7 Summary

Subject of this work was to investigate the potential spreading of replication competent and resistant HIV in Germany.

Genotypic resistance analysis of 136 HIV infections of therapy-naive patients with documented seroconversion between January 1996 and December 2001 showed that 47% of the viruses contained at least one resistance-associated mutation within the therapeutic target enzymes, protease and reverse transcriptase. Phenotypic analysis demonstrated 15 infections with *in vitro* resistant viruses (in cooperation with the National Reference Centre for Retroviruses, Erlangen). The expected phenotype, which was deduced from the genotype correlated mostly with the measured phenotype (4 NRTI, 2 NNRTI, 3 PI). In six cases resistance against two drug-classes could be detected (NRTI/PI and NRTI/NNRTI, respectively). Frequent transmission of these multi-drug resistant viruses was seen in 2000/2001, but it did not reach statistical significance.

Patients were recruited within the seroconverter study (Robert Koch-Institut, in cooperation with the Department for Infection Epidemiology). They had been infected mostly in Germany, one infection was from Thailand, one from The Netherlands. Homosexual contacts represented the main risk of infection. In 50% of the therapy-naive seroconverters blood samples could be collected during seroconversion or within three months after seroconversion.

In almost every case the examined viruses belonged to HIV-1 subtype B. HIV-1 non-B infections were detected in only two cases (one HIV-1 subtype C and one subtype D).
The *in vitro* resistance of viruses belonging to HIV-1 subtype G and CRF02-AG was studied in blood samples of therapy-naive patients from Nigeria (in cooperation with University of Jos, Nigeria). The detected subtype specific resistance-associated mutations in the investigated viruses did not result in measurable resistance in the phenotype.

In the second part of this work the viral fitness of resistant transmitted viruses was analyzed in comparison with sensitive wildtype virus. NNRTI/NRTI and NRTI/PI resistant recombinante HIV-1 clones were produced. The replication efficiency of these virus clones was examined employing a reportergene assay (SEAP), p24-antigene determination, quantification of the infectious titer ($TCID_{50}$) and of the viral RNA. Compared with the sensitive wildtype HIV clone, the resistant virus clones showed a decreased replication efficiency. Additionally a decreased RT-activity in cell culture after infection of lymphoid cells with resistant HIV clones compared with wildtype could be detected.

An influence of single key mutations, the M184V substitution of the RT for example, which is known to decrease viral fitness, could not be demonstrated.

The results of this work show that resistant and replication competent HIV-1 were transmitted in Germany. Surveillance of the dynamic of spreading and the investigation of the replication efficiency of antiretroviral resistant HIV as well as the long-term follow up of the investigated seroconverters will take place within the HIV competence network and the European program SPREAD.