Trends for transmitted drug resistance and prevalence of non-B subtypes in recent infections – results from the national molecular surveillance, Germany 2013-2016

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07.06.2017
15th European Meeting on HIV & Hepatitis
Molecular surveillance of HIV

Tool to assess:

• Transmitted drug resistance (TDR)

• HIV-1 subtypes

• Transmission cluster

➢ a broad and representative sampling strategy is needed
Robert Koch-Institute

Federal health authorities

Local health authorities

Physicians (hosp. and outpat.)

Diagnostic Laboratories

Notification electronically via SurvNet

Notification form (§ 6 IfSG)

Notification form (§ 6 Abs. 1 IfSG)

Anonymus HIV-report

Notification form § 7 Abs. 3 IfSG)

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Sampling linked to the HIV-reporting

Since 2011 implemented within the German Incidence surveillance in close joint work between RKIs epidemiologists and HIV-lab

Diagnostic labs (n~82)

Anonymus HIV-Report (IfSG)

DSS (DriedSerumSpots)

RKI

~ 60% of all HIV-new diagnosis
Workflow in the Lab

Recent Infection Testing Algorithm

**RITA**: BED CEIA + CD4 cell count (from HIV-report)

According to ECDC recommendations

Sample receipt (DSS)

Recent infections: RNA isolation

Viral load RT pol PCR (DSS)

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Workflow in the Lab

Sample receipt → RITA → Recent infections: RNA isolation → Viral load and RT-PCR → Sanger/NGS

20% co for minor variants → HIV-resistance: WHO SDRM list (PI/RTI), IAS – USA 2017 (INI)
HIV-1 Subtyp: REGA, Comet + socio demographic from HIV-report
## Results (1)

### HIV-1 genotypes (PR/RT) 2013-2016:  
\[ n = 1,879 \]

#### Characteristics of the study population of recent HIV-infections

<table>
<thead>
<tr>
<th>Study Population</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1630 (86.7)</td>
</tr>
<tr>
<td>Female</td>
<td>230 (12.2)</td>
</tr>
<tr>
<td>Not reported</td>
<td>19 (1.0)</td>
</tr>
<tr>
<td><strong>Transmission route</strong></td>
<td></td>
</tr>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>1085 (57.7)</td>
</tr>
<tr>
<td>Persons with heterosexual contacts (HET)</td>
<td>200 (10.6)</td>
</tr>
<tr>
<td>Persons with intravenous drug use (PWID)</td>
<td>69 (3.7)</td>
</tr>
<tr>
<td>Not reported/other</td>
<td>524 (27.9)</td>
</tr>
<tr>
<td><strong>Country of origin</strong></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>1151 (61.3)</td>
</tr>
<tr>
<td>Other</td>
<td>390 (20.7)</td>
</tr>
<tr>
<td>Not reported</td>
<td>338 (18.0)</td>
</tr>
<tr>
<td><strong>Country of infection</strong></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>1196 (63.7)</td>
</tr>
<tr>
<td>Other</td>
<td>214 (11.4)</td>
</tr>
<tr>
<td>Not reported</td>
<td>469 (24.9)</td>
</tr>
</tbody>
</table>
Results (2)
HIV-1 genotypes (PR/RT) 2013-2016:  n= 1,879

Transmitted PI/RTI resistance in recent infections

- Sensitive: 89.2%
- Resistant: 10.8%  (CI 95%: 9.5-12.3)

P_{trend TDR} > 0.5

N= 32/277                44/462                  68/619                 59/522

Proportion (%)

2013 | 2014 | 2015 | 2016
--- | --- | --- | ---
12 | 10 | 11 | 10

☞ stable proportion
Results (3)

HIV-1 genotypes (PR/RT) 2013-2016: n= 1,879

Transmitted PI/RTI resistance in recent infections

- **NRTI**
- **NNRTI**
- **PI**
- **Dual**
- **Multi**

**Cumulative:**
- NRTI: 32/277 (11.5%)
- NNRTI: 44/462 (9.5%)
- PI: 68/619 (11.1%)
- NRTI + PI: 59/522 (11.3%)

**P trend NNRTI 2013-2016:** > 0.05
**P trend NNRTI 2014-2016:** < 0.05

**N**
- 2013: 13/462 (2.8%)
- 2014: 32/522 (6.1%)
- 2015: 68/619 (11.1%)
- 2016: 59/522 (11.3%)

**Proportion - cumulative (%):**
- NRTI: 2.8%
- NNRTI: 6.1%
- PI: 2.8%

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Results (3)
HIV-1 genotypes (PR/RT) 2013-2016: n= 1,879

Transmitted PI/RTI resistance in recent infections

Increase of NNRTI
mainly based on K103N

73% subtype B
50% MSM; 40% unknown
no transmission cluster

normal fluctuations for small N!??
Results (4)

HIV-1 genotypes (PR/RT) 2013-2016: n= 1,879

Potential emergence of (tenofovir/emtricitabine-based) PrEP-selected primary mutations in the future?

ówi

No increase in 2016
Results (6)
HIV-1 genotypes (INT) 2014-2016: n=839

Integrade inhibitor resistance mutations in recent infections

According IAS-USA:


- 2.1% minor mutations (n=15)
- Both also present in pre-INI era (polymorphism)
- Per definition no TDR


Results (7)

HIV-1 genotypes (PR/RT) 2013-2016: n= 1,879

HIV-1 B and non-B subtypes in recent infections

- **Subtype B**: 68.8%
- **Non-B subtypes**: 31.2%

(CI 95%: 29.1-33.4)

Significant increase of non B-infections

\[ \text{P}_{\text{trend nonB}} < 0.001 \]

\[ \text{N}_{\text{nonB}} = 57/277, 112/462, 239/618, 178/522 \]
Results (8)
HIV-1 genotypes (PR/RT) 2013-2016: n= 1,879

HIV-1 B and non-B subtypes in recent infections

Significant increase of subtype A + C infections 2013-2016
Results (9)
HIV-1 genotypes (PR/RT) 2013-2016: n= 1,879

Subtype A according to origin

3 `active´ cluster (2016)
- n=11 (4 x 2016) mainly German MSM
- n=5 (2 x 2016) mainly German MSM
- n=6 (4 x 2016) mainly German MSM
Results (10)
HIV-1 genotypes (PR/RT) 2013-2016/I: n = 1,879

Subtype C infections according origin + transmission route

- Proportion of subtype C infections (%)
- N subtype C = 9/277, 18/462, 31/619, 41/522
Summary & Conclusion

- Proportion of TDR (PI & RTI) is stably high >10% in recent infections => maintain resistance testing

- No evidence for TDR (INI) according IAS-USA list

- Proportion of non-B infections in Germany is high (30%) and continues to increase => HIV-1 Subtype A and C are becoming established in the German population

- The here presented Molecular Surveillance strategie is a sensitive tool to identify
  - potential emergence of PrEP selected mutations in future
  - current transmission clusters
Thank you for your attention!

Colleagues from RKI
Barbara Bartmeyer
Karolin Meixenberger
Kirsten Hanke
Alexandra Hofmann
Claudia Kücherer
Viviane Bremer
Norbert Bannert

`Master HIV-Hep group`
Traces of the German HIV-1 Subtyp A Epidemic from Kirsten Hanke

- German subtype A epidemic is attributed to two independent virus variants
- Subtype A circulates endemically in Germany since 30 years
- 13 German clusters from which 6 are still active
- Early infections by Eastern African variant among MSM and HET (origin in Kenya, Kongo and Uganda)
- 1995-2005 strong spread of the Eastern European variant ($A_{FSU}$) among PWID
- Recent infections mainly by Eastern European variant especially among German MSM
- Most recent transmission clusters are German MSM clusters formed after 2013
What have we done?

- **183** subtype A *pol*-sequences from newly infected individuals
- **Sampling period 1993-2015**
- Reference panel: 560 closely related subtype A sequences retrieved by BLAST search of the Los Alamos HIV database
- Bayesian phylogenetic analysis using BEAST v1.8.3 discrete asymmetric diffusion models to infer epidemiological linkage among geographic regions and transmission groups
- Multitype-tree Birth-Death and Birth-Death skyline (BDSKY) analyses (BEAST v2.4) to estimate changes in effective reproduction numbers ($R_e$)
Comparison of sampled versus total new HIV-diagnosis reports

<table>
<thead>
<tr>
<th>Transmission</th>
<th>total (n=23.195)</th>
<th>DSS (n=11.805)</th>
</tr>
</thead>
<tbody>
<tr>
<td>unbekannt</td>
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<td>andere</td>
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<tr>
<td>Hetero</td>
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<tr>
<td>MSM</td>
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<tr>
<td>&gt;=55 Jahre</td>
<td></td>
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<tr>
<td>45-54 Jahre</td>
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<td>35-44 Jahre</td>
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<td>25-34 Jahre</td>
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<tr>
<td>&lt;25 Jahre</td>
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<tr>
<td>fehlende Angaben</td>
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<tr>
<td>männlich</td>
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<td>weiblich</td>
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<tr>
<td>2008</td>
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</tbody>
</table>

Proportions in subgroups is well pictured.

Source: Hofmann A RKI – Epidem.
Results (7)
HIV-1 genotypes (INT) 2014-2016/I: n = 655

Integrase inhibitor resistance mutations in recent infections

According to HIV-GRADE Algorithm 16.01.2017

- 1.4% resistance to elvitegravir
- 10% reduced susceptibility

**Sensitivity**: 88.6%

- **V260I**: 0.3%, n=2
- **T97A**: 1.1%, n=8
- **L74M**: 0.8%, n=6
- **S119R**: 6.2%, n=44
- **E157Q**: 2.1%, n=15
- **G163R/K**: 0.6%, n=4
- **D232N**: 0.3%, n=2

**Cumulative**:
- resistance to elvitegravir
- intermediate resistance to elvitegravir
- reduced susceptibility
Results (9)
HIV-1 genotypes (PR/RT) 2013-2016: \( n = 1,879 \)

According to origin

**Subtype A**

- Year: 2013
  - Proportion of subtype A infections (%)
    - others: 0.5
    - EUR-W: 0.1
    - EUR-East: 0.1
    - AF-SS: 0.1
    - D: 3.7
- Year: 2014
  - Proportion of subtype A infections (%)
    - others: 0.5
    - EUR-W: 0.1
    - EUR-East: 0.1
    - AF-SS: 0.1
    - D: 3.7
- Year: 2015
  - Proportion of subtype A infections (%)
    - others: 0.5
    - EUR-W: 0.1
    - EUR-East: 0.1
    - AF-SS: 0.1
    - D: 3.7
- Year: 2016
  - Proportion of subtype A infections (%)
    - others: 0.5
    - EUR-W: 0.1
    - EUR-East: 0.1
    - AF-SS: 0.1
    - D: 3.7

**Subtype C**

- Year: 2013
  - Proportion of subtype C infections (%)
    - others: 0.5
    - EUR-W: 0.1
    - EUR-East: 0.1
    - AF-SS: 0.1
    - D: 3.7
- Year: 2014
  - Proportion of subtype C infections (%)
    - others: 0.5
    - EUR-W: 0.1
    - EUR-East: 0.1
    - AF-SS: 0.1
    - D: 3.7
- Year: 2015
  - Proportion of subtype C infections (%)
    - others: 0.5
    - EUR-W: 0.1
    - EUR-East: 0.1
    - AF-SS: 0.1
    - D: 3.7
- Year: 2016
  - Proportion of subtype C infections (%)
    - others: 0.5
    - EUR-W: 0.1
    - EUR-East: 0.1
    - AF-SS: 0.1
    - D: 3.7
Phylogenetic analysis of subtype A

3 putative `active´ transmission clusters (incl. 2016)

1) - N=11 (4 x 2016)
   - mainly *German* MSM
   - north - south Germany
   - all PI resistance mutation M46I

2) - N=5 (2 x 2016)
   - mainly *German* MSM
   - 4/5 south Germany

3) - N=6 (4 x 2016)
   - mainly *German* MSM
   - Düsseldorf-Köln

=> Subtype A is spreading among MSM
Phylogenetic analysis of subtype C

1 putative new transmission cluster (n=18)

- 14 Germans, 1 Geek, 1 Kasachstan, 2 ?
- Area of living: 17 Munich, 1 Augsburg, 1 Hamburg
- 14 male, 3 female, 1 ?
- 26-42 years old
- 10 PWID, 2 MSM, 2 HET, 4 ?
- 1. new diagnosis 03/2015
- 16 new diagnosis 02-10/2016

=> Strong increase of PWID mediated infections in 2016
Workflow in the Lab

Sample receipt

RITA

Recent infections: RNA isolation

Viral load and RT-PCR

Sanger/NGS 20% co for minor variants

Sequenced among isolated

Proportion (%)

2013 2014 2015 2016

N= 528-277 700-462 898-619 722-522

HIV-resistance: WHO SDRM list (PI/RTI), IAS –USA 2017 (INI)

HIV-1 Subtyp: REGA, Comet
+ socio demographic from HIV-report
Results (5)
HIV-1 genotypes (INT) 2014-2016: n= 839

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Results (6)
HIV-1 genotypes (INT) 2014-2016: n= 839

Integrase inhibitor resistance mutations in recent infections

According IAS-USA:


- 0% major mutation
- 2.1% minor mutations (n=15)
- mostly as dual resistance (PI + INI; n=13)
- Not significant different from pre-INI era
  - 0.7% L74M (3/459)
  - 1.7% T97A (8/459)
  - 0.7% L74M+T97A (3/459)