



# Limited Transmission of Drug Resistant HIV-1 in the Netherlands



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## Background

Reports from several countries show that 10-30% of recent HIV-1 infections carry mutations conferring drug-resistance. Here we report the prevalence of resistant HIV-1 strains among new infections in the Netherlands between 1994 and 2004.

## Methods

New HIV-infections were identified within the Dutch ATHENA observational cohort, the Academic Medical Centre and the prospective Amsterdam Cohort Studies (ACS). Additional new infections were identified among participants entering the ACS who were unaware of their HIV positive status, by a less sensitive enzyme immunoassay (LS-EIA). The date of infection was set as a) the midpoint of a seroconversion interval  $\leq 18$  months; b) the date of the last seronegative but RNA-positive sample; c) 100 days before testing negative by the LS-EIA; d) the date of an indeterminate result on the Western blot. Pre-treatment sequences of reverse transcriptase (RT) and protease were obtained within one year after diagnosis. Resistance associated mutations were identified based on the IAS-USA resistance table. Subtypes were identified by phylogenetic analysis. Trends over time were analysed using a logistic regression model. Newly diagnosed ATHENA patients without an identified year of infection were also screened for resistance by year of diagnosis.

## Results

### Characteristics

153 recent HIV-1 infections were identified, 90% were in men and 10% in women. Median age at diagnosis was 34 years (IQR: 30-41). 67% Of the transmissions apparently took place through homosexual contact (MSM), 11% through heterosexual contact (HET) and 18% through intravenous drug use (DU). The first positive sample was sequenced for 51 primary infections and 5 by LS-EIA. For 97 seroconverters the median time between the last negative test date and the sequenced sample was 6.2 months (IQR: 4.4-8.9). The median viral load at the first positive sample was  $5.0 \log_{10}$  copies/ml (IQR:  $4.3 \log_{10}$  -  $5.5 \log_{10}$ )

### Trends in Resistance

Transmission of resistance was found in 18 (12%) cases: 3 were resistant to nNRTIs, 1 to PIs and 14 to NRTIs. No multidrug-resistance was found and none of the 15 non-B subtypes showed resistant mutations. Resistance was found in 9/40 (23%) infected before 1997 and in 9/113 (8%) infected after 1996. Since 1996, the percentage did not change with year of infection ( $P=0.92$ ; odds ratio = 0.98 per year (95%CI: 0.8-1.5)). In 429 newly diagnosed patients after 1996, 35 (8%) showed resistance, and 2 of 85 (2%) non-B subtypes carried resistant mutations (T69N and M184V).

### Fitness-Cost to Resistance

The median plasma HIV-1 RNA level at the first sample after infection, from the individuals infected with a resistant strain ( $4.4 \log_{10}$  copies/ml) was significantly lower than from the individuals infected with a non-resistant strain ( $5.0 \log_{10}$  copies/ml) ( $p=0.008$ ).

Table. Mutations conferring resistance

YEAR	RISK ROUP	MUTATIONS	DRUG CLASS
1994	MSM	M41L, T215D	NRTI
1994	MSM	M41L, T215Y	NRTI
1994	DU	L100I	NNRTI
1994	MSM	K70R	NRTI
1995	DU	M41L, T215Y	NRTI
1995	MSM	M46I	PI
1995	DU	D67N, K70R, K219Q	NRTI
1996	MSM	D67N, K70R, T215F, K219Q	NRTI
1996	MSM	T215S	NRTI
1997	MSM	A62V, T215D	NRTI
1999	MSM	T215S	NRTI
1999	MSM	M41L	NRTI
2001	MSM	L210W	NRTI
2001	MSM	T69N	NRTI
2001	MSM	V108I	NNRTI
2003	?	T69N, K70R	NRTI
2003	MSM	M184V	NRTI
2003	HET	K103N	NNRTI

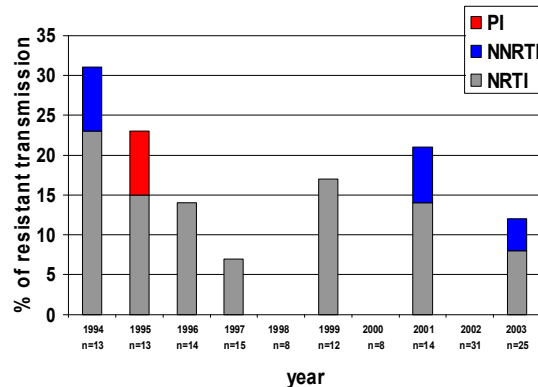


Figure. Transmission of Drug Resistant HIV-1 per drug-class in percentage of total new HIV-1 infections in the study per year.

## Conclusions

Since the introduction of HAART in 1996, transmission of drug-resistant HIV-strains in the Netherlands occurs in 8% of new infections and does not increase over time. This is reflected by the similar prevalence of resistance among newly diagnosed patients. It is important to keep monitoring baseline resistance as this trend might change.

