Monitoring of Hepatitis B and C in the German HIV-1 seroconverter cohort

Daniel Schmidt
Barbara Bartmeyer, Claudia Kücherer, Karolin Meixenberger, Klaus Jansen, Sila Aygündüz, Viviane Bremer
Robert Koch-Institute
HIV/AIDS and STI unit (FG 34)

AREVIR 2015
The cohort: Study aims

- Analysis of viral and host factors on HIV disease progression
  - Occurrence of defined clinical events, survival time of a study population

- HIV drug resistance
  - Dynamics and spread of transmitted drug resistance (TDR)
  - In vivo persistence and viral fitness
  - Occurrence, transmission and persistence of minor variants
  - Factors influencing disease progression in patients with TDR

- Dynamics and spread of HIV-subtypes in Germany

- Antiretroviral Therapy
  - Composition of first line and following regimen, treatment success, switches

- Co-infections (e.g. Hepatitis B and C)
  - Epidemiology, disease progression, treatment monitoring
The cohort: Study methods

**Type of study:** Germany-wide, multicentric cohort study since 1997

**Study population:** HIV+ patients having known or well defined timepoint of HIV-1 seroconversion („seroconverters“)

**Sites:** 110 HIV-specialised clinic ambulances and private practitioners

**Data collection:**
- Yearly collection of clinical/epidemiological data and plasma sample
- Central plasma bank and DNA at RKI study lab
- Determination of HIV-1 *pol*-sequences to identify drug resistance mutations and HIV-1 subtype
The cohort: Methods

Case definition:

**Acute HIV-Seroconverter**
- ELISA positive and Westernblot indeterminate or
- ELISA negative/borderline and HIV RNA positive
- Date of infection: date of first reactive test

**Documented HIV-Seroconverter**
- Duration between last negative and first positive HIV-1 antibody test ≤ 3 years
- Date of infection (calculated): midpoint between those two tests

- Informed consent mandatory
- Recent vote of ethical committee given (2013)
Hepatitis monitoring: Background

- HBV and HCV have partly similar transmission routes as HIV
- Assumed as frequent coinfections in HIV+ in Germany (especially MSM)
- HCV-outbreaks in MSM since 2000 in large Western cities

- Coinfections can worsen course of HIV and vice versa
- More frequent and faster progression to liver fibrosis/cirrhosis in HIV+
- Success of HCV- and HIV-therapy constrained by drug-drug-interaction and increased toxicity
- HBV vaccination recommended for HIV+ in Germany, but few data
Hepatitis monitoring: Methods

- New own Hepatitis database (HepReg) developed at the RKI and implemented in the seroconverter study
- Study population: HIV-1 seroconverters with information on HBV/HCV and co-infected seroconverter => not necessarily co-infected but any information regarding Hepatitis is recorded in the HepReg
- Information on Hepatitis recorded since 2008 in the initial questionnaires
- Since 2014 with new questionnaires extensive Hepatitis monitoring
# The cohort

*(reporting period: 01.07.1997 - 28.04.2015)*

<table>
<thead>
<tr>
<th>HIV-1 seroconverter cohort</th>
<th>HIV database HIVReg</th>
<th>Hepatitis database HepReg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population; N</td>
<td>%</td>
<td>3.022</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men; N</td>
<td>%</td>
<td>93,9%</td>
</tr>
<tr>
<td>Women; N</td>
<td>%</td>
<td>5,9%</td>
</tr>
<tr>
<td>Transsexuals; N</td>
<td>%</td>
<td>0,2%</td>
</tr>
<tr>
<td>**Age at seroconversion, Median</td>
<td>IQR**</td>
<td>33</td>
</tr>
<tr>
<td><strong>Risk of transmission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM; N</td>
<td>%</td>
<td>85,3%</td>
</tr>
<tr>
<td>Hetero; N</td>
<td>%</td>
<td>9,2%</td>
</tr>
<tr>
<td>HPC; N</td>
<td>%</td>
<td>1,1%</td>
</tr>
<tr>
<td>IDU; N</td>
<td>%</td>
<td>2,3%</td>
</tr>
<tr>
<td>Occupational exposure; N</td>
<td>%</td>
<td>0,3%</td>
</tr>
<tr>
<td>Other / unknown; N</td>
<td>%</td>
<td>1,8%</td>
</tr>
<tr>
<td>Origin Germany</td>
<td></td>
<td>86,2%</td>
</tr>
<tr>
<td>≥ 1 plasma sample at RKI</td>
<td></td>
<td>91,8%</td>
</tr>
<tr>
<td>Ever received ART; N</td>
<td>%</td>
<td>66,3%</td>
</tr>
<tr>
<td>Duration of observation: person years</td>
<td>Median</td>
<td>14255</td>
</tr>
</tbody>
</table>
The cohort

Precision of the HIV-1 seroconversion date (N=3,022)

- 36.3% Acute
- 28.4% <=1 month
- 20.1% 2-3 months
- 5.6% 4-12 months
- 8.5% 13-24 months
- 1.2% 25-36 months

72% recently infected ≤ 1 year
Hepatitis B vaccination

Age distribution at inclusion into the HepReg (N=1,848)

- Decrease in the proportion of vaccinated persons with age
- 20% not vaccinated!
- 38% (703) with indication to vaccinate or vaccination control
- Too many unvaccinated HIV-1 seroconverter
- Why?

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Not specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1028; 56%</td>
<td>371; 20%</td>
<td>332; 18%</td>
<td>117; 6%</td>
</tr>
</tbody>
</table>
Hepatitis B vaccination control

>1/3 with a titer ≤100 Units/l => no effective protection
18% titer 0-10 Units/l => no protection
64% with effective vaccine protection
Hepatitis B serology

- Decrease of vaccinated people by age
- Increase of people with cleared HBV by age
- 18% at risk for HBV-co-infection
- 9.5% unclear results, 30% missing data
Hepatitis C serology

Analysis of initial report 2008 and 2014 (N=1,301)

Anti-HCV (N=1,301)

- Negative: 89.2%
- Positive: 3.5%
- Not tested: 4.3%
- Not specified: 2.9%

HCV-RNA (N=1,301)

- Negative: 21.0%
- Positive: 2.7%
- Not tested: 71.3%
- Not specified: 5.0%
Hepatitis C genotype

HCV genotype (N=87)

- **Gt 2**: 1%
- **Gt 3**: 8%
- **Gt 4**: 16%
- **Gt 1**: 3%
- **Gt 1b**: 6%
- **Gt 1a**: 66%

- **75% genotype 1, 1a, 1b**

- Harvoni ± RBV or Viekirax + RBV
- Sovaldi + RBV or Daklinza + Sovaldi
- Sovaldi + RBV
- Harvoni ± RBV or Viekirax + Exviera ± RBV

**Harvoni Sovaldi ± RBV or Daklinza**
Hepatitis C treatment

Hepatitis C medication (N=66; time period 1995-2015)

- INF + RBV: 79%
- INF + RBV + Sofosbuvir: 9%
- INF + RBV + Telaprevir: 5%
- Simeprevir + Sofosbuvir: 3%
- Daclatasvir + Sofosbuvir: 3%
- INF + RBV + Simeprevir: 2%
Conclusions

- Despite clear recommendation for HBV vaccination and extensive vaccination campaigns, too many unvaccinated HIV-1 seroconverter
- 35% of the titer values below ≤100 units/l
- 0.6% acute/chronic HBV-co-infections and 4% HCV-co-infections, could be underestimated
- Co-infection-Screening among MSM seroconverters (Jansen et al.) => 1.9% acute/chronic HBV-co-infection & 8.2% HCV-co-infections
- Amount of new HCV medication in the cohort is low => mainly data from a time period where the standard was INF/RBV regimen
- Many missing data in the questionnaires
Conclusions

• Demand for ongoing comprehensive Hepatitis prevention in HIV+

• Need for more extensive and tailored campaigns for HBV-vaccination for HIV+ in Germany, especially for higher age groups

• Physicians specialized in HIV could be important actors for counseling about HBV prevention and vaccination

• Intensive research to improve completeness and validity of HepReg data

• More in-depth analyses of data within next months
Thanks to our sites:

Aachen
- Dres. Knechten, Habets
- Klinikum Augsburg
- Ärzteforum Seestraße
- Augusta-Viktoria Krankenhaus (Vivantes)
- Dres. Bienieck, Cordes
- Dr. Claus
- Dr. Dobao
- Dres. Dupke, Carganico
- Dres. Freiwald, Rausch
- Dr. Glaunsinger
- Dres. Götz, Moll, Schleehauf
- Dr. Hintsche
- Dres. Jessen
- Dres. Köppe
- Dr. Reuter
- Dres. Schlotte, Lauenroth-Mai, Schuler
- Dr. Schmidt
- Dr. Schüler-Maué
- Dres. Schranz, Fischer
- Universitätsmedizin Berlin Charité

Augsburg
- Klinikum Augsburg

Berlin
- Ärzteforum Seestraße
- Auguste-Viktoria Krankenhaus (Vivantes)
- Dres. Bienieck, Cordes
- Dr. Claus
- Dr. Dobao
- Dres. Dupke, Carganico
- Dres. Freiwald, Rausch
- Dr. Glaunsinger
- Dres. Götz, Moll, Schleehauf
- Dr. Hintsche
- Dres. Jessen
- Dres. Köppe
- Dr. Reuter
- Dres. Schlotte, Lauenroth-Mai, Schuler
- Dr. Schmidt
- Dr. Schüler-Maué
- Dres. Schranz, Fischer
- Universitätsmedizin Berlin Charité

Hamburg
- ifi Allg.Krankenhaus St. Georg
- ICH, Infektionsmedizinisches Centrum Hamburg
- Dr. Gellermann
- Universitätsklinik Eppendorf

Hannover
- Med. Hochschule Hannover
- Dr. Buch, Leugner

Karlsruhe
- Landratsamt Karlsruhe

Koblenz
- Krankenhaus Kemperhof

Köln
- Dr. Bihari
- Dr. Ferdinand
- Dr. Scholten
- Universitätsklinik Köln
- Universitätsklinik Leipzig

Magdeburg
- Universitätsklinik Otto-v.-Guericke Universität Klinikum

Mainz
- Joh.-Gutenberg-Universität

München
- Ludwig-Maximilians-Universität München
- Dr. Malm
- Dres. Jäger, Jägel-Guedes
- Dr. Rieger
- Technische Universität München

Münster
- Universitätsklinik Münster
- Dr. Soldan

Norderstedt
- Klinikum Nürnberg

Nürnberg
- Städt. Klinik Natruper Holz

Osnabrück
- Universitätsklinik Regensburg

Regensburg
- Dres. Steege, Walter
- Dr. Kreft

Rostock
- Universitätsklinik Rostock

Stuttgart
- Dres. Schnaitmann, Schaffert, Trein, Ißler
- Dres. Ulmer, Frietsch, Müller
- Justizvollzugsanstalt Stuttgart

Ulm
- Universitätsklinik Ulm

Viernheim
- Dr. van Treek

Wiesbaden
- Dr. Starke
Thank you

Seroconverter-Team RKI-unit 18:
Claudia Kücherer, Karolin Meixenberger, Sybille Somogyi, Norbert Bannert, Sabrina Neumann, Hanno von Spreckelsen, Katrin Arndt

Seroconverter-Team RKI-unit 34:
Barbara Bartmeyer, Klaus Jansen, Parvin Ghassim, Sila Aygündüz, Viviane Bremer, our students

The colleagues of the network project
„Monitoring of resistant HIV in Germany“

Thank you for your attention!!!