Surveillance of Transmitted HIV-1 Drug Resistance in the German HIV-1 Seroconverter Cohort from 1996 to 2010

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Background

Primary drug resistance in drug-naïve newly infected patients occurs after transmission of drug resistant HIV-1 from treated patients failing combination antiretroviral therapy (cART) or from therapy-naïve patients by onward transmission. Prevalences and trends of transmitted drug resistance were monitored in patients of the German HIV-1 Seroconverter Cohort from 1996 to 2010 to improve the first-line cART of HIV-1 patients.

Material & Methods

Genotypic resistance testing of 1.764 drug-naïve patients with known date of HIV-1 infection was performed between 1996 and 2010 (year of seroconversion). Population-based sequences of the HIV-1 *pol*-region were analysed (ViroSeq® HIV Genotyping System, inhouse *pol*-RT-PCR) to predict genotypic resistance. Resistance mutations were identified according to the surveillance drug mutation list for drug-naïve patients (Bennett et al, PLoS ONE, 2009). Chi²-test and logistic regression were used to compare categorical variables and to calculate time trends.

Results

Characteristic	total	susceptible HIV-1	resistant HIV-1
drug-naive patients (%)	1764	1564 (88.7)	200 (11.3)
Gender			
male (%)	1676 (95.0)	1482 (94.8)	194 (97.0)
female (%)	88 (5.0)	82 (5.2)	6 (3.0)
Transmission risk			
MSM (%)	1548 (87.8)	1366 (87.3)	182 (91.0)
HET (%)	143 (8.1)	132 (8.4)	11 (5.5)
IDU (%)	23 (1.3)	22 (1.4)	1 (0.5)
HPL (%)	14 (0.8)	13 (0.8)	1 (0.5)
occupational exposure (%)	4 (0.2)	4 (0.3)	0 (0.0)
unknown (%)	32 (1.8)	27 (1.7)	5 (2.5)
Subtype			
B (%)	1564 (92.0)	1429 (91.4)	194 (97.0)
non-B (%)	141 (8.0)	135 (8.6)	6 (3.0)
Country of risk			
Germany (%)	1505 (85.3)	1337 (85.5)	168 (84.0)
other countries (%)	259 (14.7)	227 (14.5)	32 (16.0)
median age [years] ($CI_{95\%}$)	33 (27-39)	33 (27-39)	34 (28-39)
median viral load [log_{10}/ml] ($CI_{95\%}$)	4.84 (4.24-5.54)	4.82 (4.24-5.10)	4.90 (4.20-5.64)
median CD4 cell count [n/µl] ($CI_{95\%}$)	473 (340-646)	473 (339-643)	474 (354-659)

Fig. 1. Characteristics of study population

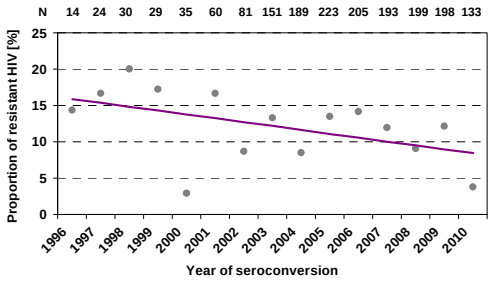

Fig. 2. Trend of primary drug resistance

The overall prevalence of transmitted drug resistance (200/1764) was 11.3% [$CI_{95\%}$: 9.9-12.8] with decreasing trend over time (p_{trend} = 0.045).

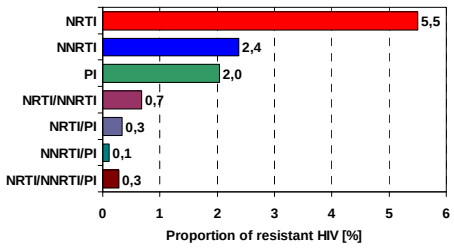

Fig. 3. Prevalences of resistance classes

Total prevalence of transmitted drug resistance divided by resistance classes. NRTI resistance was the most predominant transmitted drug resistance. Multi-resistant viruses were rarely detected (5/1764), however, still observed in recent years.

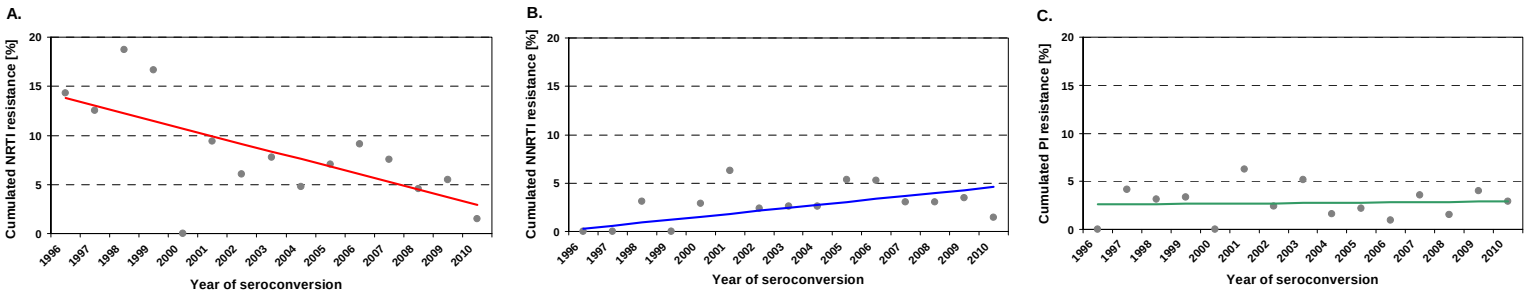

Fig. 4. Trends of drug classes

Resistances of each drug class were cumulated from mono-, dual- and triple-resistant viruses.

A. NRTI resistance (120/1794) decreased over time (p_{trend} = 0.001) **B.** NNRTI resistance (61/1794) showed no trend over time (p_{trend} = 0.82) **C.** PI resistance (49/1794) showed no trend over time (p_{trend} = 0.77)

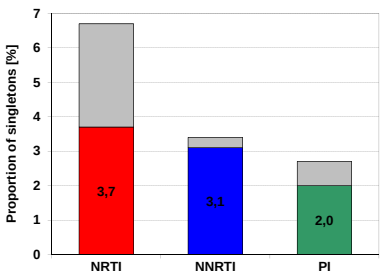

Fig. 5. Prevalences of singletons

Proportion of singletons among cumulated resistances of each drug class. In particular NNRTI resistance was predominantly caused by single resistance mutations (90.2%). Viruses with more than one NNRTI resistance mutation were only observed after 2002 (data not shown).

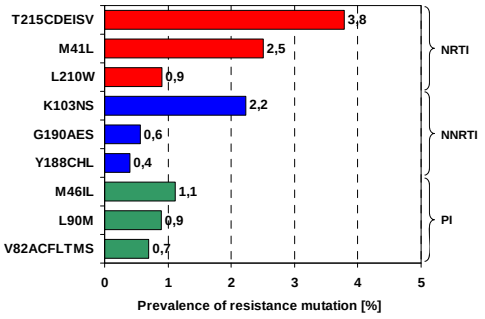

Fig. 6. Prevalences of resistance mutations

Prevalences of the three most frequent resistance mutations of each drug class. 82.5% of NRTI resistant viruses carried TAMs. T215rev occured 6 times more often than T215FY (data not shown).

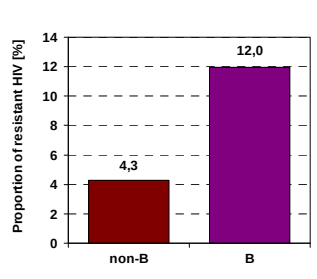

Fig. 7. Primary drug resistance and subtype

Transmitted drug resistance correlated with subtype B infection (p = 0.006), B (194/1623) [$CI_{95\%}$: 10.4-13.7], non-B (6/141) [$CI_{95\%}$: 1.7-9.4].

Conclusions

The decrease of transmitted drug resistance seems to reflect sustained treatment success and reduction of resistance development in treated patients achieved by introduction of new drugs in cART regimens and implementation of genotypic resistance testing. Nevertheless, a considerable proportion of resistant HIV-1 in the drug-naïve HIV-1 infected population can be observed likely due to persistance of resistance mutations combined with onward transmission. NRTI resistance declined over time, but was even in recent years the most predominant resistance class among transmitted drug resistance. Because of the lasting high prevalence of transmitted TAMs, first-line regimens containing Zidovudine are supposed to fail more often than other drug combinations. In the observation period from 1996 to 2007 an increase of NNRTI resistance was identified (B. Bartmeyer et al, PLoS ONE, 2010) that did not continue afterwards.

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