Impact of transmission of drug-resistant HIV on the course of infection and the treatment success. Data from the German HIV-1 Seroconverter Study

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Background
Data on the clinical course of infection in patients with transmitted drug-resistant HIV before and after initiation of treatment are scarce.

Patients and methods
Genotypic resistance was analysed in 504 therapy-naïve individuals with a known date of infection. Resistance was predicted using the Stanford algorithm. Clinical parameters for 80 individuals with transmitted drug-resistant HIV and for 424 patients with susceptible virus were analysed.

Results
In 16% of the individuals transmitted drug-resistant HIV was found. Detection of drug-resistant HIV was more likely in individuals with acute primary HIV infection [odds ratio (OR) = 1.529; 95% confidence interval (95% CI) 1.001; 2.236]. At the time of infection patients with an acute infection with resistant HIV had lower viral loads. CD4 cell counts tended to be higher and the CD4 cell loss more pronounced in the group with resistant HIV. Suppression of the viral load below the detection limit was achieved in 64% of the group with resistant HIV and in 85% of the group with susceptible HIV 6 months after initiation of therapy ($P = 0.199$). The majority of the group with resistant HIV (74%) received at least one compromised drug.

Conclusion
First-line treatment including drugs with predicted resistance can impair virological success in some patients. Factors influencing the decision to include compromised drugs need to be investigated.

Keywords: antiretrovirals, antiretroviral drug resistance, HIV-1, seroconverter, T-helper cells, viral load

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Introduction
The development of drug resistance is one of the major obstacles to the success of HIV therapy. It has been estimated that virological failure occurs in as many as 30–50% of HIV-1-infected individuals within 2 years after initiation of highly active antiretroviral therapy (HAART) [1–3]. In Canada, drug-resistant mutations were detected in about 25% of the study population in whom HAART was initiated during a follow-up period of 30 months [4]. Furthermore, in a random sample of 1797 HIV-infected individuals receiving medical care in early 1996 and who were viraemic in 1998, 76% showed resistance to one or more antiretroviral drugs [5]. The widespread use of HAART among patients in the early or later stage of infection may increase the number of individuals in whom drug resistance is selected during therapy and therefore increase the risk of the transmission of drug-resistant HIV. The transmission of resistant HIV has been described for all available nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) by heterosexual, homosexual and vertical transmission as well as by the intravenous route. The proportion of transmitted
drug-resistant HIV (primary drug resistance) in patients with recent infections has been found to vary between 0 and 51% (Table 1). In newly diagnosed HIV-infected patients, drug-resistant HIV has been detected in 4–14% of patients [9,28]. The transmission of multidrug-resistant HIV has been described and is of public health concern [16,29–32]. Transmitted resistant HIV may affect the patient in various ways. The clinical course of the disease might be influenced by the presence of resistant HIV. It has been postulated that, because of the lower fitness of the resistant virus, the immune system of the patient might be less impaired. Retrospective studies have shown higher CD4 cell counts in patients with resistant HIV compared with patients with susceptible HIV. However, there are case reports indicating that transmitted multidrug-resistant HIV can result in elevated viral load and a rapid decrease of CD4 cells, indicating a high level of replicative fitness and pathogenicity of these drug-resistant viruses [33,34]. Treatment options might be compromised in patients with transmitted resistant HIV [8,19,31]. Primary drug resistance can persist either as dominant species or as an archived variant in the latent pool [35]. Retrospective studies have shown that virological success was achieved later and the percentage of patients with suppression of viral load under the detection limit was lower in patients when the treatment was not resistance-assay guided [8,24,29,30,36].

The use of a suboptimal treatment regimen in a person infected with drug-resistant virus might be expected to limit the magnitude and durability of an antiviral response and might preclude the preservation of HIV-specific immune responses associated with early, effective antiretroviral therapy (ART) [31].

In Germany, the number of newly diagnosed HIV infections has increased and stabilized since 2004 at a high level. The increase was largely seen in men who have sex with men (MSM) in larger cities. In 2006, it is estimated that approximately 2700 individuals acquired an HIV infection. Here we present results from the German HIV-1 Seroconverter Study assessing the impact of primary HIV drug resistance on the course of infection. We analysed baseline viral load and CD4 cell counts in therapy-naïve patients with transmitted resistant or susceptible HIV; furthermore, we compared virological outcome and CD4 response after the initiation of ART between these groups.

### Methods

#### Study population

The German HIV-1 Seroconverter Study is a nationwide observational study based on an open cohort of HIV-infected persons for whom the date of seroconversion can be reliably determined...
estimated. Study participants are recruited by clinical centres and by private practitioners. Individuals with a first positive and last negative HIV-antibody test with a maximum 3-year interval between the tests as well as patients with an acute seroconversion confirmed by laboratory criteria are eligible for the study. The criteria for an acute seroconversion are detectable HIV-1 RNA antigen or p24 antigen before detectability of HIV antibodies or reactive enzyme linked immunosorbent assay (ELISA) with indeterminate Western blot. In persons recruited at the time of seroconversion (primary HIV infection) the date of the first reactive test (date of RNA-positive sample and simultaneous indeterminate or negative immunoblot or the date of the indeterminate immunoblot) is used as a proxy for the infection date. Otherwise the midpoint between the dates of the first positive and the last negative HIV-antibody test is used to estimate the time of infection. Demographic, clinical and laboratory data are collected on a standardized questionnaire with yearly follow-ups. The database used for analysis included information for patients for whom genotypic resistance testing was performed until 31 January 2005.

Genotypic resistance testing

At enrolment, baseline blood samples were collected from each individual. Genotypic resistance testing was performed for ART-naïve patients. The methods have already been described elsewhere [37]. Briefly, viral RNA was extracted from plasma using the viral RNA Kit (Qiagen, Hilden, Germany) and reverse-transcribed (200 μL of plasma equivalents) with superscript II (Invitrogen, Karlsruhe, Germany) and a 1453-bp fragment encoding the viral protease (99 amino acids) and 303 amino acids of the reverse transcriptase was amplified with the Expand High Fidelity PCR System (Roche Diagnostics, Mannheim, Germany) [37] and directly sequenced (Big Dye versions 1.1 and 3.1; Abbott, Wiesbaden, Germany) Alternatively, the ViroSeq HIV-1 Genotyping System was used (version 2; Abbott). Resistance mutations in the viral enzymes were identified according to the International AIDS Society (IAS) list [38]; protease: L10F/I/R/V, K20M/R, L24I, D30N, V32I, L33F, M36I/V/L, M46I/L/V, I47V/A, G48V/M, I50V/L, F53L, I54V/L/A/M/T/S, A71V/T, L63P, G73S/A, V77I, V82A/F/S/T, I84V/A/C, N88D/S/T and L90M (major mutations underlined); reverse transcriptase NRTI resistance mutations: M41L, E44D, A62V, K65R, D67N, T69 insertion, T69D/N/S/A, K70R, L74V, V75I/L, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, T215C/D/S/E/A and K219Q/E; reverse transcriptase NNRTI resistance mutations: L100I, K103N, V106A/M, V108I, Y181C, Y188L/H/D, G190A/S, P225H, M230L, L234I and P236L. In addition to the IAS list [37], T69A/S/N, F77L and the revertant substitutions T215C/D/S/E/A in the reverse transcriptase were assessed as transmitted drug resistance. V118I was only observed in association with V75L and F77L. In the protease, the M46V substitution was included as resistance-associated. Strains carrying one or more of the minor resistance-associated mutations L10F/I, K20I/R, M36I, L63P, A71V/T and V77I were considered PI-sensitive. The other minor PI mutations never occurred alone. Transmitted drug resistance was assumed if one or more of the other mutations listed were identified. Resistance levels to each of the ARV drugs were predicted using the Stanford algorithm (http://hivdb.stanford.edu/pages/alg3/HIVdb.html version 4.0). If the Stanford algorithm predicted a ‘potential resistance level’, the strain was considered as sensitive to the drug.

Statistical analyses

Medians are given with interquartile ranges (IQRs). Pearson’s χ² test and, where appropriate, Fisher’s exact test were used to compare proportions. The Mann-Whitney test was used to compare viral loads and CD4 cell counts between patients with and without transmitted drug-resistant HIV. Therapeutic success was defined as viral suppression under the detection limit within 6 months after initiation of therapy, and viral load measurements were undertaken between 1 and 6 months after the start of therapy. The detection limit was determined according to the test system and version of the test system used (<500 HIV-1 RNA copies/mL; <50 copies/mL). All P-values are two-sided, and a P-value of <0.05 was considered significant.

Results

Patient characteristics

A total of 504 study participants for whom genotypic resistance testing was performed were included in the analysis (Table 2). The study participants seroconverted between the years 1988 and 2004, and 70% (n = 353) acquired the HIV infection between 2001 and 2004. The HIV diagnoses were made in 213 patients (42%) at the time of seroconversion and recruitment was 35 months for 23 study participants. The majority of study participants were Germans (447; 89%), were men having sex with men (MSM; 444; 88%) and lived in Berlin (362; 72%). The other study participants lived in 27 different cities (85; 17%) or rural areas (57; 11%). The time interval between seroconversion and recruitment was <12 months for 294 (58%) of the study participants, between 12 and 24 months for 178 individuals (35%), <36 months for 23 study participants (5%) and 36 months or more for nine patients (2%).

Resistance testing

Plasma samples were taken from patients with an acute HIV infection on average 4 weeks (IQR 0–12 weeks) after the first reactive test and in patients who had already seroconverted on average 36 months (IQR 15–58 months) after the calculated infection date. Resistant HIV with a reduced susceptibility to at least one drug was detected in 80 patients (16%). The majority of patients were infected with HIV with reduced susceptibility to NRTI (46 of 80 patients), followed by infection with NNRTI and PI drug-resistant HIV (10 of 80 and 14 of 80, respectively). Drug resistance against two and three drug classes was detected in seven and three patients, respectively. The detection of drug-resistant HIV was more likely in patients for whom the genotypic resistance testing was performed at the time of the acute seroconversion \( \text{OR} = 1.529; \text{95% confidence interval} (95\% \text{ CI}) 1.002; 2.236 \). The majority of these patients originated from Germany \( (n = 61; 76\%) \), three study participants were from Poland and one each was from Italy, Spain, the Philippines and Cameroon. Sixty-one patients with resistance-associated mutations were living in Berlin (76%). The demographic characteristics did not differ from the overall patient characteristics with regard to age, sex and country of origin.

Virological and immunological parameters at the time of infection

The baseline median viral load and CD4 cell count at the time of seroconversion did not differ between the individuals with susceptible and resistant HIV. In patients with an acute primary HIV infection, that is, patients in whom the time of infection could be assessed with the greatest accuracy, a significantly higher first viral load was detected in patients with susceptible HIV \( (n = 185) \) compared with patients with resistant HIV \( (n = 28; \text{Table } 2) \). Furthermore, in the 2 years following seroconversion, the viral load remained lower in persons with resistant virus \( (\text{Fig. } 1) \), but because of low numbers this difference was not statistically significant. One year after infection the CD4 cell loss was more pronounced in patients with resistant virus than in those with wild-type virus \( (139 \text{ vs } 20 \text{ cells/µL}) \).

AIDS-defining diseases occurred in 10 patients (2.4%) with wild-type HIV infection, on average 48 months after infection \( (\text{IQR } 9.5–62.8) \) and in one patient (1.3%) with transmitted resistant HIV 65 months after infection.

ART

In 31 patients (38.8%) with transmitted drug resistance and in 170 patients (40.1%) with susceptible HIV, ART was

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Table 2 Baseline characteristics of patients with transmitted drug-resistant HIV infection and patients infected with susceptible HIV enrolled in the HIV-1 Seroconverter Cohort between 1997 and 2004 for whom a genotypic resistance test was performed

<table>
<thead>
<tr>
<th>Study participants</th>
<th>With transmitted drug-resistant HIV ( (n = 80) )</th>
<th>With susceptible HIV ( (n = 424) )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex [ n/total (%)]</td>
<td>Male 77/80 (96.3)</td>
<td>399/424 (94.1)</td>
<td>0.598</td>
</tr>
<tr>
<td>Female 3/80 (3.8)</td>
<td>25/424 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at seroconversion (years) [median (IQR)]</td>
<td>Male 32 (27.5; 36)</td>
<td>32 (27; 37)</td>
<td>0.959</td>
</tr>
<tr>
<td>Female 30 (20; 33)</td>
<td>29 (23; 31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group [n (%)]</td>
<td>MSM 72 (90.0)</td>
<td>373 (88.0)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual transmission 3 (3.8)</td>
<td>33 (7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous drug user 2 (2.5)</td>
<td>10 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown 3 (3.8)</td>
<td>8 (1.9)</td>
<td>0.348</td>
<td></td>
</tr>
<tr>
<td>Baseline values at seroconversion</td>
<td>Viral load (log10 copies/mL) [median (IQR)]</td>
<td>All study participants 4.96 (4.29; 5.55)</td>
<td>5.09 (4.45; 5.70)</td>
</tr>
<tr>
<td>Acute seroconversion 4.97 (4.46; 5.50) *</td>
<td>5.59 (4.45; 5.70) *</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>CD4 count [cells/µL] [median (IQR)]</td>
<td>514 (378; 620)</td>
<td>469 (350; 696)</td>
<td>0.953</td>
</tr>
<tr>
<td>Values at time of initiation of HAART</td>
<td>Viral load (log copies/mL) [median (IQR)]</td>
<td>4.97 (4.43; 5.54) *</td>
<td>5.47 (4.67; 5.88) *</td>
</tr>
<tr>
<td>CD4 count [cells/µL] [median (IQR)]</td>
<td>490 (349; 595) *</td>
<td>405 (277; 630) *</td>
<td>0.494</td>
</tr>
</tbody>
</table>

\*n = 28; \*n = 185; \*n = 19; \*n = 129; \*n = 22; \*n = 131.  
HAART, highly active antiretroviral therapy; IQR, interquartile range; MSM, men who have sex with men.
initiated, starting on average 3 months (IQR 0–11 months) and 6 months (IQR 1–17 months) after infection (P = 0.067), respectively. During the course of the ART, the increase in CD4 cell count was less pronounced in patients with transmitted drug-resistant HIV (Fig. 2).

A first-line treatment excluding drugs with predicted resistance was initiated in eight patients (26%) with transmitted resistant HIV. For 23 patients (74%) compromised drugs were included in the regime. The majority (n = 18) received a NRTI with predicted resistance. The following compromised drugs were used: 10 patients received zidovudine, three patients each received lamivudine or abacavir, five patients received didanosine and six patients were treated with stavudine. In four cases, PIs were included in the treatment regime despite predicted resistance to this drug class (all patients with predicted multidrug resistance). None of the patients with predicted resistance to NNRTI received a compromised NNRTI drug in first-line treatment.

Viral load measurements were available for 69 patients within 6 months after the initiation of therapy. Suppression of viral load below the detection limit was achieved in 84.5% (49 of 58) and 63.6% (seven of 11) of patients with susceptible and resistant HIV, respectively (P = 0.199). In patients with predicted resistance to NRTI, who had been treated with compromised NRTI, the viral load fell to below the detection limit in 57% (four of seven) of the study participants after initiation of ART.

Discussion

A considerable number of drugs are now available for the treatment of HIV infection; however, the occurrence of drug-resistant HIV is increasing in the HIV-infected population [39]. In a mathematical model used to forecast the evolution of the transmission of drug-resistant HIV from 1996 to 2005 based on data from a cohort of MSM in San Francisco, Blower et al. [40] identified the increasing treatment rates as a key factor driving the transmission of resistant HIV. The situation with regard to the frequency of transmission of resistant HIV is heterogeneous. In some countries the frequency has stabilized at a high level, while in other countries increases in transmission frequency to levels of up to 20% of new infections or decreases in transmission frequency have been seen [41]. A number of studies indicate that resistance mutations of transmitted drug-resistant HIV can persist for a considerable time in untreated patients and that strains of HIV-1 with drug-selected resistance mutations can actively circulate [42,43]. The available data on clinical outcome for patients carrying primary resistant strains are not conclusive. In Italian and Spanish cohorts, differences in baseline viral load and CD4 counts between patients with resistant and susceptible HIV could not be detected [11,44]. In contrast, our findings are consistent with results from cohorts in the USA and France showing lower baseline viral load levels in patients with transmitted drug resistance [6,7,9,19]. However, we could only assess lower viral loads in HIV-infected patients with primary HIV infection, that is, in patients for whom viral load measurements were available in the early stage of
infection. Varying intervals between infection and the first viral load measurement might be an alternative explanation for the different results seen in the European cohorts. Furthermore, additional factors might influence viral load, such as the type of resistance occurring in the transmitted virus. In a more detailed analysis of baseline viral loads, Little et al. [45] detected lower viral loads in the presence of high-level NRTI or PI resistance compared with patients with susceptible HIV, whereas patients with NNRTI-resistant HIV had significantly higher viral loads than patients with a wild-type infection. The viral set points followed the same pattern. As the HIV viral set point during the disease-free interval has been strongly associated with future risk of disease progression, this finding might be of importance for the progression of disease [46,47]. In our study group, no difference with regard to the occurrence of AIDS-defining diseases was found between the individuals with and without transmitted drug-resistant HIV (2.4 vs 1.9%). This is consistent with the results of the FORECAST study, a prospective substudy of the European SPREAD project which aims to investigate the spread of drug-resistant HIV in 18 European countries. Seventy-eight patients infected with HIV variants carrying drug-resistance mutations were compared with 77 patients whose virus had no resistance mutations. During 16 months of follow-up, 5.3 and 5.6% of the two groups experienced disease progression, defined as progression to AIDS or immunological deterioration. There was no evidence of different rates of disease progression according to the degree of drug resistance: virus resistant to two or three classes of drugs caused progression at the same rate as virus resistant to just one class [48].

Higher baseline CD4 cell counts have been reported in patients with primary HIV drug resistance [7,19]. Results from the UK Register of HIV Seroconverters and the CASCADE Virology Group indicate that the initial CD4 cell counts were higher in patients with transmitted resistant HIV (658 vs 554 cells/μL and 698 vs 604 cells/μL, respectively) and converged after 1 year, suggesting a faster cell loss in patients with transmitted resistant HIV [49]. We observed a higher cell loss in patients with primary HIV drug resistance, but longer follow-up periods are essential to validate these findings. In the Spanish cohort, no difference with regard to CD4 cell counts could be detected in patients with and without transmitted drug resistance [44].

Available reports on therapeutic success in patients with transmitted drug resistance are not consistent. Whereas in some studies CD4 cell counts and virological response to treatment were similar in patients with and without transmitted drug-resistant HIV [11, 6, 50, 51], other reports suggested that the virological and immunological responses to therapy were poorer in the presence of transmitted resistant HIV [31, 32].

In our study, the treatment success rate was lower in patients with transmitted drug-resistant HIV. The majority of patients with primary HIV drug resistance were not treated according to genotypic test results. In France (ANRS 053 and PRIMO Cohorts), reduced efficacy was seen when compromised drugs were used. Patients prescribed at least two drugs with predicted resistance reached the viral threshold of 400 or 50 copies/mL more slowly than other patients [8]. Recent results from the French PRIMO Cohort Study Group suggest that, in patients achieving undetectable plasma HIV RNA despite the use of two drugs with predicted resistance, other factors such as neutralizing antibodies, specific human leucocyte antigen types or host genetic factors might have played a role [35].

The physician’s choice to initiate a test-guided ART might be influenced by several factors. If it has been decided to initiate early treatment, the test results might not yet have been available at the time of ART initiation and the initial therapy regimen might not have been changed thereafter. When choosing a NRTI backbone, factors such as efficacy, side effects and dosing regimens are relevant for the patient. Therefore, the disadvantages perceived by the provider in using a compromised drug might be balanced against the advantages seen in the use of a specific NRTI backbone. In the German HIV-1 Seroconverter Study, the majority of the resistance mutations were NRTI-associated mutations, including drugs recommended as a backbone for the initial treatment [52]. An analysis of the medication of the German ClinSurv cohort showed that, for example, in 2004 the most frequently used regimen was lamivudine/zidovudine in combination with nevirapine or efavirenz, representing 63% of the regimens [53]. In our study, either zidovudine or lamivudine was included in the first-line treatment in 12 patients despite predicted resistance (39%).

Several limitations of the German HIV-1 Seroconverter Study have to be taken into account. The number of patients with transmitted HIV drug resistance is still limited and the observation time for the study participants for whom a genotypic resistance test has been performed is still short; individuals with transmitted drug-resistant HIV are under observation for an average time of 9.5 months (IQR 3 to 18 months). In the future, with increasing cohort size and longer follow-up periods, it will be possible to perform in-depth analysis to adjust for confounding factors, such as age, calendar year, transmission mode and ARV regimen, possibly influencing the clinical outcome in patients with transmitted drug resistance.

Current guidelines recommend that the initial ART should contain two NRTIs and either a NNRTI or preferably...
a boosted PI [54–57]. Resistance testing is a component in the optimization of drug selection after treatment failure. However, regarding resistance testing in therapy-naïve patients, the guidelines are not consistent. Whereas some guidelines recommend resistance testing for all drug-naïve patients prior to commencing treatment using the nearest available sample to seroconversion or presentation [53–55], the American guidelines recognize the potential value of resistance testing in drug-naïve patients, but the experts do not see enough evidence to recommend such use [57].

In the German HIV-1 Seroconverter Study, the detection of drug-resistance mutations was more likely in patients with a primary HIV infection; furthermore, only in these patients could a lower viral load be detected compared with patients infected with susceptible HIV at the time of diagnosis, a pattern that was also seen 1 year after infection. The results of the German HIV-1 Seroconverter Study show frequent use of compromised NRTIs as the backbone for initial treatment. The reasons for decisions to use compromised drugs need to be analysed and the issue of assay-guided initial treatment should be addressed in guideline recommendations.

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