UNIKLINIK KÖLN | Department I of Internal Medicine University Hospital of Cologne

CROI Conference on Retroviruses and Opportunistic Infections

CFAR SAN DIEGO | CENTER FOR AIDS RESEARCH

DZIF German Centre for Infection Research

# PRE-TREATMENT HIV DRUG RESISTANCE SPREAD IN SIX GERMAN METROPOLITAN REGIONS

**Poster no.**
**0864**

Melanie Stecher[1,2*], Martin Hoenigl[3,4*], Philipp De Leuw [5], Josef Eberle[6,7], Jan-Christian Wasmuth[8], Georg Behrens[9,10], Guido Schäfer[11], Christoph Spinner[12,13], Christoph Stephan[5], Elena Knops[14], Sanjay Mehta[3], Jörg Janne Vehreschild[1,2], Antoine Chaillon[3], for the Translational Platform HIV (TP-HIV) Molecular Epidemiology Team

[1]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I for Internal Medicine, Cologne, Germany; [2]German Center for Infection Research (DZIF), partner site Bonn -Cologne, Cologne, Germany; [3]Division of Infectious Diseases, University of California San Diego, San Diego, CA; [4]Division of Pulmonology and Section of Infectious Diseases, Medical University of Graz, Graz, Austria; [5]HIV Center, University Hospital of Frankfurt, Frankfurt, Germany; [6]Max von Pettenkofer Institute & Gene Center, Virology, National Reference Center for Retroviruses, Faculty of Medicine, LMU München, Munich, Germany; [7]German Centre for Infection Research (DZIF), partner Munich, Munich, Germany; [8]Department for Internal Medicine I, University Hospital of Bonn, Bonn, Germany; [9]Department for Clinical Immunology and Rheumatology, Hannover Medical School, Hannover, Germany; [10]German Centre for Infection Research (DZIF), partner Hannover, Hannover, Germany, [11]University Hospital Hamburg Eppendorf, Hamburg, Germany; [12]German Centre for Infection Research (DZIF), partner Munich, Munich, Germany; [13]Department of Medicine II, Technical University of Munich, Munich, Germany; [14]Institute of Virology, University Hospital of Cologne, Cologne, Germany
*Martin Hoenigl and Melanie Stecher contributed equally to this work

## Background

- In Germany, the prevalence of HIV-1 drug resistance mutations (DRM) remains high [1].
- Nation-wide estimates of DRM are not available in Germany, and reported DRM differs between regions with a maximum of 17.2% [1; 2].
- Transmitted HIV-1 DRM impacts the choice of Antiretroviral Therapy (ART) and may allow viral escape from pre- and post-exposure prophylaxis strategies [3].
- The occurrence of transmitted DRM varies between risk groups, with the highest prevalence among men having sex with men (MSM) (12.5%), followed by heterosexuals (HTS) (10.3%), and then persons who inject drugs (PWID) (4.8%) [4].
- The metropolitan regions Munich, Cologne, and Frankfurt report the highest rates of new HIV infections (17.3; 13.3 and 12.3 per 100k) in 2017 [5].

## Objective

**Determine the dynamics and spread of HIV-1 DRM transmission in Germany**

## Methods

### Data:

- Sociodemographic, geographic, and HIV-1 *pol* sequence data were collected from newly diagnosed person living with HIV (PLWH) in six metropolitan cities across Germany (Bonn, Cologne, Frankfurt, Hamburg, Hannover, and Munich) between 2001 and 2018.

### Network inferences:

- Phylogenetic and network analyses were performed to infer putative relationships and shared DRM.
- Partial *pol* sequences were subtyped, using the Subtype Classification Evolutionary Algorithms (SCUEAL) program [6].
- The genetic transmission network was inferred based on the Tamura-Nei 93 pairwise genetic distance (GD) between all sequences by HIV-TRACE (www.hivtrace.org) and a putative linkage was inferred when the GD was ≤1.5% [7].

### DRM screening:

- DRM screening was performed according to the Stanford University Genotypic Resistance Interpretation (https://hivdb.stanford.edu/).
- Shared DRM were defined as any DRM present in two or more genetically linked individuals (≤1.5% GD) [8;9].
- Sociodemographic and geographic data were used to characterize transmission clusters (Table 1).

### Geospatial analyses:

- Geospatial dispersal of the clusters was determined by calculating the average distance between reported residence (centroids of 3-digit zip code, ArcGIS®) of genetically linked individuals.

## Results

- A total of 1,397 HIV-1 *pol* sequences from HIV-1 ART naïve PLWH were obtained.
- The majority were male (1,158/1,397; 82.9%), infected with subtype B (1,017/1,397; 72.8%) and reporting MSM as main risk factor (792/1,397; 56.7%) (Table 1).
- Prevalence of any DRM at the time of diagnosis was 17.0% (237/1,397) and was highest in Cologne (105/237; 44.3%), Hannover (53/237; 22.4%), and Frankfurt (31/237; 13.1%) (Table 1).
- Frequency of any DRM was highest among MSM (134/792; 16.9%) and individuals <25 years of age (18/111; 16.2%) (Table 1).
- Genetic transmission network analyses showed comparable frequencies of DRM in clustering and not-clustering individuals (16.3% versus 18.1%; p=0.46).

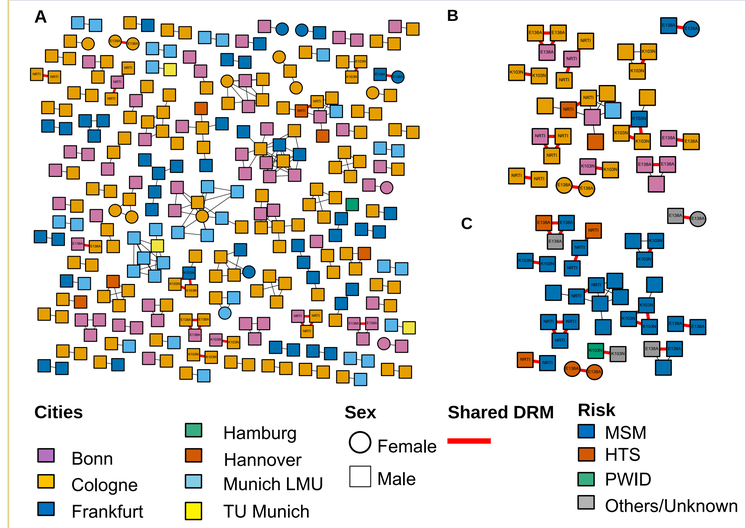
**Table 1. Prevalence of any DRM at time of diagnosis was 17.0% and highest among individuals <25 years and MSM.**

| | Study population, N (%) | DRM N (%) | Shared DRM N (%) | P-value** |
|---|---|---|---|---|
| **Total** | 1,397 (100) | 237 (17.0) | 19 (8.1) | |
| **Age** | | | | **0.032** |
| >45 | 430 (30.8) | 81 (34.2) | 2 (10.5) | |
| 25-45 | 856 (61.3) | 138 (58.2) | 13 (61.3) | |
| <25 | 111 (7.9) | 18 (7.6) | 4 (21.1) | |
| **Gender** | | | | 0.058 |
| Female | 239 (17.1) | 36 (15.2) | - | |
| Male | 1,158 (82.9) | 201 (84.8) | 19 (100) | |
| **Subtype** | | | | |
| non-B | 380 (28.2) | 65 (27.4) | | |
| B | 1,017 (72.8) | 172 (72.6) | 19 (100) | |
| **Risk*** | | | | 0.164 |
| HTS | 302 (21.6) | 45 (19.0) | 2 (10.5) | |
| MSM | 792 (56.7) | 134 (56.5) | 15 (78.9) | |
| ENDEMIC | 133 (9.5) | 22 (9.3) | - | |
| PWID | 24 (1.7) | 4 (1.7) | 1 (5.3) | |
| Others/Unknown | 146 (10.5) | 1 (0.7) | 1 (5.3) | |
| **City** | | | | 0.051 |
| Bonn | 152 (10.9) | 18 (7.6) | 3 (15.8) | |
| Cologne | 582 (41.7) | 105 (44.3) | 14 (73.7) | |
| Frankfurt | 215 (15.4) | 31 (13.1) | 1 (5.3) | |
| Hamburg | 48 (3.4) | 9 (3.8) | - | |
| Hannover | 169 (12.1) | 53 (22.4) | 1 (5.3) | |
| Munich | 231 (16.5) | 21(8-9) | - | |

Legend. Baseline sociodemographic, risk- and viral characteristics in individuals harboring drug resistance mutations (DRM) and shared DRM. *HTS, heterosexual; MSM, men who have sex with men; ENDEMIC, recent immigration from a country with a HIV prevalence >1%, PWID, people with injection drug use. **Chi-square and Fisher's exact test as appropriate. P-values given in bold depict significant results (p<0.05).

- Of the 47 sequences harboring DRM in the inferred transmission network, 19 (23.4%) were shared by HIV-1 genetically linked partners, predominantly among residents of Cologne (14/19, 73.7%) and Bonn (3/19, 15.8%) (Figure 1A&B).
- Individuals <25 years of age (4/111; 3.6%) were more likely to harbor shared DRM compared to individuals between 25-45 (13/856; 1.5%) and >45 years of age (2/430; 0.47%; p=0.032).
- The prevalence of shared DRMs were highest among the risk group of MSM (15/19; 78.9%) (Figure 1C).
- The most frequently transmitted DRM was K103N (9/19 in individuals sharing DRMs, 4 clusters) (Figure 1B&C).

**Figure 1. Individuals harboring shared DRMs were predominantly MSM living in Cologne and Bonn.**




Legend. **A)** HIV-1 genetic transmission clusters in six metropolitan regions. The color indicates the location of residence. Shape indicates gender (male-square, female-circle). All edges represent a genetic distance of ≤1.5%. Lines in bold red indicate shared drug resistance mutations (DRM). **B)** Enlargement demonstrates clustering individuals harboring shared DRMs by cities, labeled with each nodes. N|NRTIs indicate the presence of ≥1 nucleoside or non-nucleoside reverse transcriptase inhibitor resistance(s). **C)** Enlargement demonstrates clustering individuals harboring shared DRMs by risk groups (MSM, men who have sex with men; HTS, heterosexuals; PWID, people with injection drug use).

## Conclusion

- We observed high rates of DRMs in newly diagnosed individuals in Cologne, Hannover, and Frankfurt.
- Network analysis also revealed frequent cases of shared DRMs among genetically-linked individuals, especially K103N.
- Our findings highlight regional differences in transmitted drug resistance and the necessity to focus prevention efforts on specific areas and the risk group of young MSM, to prevent onward transmission across Germany.

References:
[1] Schmidt D, Kollan C, Falkenheuer G, Schulter E, Stellbrink HJ, Noah C, et al. Estimating trends in the proportion of transmitted and acquired HIV drug resistance in a long term observational cohort in Germany. PLoS One. 2014;9(8):e104474.
[2] Stecher M, Chaillon A, Eberle J, Eis-Huebinger AM, Lehmann C-P,Falkenheuer G, Wasmuth JC, Knops E, Vehreschild JJ, Mehta S, Hoenigl M. Pretreatment human immunodeficiency virus type 1 (HIV-1) drug resistance in transmission clusters of the Cologne-Bonn region, Germany, CMI 2018, PMID: 30319507.
[3] Wittkop L, Günthard HF, de Wolf F, Dunn D, Cozzi-Lepri A, de Luca A, et al; EuroCoord-CHAIN study group. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. Lancet Infect Dis. 2011;11:363–371. pmid:21354861
[4] Bartmeyer B, Kuecherer C, Houareau C, Werning J, Kerenn K, Somogyi S, et al. Prevalence of transmitted drug resistance and impact of transmitted resistance on treatment success in the German HIV-1 Seroconverter Cohort. PLoS One. 2015;5(10):e12718.
[5] Epidemiologisches Bulletin 39 (http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2018/39_18.pdf?__blob=publicationFile)
[6] Pond SL, Posada D, Gravenor MB, Woelk CH, Frost SD. Automated phylogenetic detection of recombination using a genetic algorithm. Molecular Biology and Evolution. 2006;23(10):1891-901.
[7] Kosakovsky Pond SL, Posada D, Stawiski E, Chappey C, Poon AF, Hughes G, et al. An evolutionary model-based algorithm for accurate phylogenetic breakpoint mapping and subtype prediction in HIV-1. PLoS Comput Biol. 2009;5(11):e1000581.
[8] Hoenigl M, Chaillon A, Kassaye NK, Haas B, Stenzl E, Weninger K, et al. Characterization of HIV Transmission in South-East Austria. PLoS One. 2016;11(3):e0151478.
[9] Wertheim JO, Leigh Brown AJ, Hepler NL, Mehta SR, Richman DD, Smith DM, et al. The global transmission network of HIV-1. J Infect Dis. 2014;209(2):304-13.

Acknowledgments:
This research was supported by funds from the following:
German Center for Infection Research (DZIF); NIH (MH062512, AI106039-05, MH113474, AI036214) and from the Center for AIDS Research CFAR.

Corresponding Authors:
Antoine Chaillon, MD, PhD achaillon@ucsd.edu
Melanie Stecher, melanie.stecher@uk-koeln.de