Poster #522

Evolution of HIV-1 Set-Point Viral Load within Transmission Networks

Daniela Bezemer[1], Luuk Gras[1], Ard van Sighem[1], Ben Berkhout[2], Christophe Fraser[3], Frank de Wolf [1, 3]

[1]HIV Monitoring Foundation, Amsterdam, the Netherlands ; [2]Department of Medical Microbiology, Academic Medical Centre, Amsterdam, The Netherlands ; [3] Department of Infectious Disease Epidemiology, Imperial College London, UK

Daniela Bezemer
Stichting HIV Monitoring
E: d.o.bezemer@amc.uva.nl
T: +31 20 56667180
www.hiv-monitoring.nl

Background

Results from two studies suggest an increase over time of HIV-1 set-point viral load (Gras et al.2009) and virulence (Gali et al., 2007) in the Netherlands. We aim to investigate to what extent these findings can be explained through selection of different transmission networks with viral strains replicating at a higher level, or through evolution to higher replicating virus within transmission networks.

Patient Selection

HIV-1 subtype B polymerase nucleotide sequences obtained from 395 therapy-naïve men having sex with men (MSM) with an identified date of infection described in our study (Gras et al., 2007) were selected from the ATHENA national observational cohort.

Set-Point Viral Load

The first HIV-1 RNA concentration measured 9-27 months after seroconversion, before start of cART.

Phylogenetic Trees

Sequences contained whole protease and the first 325 amino acid positions of reverse transcriptase (RT). Two phylogenetic trees were constructed; a 1000 bootstrap Neighbour-Joining K2 tree; and a 100 bootstrap maximum likelihood GTR tree.

Selection of Transmission Clusters

Significant clusters that contained sequences both from patients infected before 1992 and after 1999 were selected.

Consensus Sequences

Constructed for 4 time intervals by year of infection; 1985-1991; 1992-1995, 1996-1999, 2000-2010. A reference comparison was made to the consensus subtype B sequence from 28 drug users infected between 1987-1999.

Results – load cluster

In both phylogenetic trees we found 5 sequences from MSM that seroconverted ≤1995 (1985, 1989, 1990, 1992,1995) in 5 clusters together with in total 10 sequences from MSM that seroconverted ≥2000.

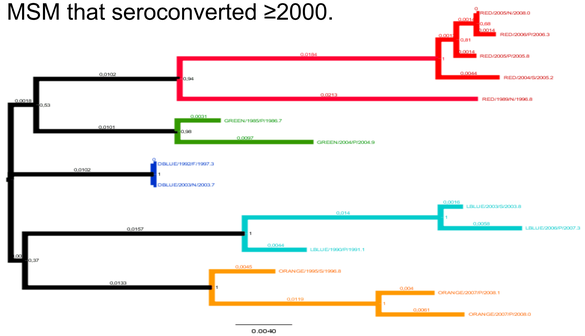

Figure 1, Phylogenetic Maximumlikelihood GTR tree of 15 HIV-1 pol sequences from MSM seroconverters, showing 5 clusters over time.

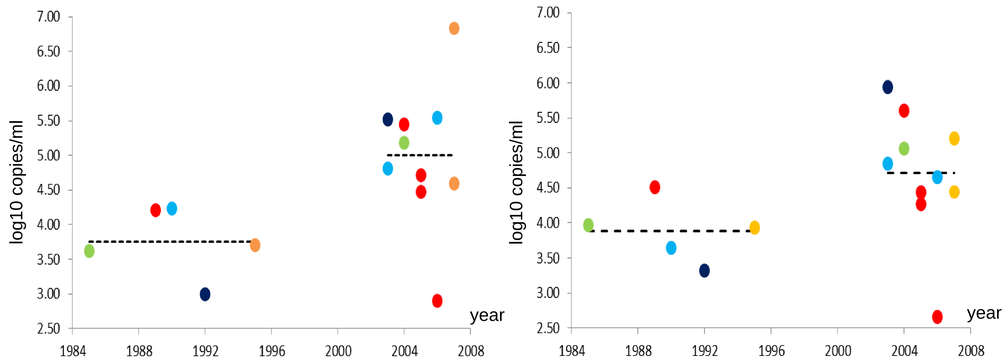

Figure 2. Left. Set-point viral load per patient, coloured by cluster. The average set-point viral load is indicated with the black dotted line; for those infected ≤1995 its was 3.75 log10 copies/ml which differs significantly by a factor of 1.25 from the average 5.00 log10 copies/ml for those infected ≥2000 (p=0.02).
Right. Mean viral load per patient of in total 61 viral load measurements between 9-27 months after seroconversion, all before start of cART. The average for those infected ≤1995 was 3.88 log10 copies/ml and for those infected ≥2000 the average was 4.71 log10 copies/ml (p=0.04).

Results – consensus

The consensus polymerase sequence for infections found in MSM infected ≤1992 (n=32) differed from the consensus amongst MSM infected ≥2000 (n=311): at 3 nucleotide positions, resulting in Arginine change to Lysine at RT211 and RT277, and Isoleucine change to Valine at RT293. For comparison the consensus sequence for infections found in MSM before 1992 differed at 7 nucleotide positions from the consensus amongst 28 drug users (183 on protease, and 111, 248, 486, 813, 830, 889 on RT).

Results – mutations – load

Amino acid differences found over time in the consensus and in the clusters were tested for set-point viral load in all 395 therapy-naïve seroconverters.

Overall infections with **PR37S** (4.86 log10 copies/ml , n=35) had a significantly higher set-point viral load then infections with P37N (4.62 log10 copies/ml, n=127) (p = 0.035). However in the green cluster, PR37S corresponds to the early sequence with a lower viral load.

Conclusions

The increase in HIV-1 set-point viral load over time in transmission clusters as well as the consistency of the consensus sequence over time indicate selection within transmission networks rather than the introduction of a more virulent strain.