LIMITED RECENT TRANSMISSION OF DRUG RESISTANT HIV-1 IN AMSTERDAM.

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Objective: Reports from several countries show that 10-30% of primary human immunodeficiency virus type 1 (HIV-1) infections carry mutations conferring drug-resistance. Symptomatic HIV infections are over-represented in these mainly hospital-based studies. Here we report the prevalence of resistant HIV-1 strains among new infections in Amsterdam in the period 1994-2002.
Methods: New infections were identified within the Amsterdam Cohort Studies (ACS) on HIV and AIDS among homosexual men and drug users, and at the Academic Medical Center (AMC). At the AMC new HIV-1 infected patients were identified, often with symptoms of acute retroviral syndrome. Participants within the ACS seroconvert during follow-up, which makes it possible to include asymptomatic new infections in our study. Additional new infections were identified among participants entering the ACS, unaware of their HIV positive status, using a less sensitive enzyme immunoassay (LS-EIA). Sequences of reverse transcriptase (RT) and protease were obtained by population-based nucleotide sequence analysis of the HIV-1 *pol* gene of the first HIV-1 RNA positive sample available. Mutations were identified based on the IAS-USA resistance table. Subtypes were identified by phylogenetic analysis of the RT and protease sequences.
Results: Hundred new HIV-1 infections were identified; 32 primary infections at the AMC; and within the ACS 5 by LS-EIA and 63 seroconversions. One of the homosexual ACS participants and six heterosexual patients from the AMC were infected with non-B subtypes. In four cases the subtype corresponded with the prevalent subtype in the presumed country of infection. The non-B subtypes in our study did not show any resistance mutations. Transmission of HIV with resistance mutations against a single antiretroviral drug was found in 13 infections (13% CI: 7–21%). No multi-drug resistance pattern was observed.

Table. Mutations conferring resistance

YEAR	GROUP	MUTATIONS	DRUG CLASS
1994	MSM primo	M41L, T215D	NRTI
1994	MSM primo	K70R	NRTI
1994	sc: DU	L100I	NNRTI
1994	sc: MSM	M41L, T215Y	NRTI
1995	sc: DU	M41L, T215Y	NRTI
1995	sc: DU	D67N, K70R, K219Q	NRTI
1995	LS-EIA: MSM	M46IM	PI
1996	sc: MSM	D67N, K70R, T215F, K219Q	NRTI
1996	sc: MSM	T215S	NRTI
1997	LS-EIA: MSM	A62V, T215D	NRTI
1999	sc: MSM	T215S	NRTI
2001	sc: MSM	V108I	NNRTI
2001	MSM primo	T69N	NRTI

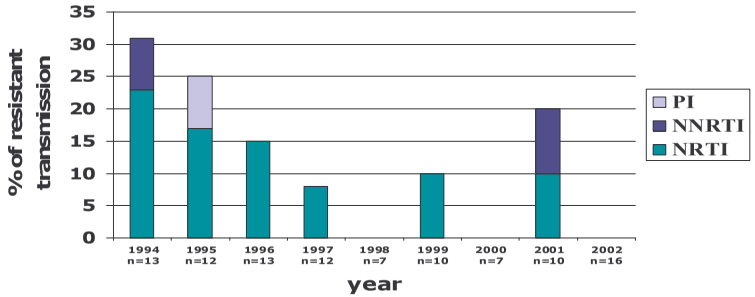

Figure. Transmission of Drug Resistant HIV-1 per drug-class in percentage of total new HIV-1 infections in the study per year.

Trends in Time

•The proportion of new HIV-1 infections with drug-resistant strains decreased over calendar time, before 1998 we found that 20% of 50 new infections involved a virus bearing drug-resistant mutations versus only 6% of 50 new infections after 1997 ($p = 0.074$). A linear logistic regression model with calendar time as a continuous variable showed a significantly declining trend in the rate of transmitted resistance ($p = 0.03$) (odds ratio = 0.75 per year). Addition of a quadratic term did not significantly improve the fit of the model to the data.

•Since 1996 only revertant mutations in codon 215 are seen. Is this an effect from earlier transmissions by people on AZT mono therapy in the pre-HAART era?

Are resistant infections different? ~*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) ($p=0.036$). For those participants with a (pre-treatment) follow-up sample available the viral load was comparable for both groups ($p= 0.9$). (Median time since estimated infection-date was 7.6 IQR: 6.4-9.8 months).

•Individuals infected with resistant versus non-resistant virus did not significantly differ by: CD4 cell count, or (reported) presence of fever at acute infection.

Conclusions

The transmission of drug-resistant HIV-1 in Amsterdam has decreased over time, and is still limited. As conditions for transmission of drug-resistant strains are present, it is important to continue to monitor their rate of transmission.

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STICHTING AIDS FONDS