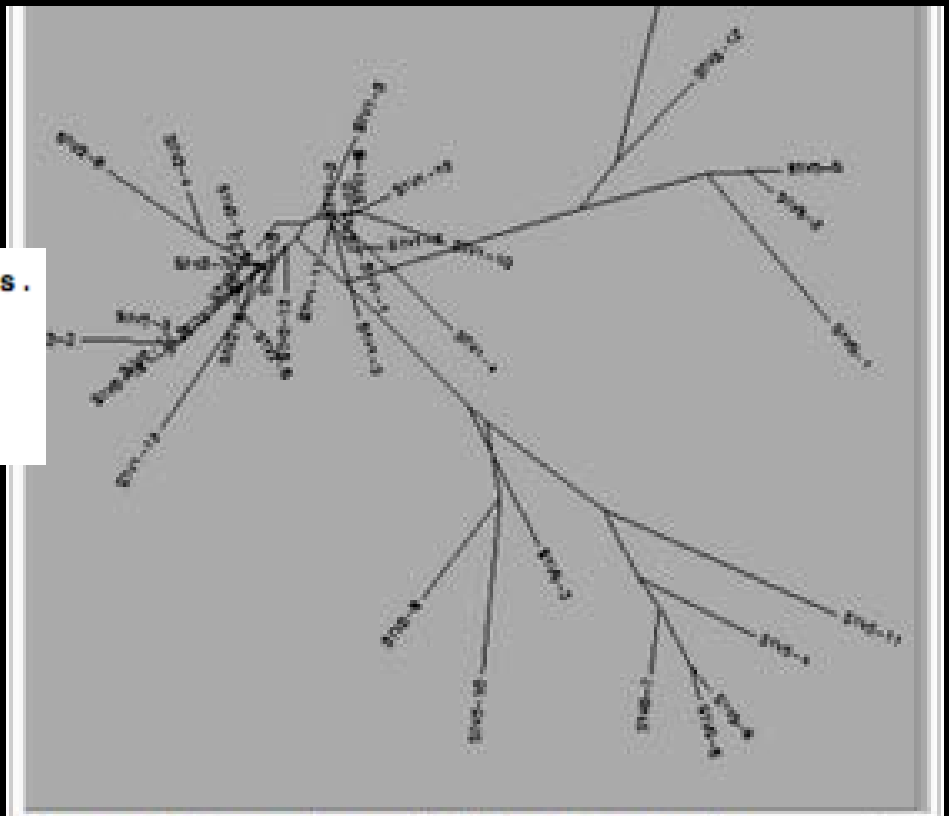

Figure 1.Unrooted tree of HIV-1 viral strains for subjects 1, all visits.

Methods/Results

Subject 2, all visits

Table 2. Clustadist analysis of the sequences from Subject 2 all visits .

Subject	Visits	S	Min Difference	Max Difference
Subject 2	3	36	0	14

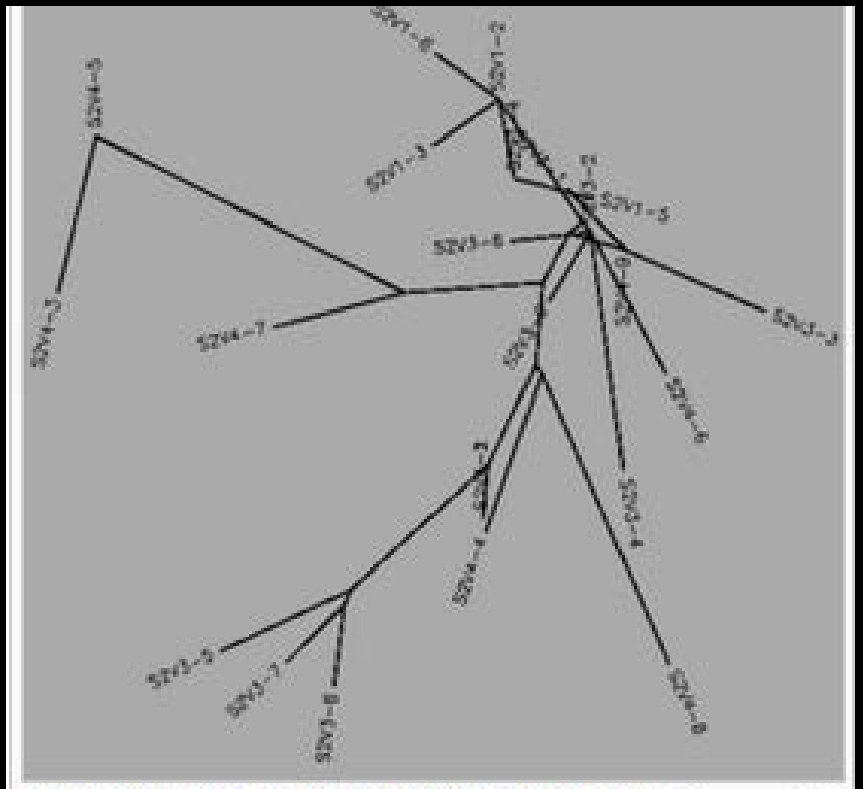

Figure 2.Unrooted tree of HIV-1 viral strains for subjects 2, all visits.

Methods/ Results

Subject 1 & 2, Visit 1

Table 2.1 Clustadist analysis of the sequences from Subject 1 and 2, visit 1.

Subject	Visit	S	Min Difference	Max Difference
Subject 1 & 2	1	30	0	14

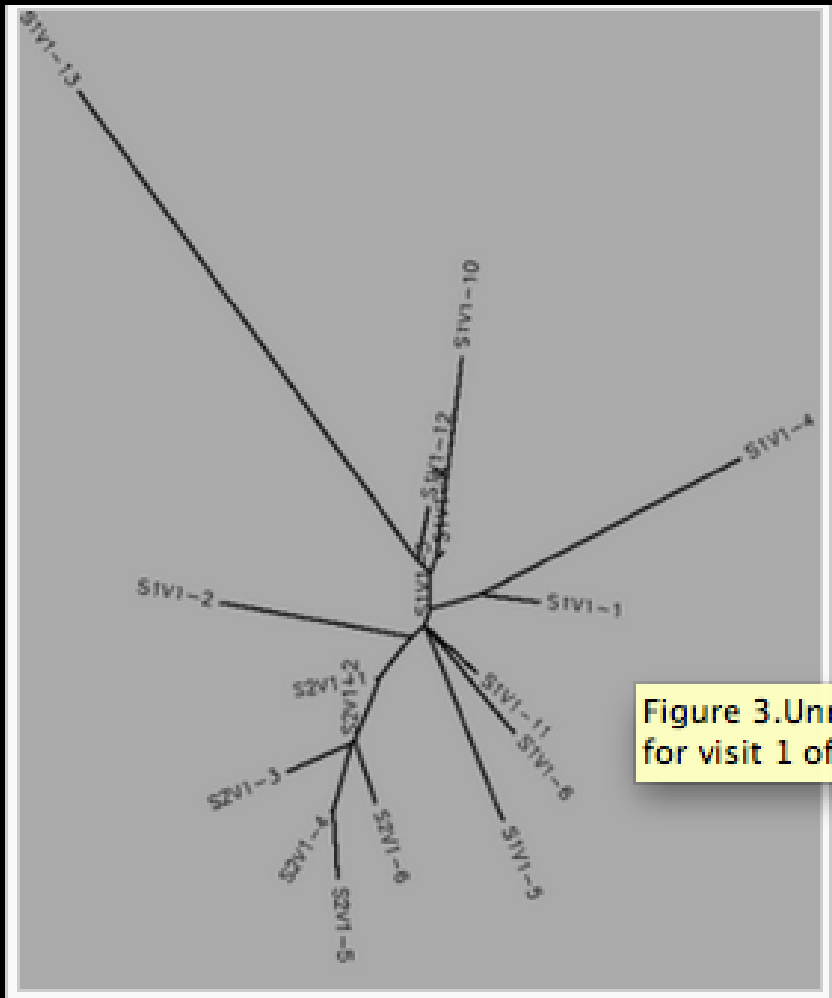

Figure 3. Unrooted tree of HIV-1 viral strains for visit 1 of subject 1 & 2.

Method/ Results

Subject 1 &2 , last visit

Table 4. Clustadist analysis of the sequences from Subject 1 and 2 , last visit

Subject	S	Min Difference	Max Difference
Subject 1 & 2	73	0	35

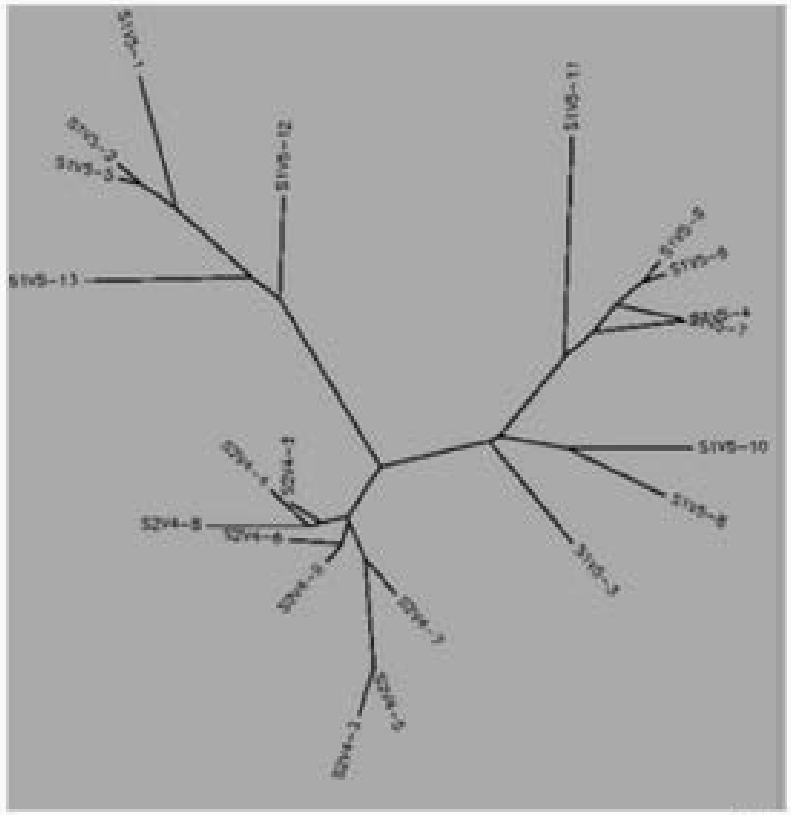

Figure 4. Unrooted tree of HIV-1 viral strains for the last visit of subject 1 & 2.

Comparing

Table 2.1 Clustadist analysis of the sequences from Subject 1 and 2, visit 1.

Subject	Visit	S	Min Difference	Max Difference
Subject 1 & 2	1	30	0	14

Table 1.2 Clustadist analysis of the sequences from Subject 1, visit 1.

Subject	Visit	S	Min Difference	Max Difference
Subject 1	1	26	0	14

Table 3. Clustadist analysis of the sequences from Subject 2 , first visit

Subject	S	Min Difference	Max Difference
Subject 1	5	1	3

Phylogenetic Tree: Progressiveness

First Visit

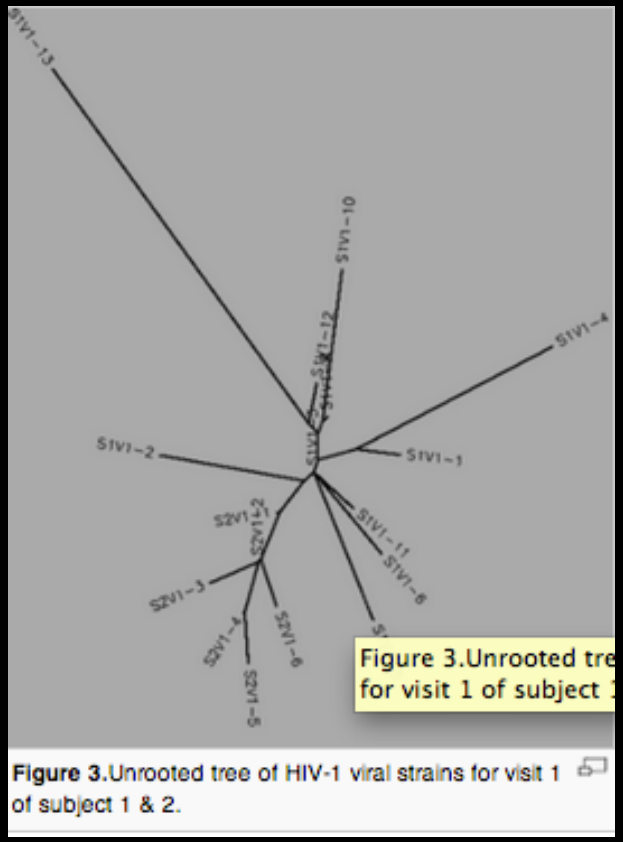

Figure 3. Unrooted tree of HIV-1 viral strains for visit 1 of subject 1 & 2.

Last Visit

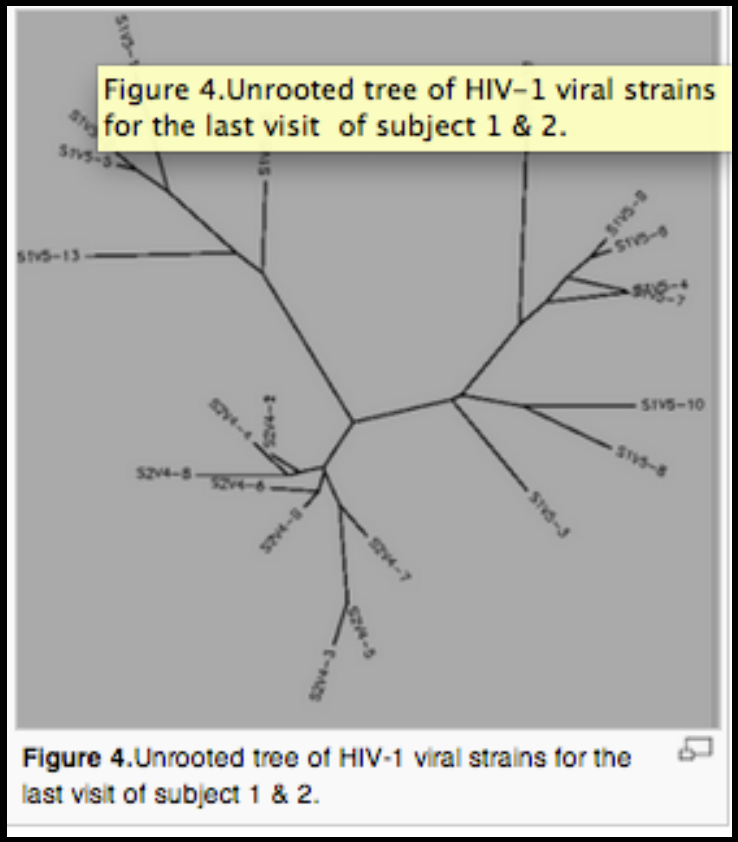

Figure 4. Unrooted tree of HIV-1 viral strains for the last visit of subject 1 & 2.

Conclusion

- 1st visit subjects were genetically similar
- Last visit the subject has diverged greatly in term of clones
- Subject 1 showed traits indicative to a rapid progressor
- Subject 2 showed traits indicative to a non-progressor
- Genetically more similar when alone

Future Studies

- Study the clones that were the same in both the subject and see how in particular they evolved over time
- Study if diversity and the number of a particular clone plays a part in the difference progressiveness of HIV

References

- Markham, R.B., Wang, W.C., Weisstein, A.E., Wang, Z., Munoz, A., Templeton, A., Margolick, J., Vlahov, D., Quinn, T., Farzadegan, H., & Yu, X.F. (1998). Patterns of HIV-1 evolution in individuals with differing rates of CD4 T cell decline.*Proc Natl Acad Sci U S A. 95*, 12568-12573. doi: 10.1073/pnas.95.21.12568

Acknowledgments

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