Poster # 677

Transmission Networks of Resistant HIV-1 among Men Who Have Sex with Men: The Netherlands

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Objective

To obtain insight in the HIV-1 epidemic among MSM in the Netherlands we analysed transmission networks.

Study population

• The ATHENA national observational cohort in the Netherlands collects anonymized information on all patients infected with HIV who were in follow-up at one of the 24 HIV treatment centres.

• 12,951 HIV-1 infected persons.

• 6845 (53%) reported to be infected by MSM contact.

• 4090 HIV-1 subtype B *polymerase* gene sequences of 2877 persons.

• In total, 101 (3.5%) persons had their first sequence obtained before 1996, 503 (17.5%) patients in the period 1996 and 2000, 1114 (38.7%) in 2001 to 2004, and 1159 (40.3%) after 2004.

• 2022 (70%) reported to be MSM, 30 % of all MSM have a subtype B sequenced.

• **404** (20%) were identified as **new infections** (Tabel 1): **<=** 18 months between last negative and first positive test / diagnosis of acute infection and sequence date <= 18 months of their estimated seroconversion date.

Methods

• Pairwise sequence distances between all available entire protease sequences and RT sequences cut to equal lengths of 251 amino acids were calculated taken into account ambiguous sites according to a mixed weighted distance method.

• A phylogenetic tree was constructed from polymerase sequences isolated from 2877 HIV-1 subtype B infected patients, with the Neighbour-Joining method within the MEGA program.

• For MSM with a known date of infection, most similar sequences were selected as potential transmission pairs when they clustered with bootstrap value ≥99%.

• Time from infection to onward transmission was estimated as the median time between dates of infections for each transmission pair.

• The source of infections with a resistant strain was traced using the entire phylogenetic tree.

Results

• Of 404 MSM with a known date of infection between 1987 and 2007, 175 (43%) formed 63 clusters with bootstrap value ≥99%.

• Median estimated time to onward transmission was 1.4 years (IQR 0.6-2.7), indicating that 25% of onward transmissions occur within 7 months after infection, half of transmissions within 17 months, and 75% within 2.7 years (Tabel 2).

• 24 of 404 (6%) newly infected MSM have a resistant strain (Fig. 1a).

• 14 of 24 resistant strains (58%) had a mutation at position 215 in RT.

• After 1996, only revertant mutations were found at position 215 (Fig. 1b).

• 13 of 24 (54%) newly infected patients with a resistant strain are in 8 clusters together with sequences of 28 other men in the phylogenetic tree of all 2877 persons with an HIV-1 subtype B *polymerase* gene sequence (Fig 2).

• Twenty-five persons in four clusters comprised sequences with a revertant mutant at position 215 in RT, specifically 215C in cluster 1 and 8, 215S in cluster 5, and 215F in cluster 7 (Fig 2).

Conclusions

Onward transmission of HIV-1 from infected MSM happens both during and after primary infection. Transmission of resistant strains from the antiretroviral-treated population is limited, but strains with resistance-related mutations have formed sub-epidemics.

Tabel 1. Characteristics of 404 MSM identified with an HIV-1 subtype B infection with a known date of infection in the period 1987 – 2007.

Number of MSM with new infections and sequence	404
Median age at estimated time of infection, in years	35.3 (IQR 30.1 – 42.2) (range 21.0 – 61.9)
Percentage Born in The Netherlands	80
Number of acute infections	107
Median interval between the last antibody negative and the first RNA positive visit, in months	5.7 (IQR 0.3 – 8.0), for 297 seroconverters
Median interval between the estimated date of seroconversion and the sequenced sample, in months	3.3 (IQR 1.3 – 6.1)
Median interval between the first RNA positive visit and the sequenced sample, in months	0.4 (IQR 0.0 – 1.4)
Median plasma HIV-1 RNA concentration at first RNA positive sample in copies/ml	77867.5 (IQR 16976.0 - 249744.5)
Median CD4 count at diagnosis (10^6 cells/l)	0.49 (IQR 0.36 - 0.67)
Percentage ambiguous sites	0.08 (IQR 0.0 – 0.4)

Fig 1a. Annual proportion of sequences with resistance-associated mutations among 404 MSM with a new HIV-1 subtype B infection.

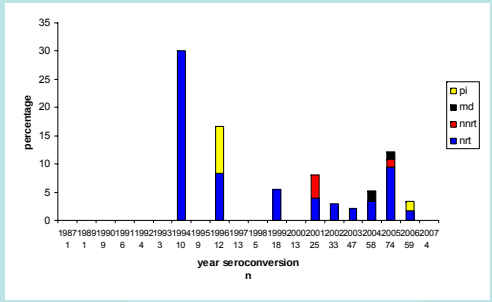
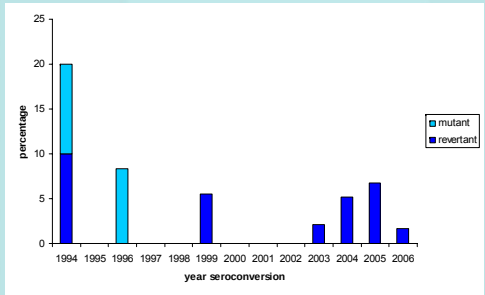


Fig 1b. Shows percentages for the mutation at position 215 of RT (215 Y or F) and its revertant (215 C, D, E, or S).

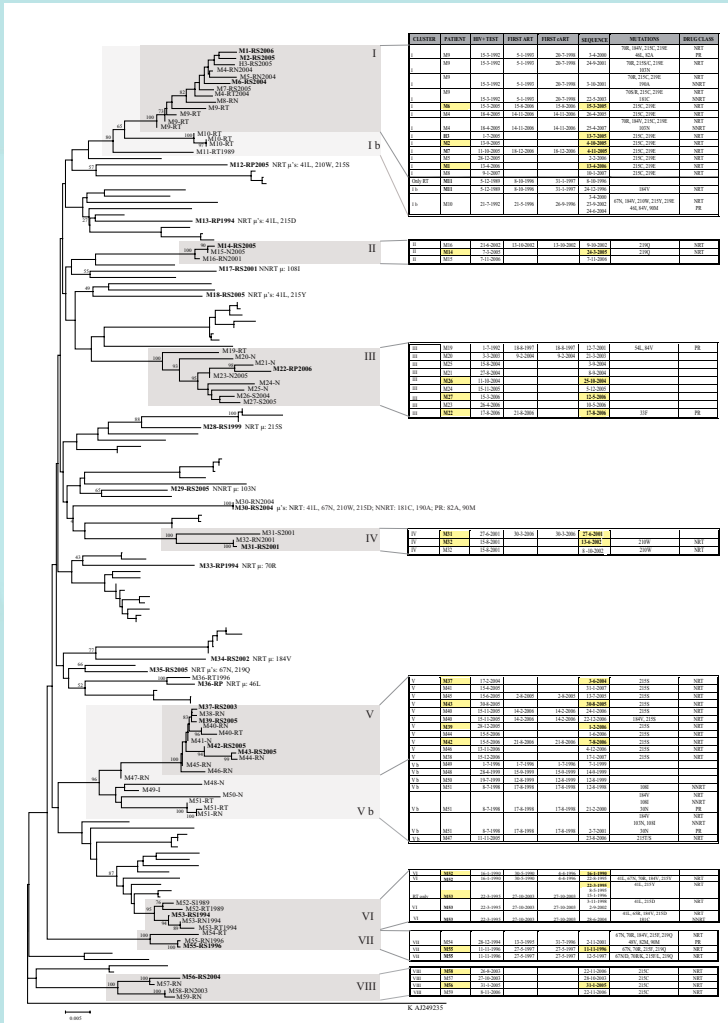


Tabel 2. For various patient selections of 404 MSM with a new subtype B infection the smallest pair-wise sequence distance to another "closest" patient and the corresponding difference in their estimated date of infection.

#	Data selection	distance between sequences (%)	time difference between dates of infection (years)	N	rate**	P
		median (IQR)	median (IQR)			
1	**All 404 MSM with a new HIV-1 subtype B infection**	2.3 (1.0- 3.5)	2.9 (1.1 - 7.3)	404	0.36	<0.0001
2	**In cluster with bootstrap ≥ 99**	0.9 (0.5 - 1.5)	1.4 (0.6 - 2.7)	175	0.33	<0.0001
3	**Distance to closest sequence ≤ 1.5%**	0.7 (0.4 - 1.1)	1.2 (0.5 – 2.0)	157	0.27	<0.0001
4	**Distance to closest sequence ≤ 1.5% and in cluster with bootstrap ≥ 99**	0.7 (0.3 - 1.1)	1.1 (0.5 – 2.0)	133	0.25	<0.0001
5	**Synonymous distance to closest sequence in cluster with bootstrap ≥ 99**	2.8 (0.9 – 4.5) ***	1.4 (0.5 - 2.9)	175	0.92 ***	<0.0001
6	**Synonymous distance to closest sequence ≤ 4.5%**	0.7 (0.4 - 1.1)	1.2 (0.5 – 2.0)	145	0.25	<0.0001
7	**Synonymous distance to closest sequence ≤ 4.5% and in cluster with bootstrap ≥ 99**	0.7 (0.3 - 1.0)	1.2 (0.5 – 2.1)	129	0.24	<0.0001
8	**Distance to closest sequence of any infection in the database**	1.4 (0.7 - 2.7)	2.1 (0.7 - 5.7) *	404	0.30	<0.0001
9	**Distance to closest sequence of any infection in the database ≤ 1.5%**	0.7 (0. 4 - 1.1)	1.2 (0.4 - 2.4) *	220	0.22	<0.0001
10	**Any infection in the database closest to any infection in the database ≤ 1.5% for RT only**	0.8 (0.5– 1.2) ***	1.4 (0.4 – 3.0) *	817	0.16	<0.0001

* Absolute time difference between estimated dates of infection, except for patients in selection 8, 9 and 10 for whom it represents the absolute time between the dates of first HIV diagnosis; **rate in % distance / year; *** Here the % sequence distance refers to the synonymous distance only; ****sequence distance refers to distance between RT sequences only; P is the correlation between distance and time; IQR: inter-quartile range.

Fig 2. Transmission networks of newly infected MSM with a resistant strain



New infections are coded as M#-RCYEAR, which codifies respectively; M = MSM; # = unique number; R = resistant; C = the code to which phase the sequences belong: P = primary infection, S = seroconverter, N = therapy-naïve; T = during treatment. I = during treatment interruption; and YEAR = the estimated calendar year of seroconversion. (N)NRT = (non-) nucleoside reverse transcriptase; PR = protease; μ = mutation. Undated infections are coded similarly but without a year, and an H instead of M stands for Heterosexual transmission. The 24 new resistant infections from Fig. 1 are in bold, with resistance conferring mutations, in the table when part of significant cluster, or following the branch name in the tree. In the table, next to the significant clusters, dates and mutations of the clustering sequences are specified. Patients selected from Figure 1 are indicated in yellow, and the dates of sequences corresponding to new infections are shown in yellow. In the table under 'cluster' where it is stated 'RT only', these sequences do cluster, but they are not part of the phylogenetic tree presented.