Does Hepatitis C virus (HCV) genotype or viral load predict the risk of all-cause mortality of HIV/HCV coinfection?

Background

• Previous analyses from EuroSIDA showed:
  ▪ No increased risk for clinical progression (AIDS or death) associated with HCV status (determined by HCV antibodies alone)
  ▪ Increased risk for liver-related death in HIV/HCV-coinfected individuals
  ▪ HCV-coinfection did not influence virological and immunological response to HAART

Rockstroh J et al., J Infect Dis 2005
Objectives

• To investigate the relationship between HCV-genotype and/or HCV-RNA level and the risk for developing liver disease related death, or all cause mortality within the EuroSIDA cohort.
EuroSIDA - information collected

- **Core information:**
  - Demographics
  - All CD4 cell counts/plasma viral loads
  - Treatments (HIV and OI’s)
  - AIDS-related clinical events
  - Death and cause of death

- **Other:**
  - Potential toxicity
  - Admission to hospital
  - Hepatitis, pregnancy, etc
  - Plasma bank

EuroSIDA
Methods

• Serum HCV-RNA testing was performed by a reliable quantitative assay for distinct genotypes (Versant)
• HCV genotyping (LiPA) was carried out in all viremic subjects
• All patients with known HCV-genotype were included (n=1677)
• An additional 586 patients were included who had a HCV-RNA < 615 IU/ml but were HCV-antibody positive (HCV cleared = HCV-c)
• Data on genotype was available from 2 sources: the sample repository testing and EuroSIDA follow-up forms; where data was available from both sources, the results from the sample repository were used.
Statistical Analyses

- Kaplan-Meier and Poisson regression analyses were used to determine progression to death from any cause or from liver related disease and compared between genotypes and patients with positive HCV-antibodies but undetectable HCV-RNA (HCV-c).

- Models were adjusted for demographic variables (gender, exposure group, region of Europe), data source (sample repository or EuroSIDA follow-up forms), source of HCV+ test, prior AIDS diagnosis, treatment regimen started at or before baseline, age, CD4, CD4-nadir, date of HCV genotype test or HCV-RNA measurement and date enrolled in EuroSIDA.
Results

- 340 patients (15%) died during follow-up (Total PYFU 9048)
- 91 died from liver disease
- After adjustment no other HCV genotype nor HCV infected patients who cleared HCV infection had a significantly different incidence of death compared to HCV genotype 1 infection ($p > 0.01$).
- Risk of liver related deaths did not differ depending on HCV-c status nor HCV genotype and HCV-RNA level, although the power of detecting differences using this outcome was lower.
Kaplan-Meier progression to death (any cause)  
(univariate analysis)

P=0.057, log-rank test

months since HCV genotype test

% deaths

N under follow-up

GT 1  GT 2  GT 3  GT 4  HCV-c

EuroSIDA
Kaplan-Meier progression to death (LRD) (univariate analysis)

N under follow-up
1 890 738 621 515 411 301 246 192
2 51 48 42 36 32 28 26 19
3 500 406 340 277 225 164 131 101
4 236 194 170 124 102 64 51 41
HCV-c 586 451 374 288 236 172 146 117

Months since HCV genotype test

% deaths
P=0.89, log-rank test
Event rates and incidence rate ratios (IRR per 100 PYFU)

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>HCV-c</th>
</tr>
</thead>
<tbody>
<tr>
<td>PYFU</td>
<td>3684.2</td>
<td>287.9</td>
<td>2008.0</td>
<td>885.3</td>
<td>2182.7</td>
</tr>
<tr>
<td>Deaths (any cause)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>142</td>
<td>13</td>
<td>67</td>
<td>22</td>
<td>96</td>
</tr>
<tr>
<td>% progressed at 5 years (95% CI)</td>
<td>17.4 (14.2 – 20.5)</td>
<td>23.6 (10.6 – 36.7)</td>
<td>13.7 (9.8 – 17.6)</td>
<td>10.3 (5.4 – 15.2)</td>
<td>19.6 (15.5 – 23.7)</td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>3.85 (3.22 – 4.49)</td>
<td>4.52 (2.40 – 7.70)</td>
<td>3.34 (2.54 – 4.14)</td>
<td>2.49 (1.45 – 3.52)</td>
<td>4.40 (3.52 – 5.28)</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>1.00</td>
<td>1.23 (0.70 – 2.18)</td>
<td>0.86 (0.64 – 1.15)</td>
<td>0.63 (0.40 – 0.99)</td>
<td>1.19 (0.92 – 1.54)</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>0.47</td>
<td>0.31</td>
<td>0.045</td>
<td>0.19</td>
</tr>
<tr>
<td>Adjusted IRR* (95% CI)</td>
<td>1.00 (0.55 – 2.34)</td>
<td>1.13 (0.77 – 1.53)</td>
<td>1.09 (0.61 – 1.78)</td>
<td>1.04 (0.56 – 1.14)</td>
<td>0.80 (0.56 – 1.14)</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>0.73</td>
<td>0.63</td>
<td>0.89</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Analysis adjusted for data source, gender, exposure group, region of Europe, coinfection with HBV, race, prior AIDS, age, CD4 at GT, data recruited to ES, treatment regimen and date of HCV GT testing.
Kaplan-Meier progression and HCV-RNA
(univariate analysis; patients with undetectable HCV-RNA are included)

P=0.055, log-rank test

Months since HCV RNA test

% deaths

N under follow-up

<500k 1365 1090 933 741 619 458 375 300

>500k 705 610 532 445 374 270 234 181

EuroSIDA
Kaplan-Meier progression and HCV-RNA  
(univariate analysis; only including viremic patients)

P=0.0022, log-rank test

HCV-RNA  
<=500,000  >500,000

% deaths

Months since HCV RNA test

N under follow-up
<500k 667 565 482 391 327 237 193 151
>500k 705 610 532 445 374 270 234 181

EuroSIDA
Results : HCV Viremia

• Results:

  • Per log10 increase in HCV-RNA the risk of all cause mortality increased by 23% (IRR=1.23 (1.05-1.45), p=0.01), but after adjustment for confounders, this was no longer significant (IRR=1.06 (0.90-1.25), p=0.46).
Conclusion

- Within the EuroSIDA cohort no association between HCV-RNA levels nor HCV genotype and risk of all cause mortality was detected.

- Risk of liver related deaths did not differ depending on HCV-c status nor HCV genotype and HCV-RNA level, although the power of detecting differences using this outcome was lower.
The EuroSIDA Study Group

Argentina: (M Losso), A Duran, Hospital JM Ramos Mejia, Buenos Aires. Austria: (N Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna. Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; O Suettov, Regional AIDS Centre, Svetlogorsk. Belgium: (N Clumeck) S De Wit, B Pol, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp Bulgaria: K Kostov, Infectious Diseases Hospital, Sofia, Croatia; J Begovac, University Hospital of Infectious Diseases, Zagreb. Czech Republic: (L Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. Denmark: (J Nielsen) J Lundgren, T Benfield, O Kirke, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A B E Hansen, P Skinhoj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense, L Oestergaard, Skejby Hospital, Aarhus. Estonia: (K Zilmer) West-Tallinn Central Hospital, Tallinn, Jelena Smidt, Nakkusosakond Siseiklinik, Kohtla-Järve. Finland: (M Ristola), Helsinki University Central Hospital, Helsinki. France: (C Katlama) Hôpital de la Pitié-Salpêtrière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, Université Claude Bernard, Lyon; C Pradier, Hôpital de l'Arche', Nice; F Dabis, Unité INSERM, Bordeaux. Germany: (J Rockstroh) Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; S Staszweski, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fäkteneheuer, Universität Köln, Cologne. Greece: (I Kosmidis) P Gargalianos, G Xylomenos, J M Perdios, Athens General Hospital; G Panos, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Villo, M Lichtner, University of Rome la Sapienza, Rome; A Chiari, E Montesarchio, G Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, F Tacconi, P Nardulli, C Vlassi, M Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; G Galli, A Righi, A Spada, S Rossetti, Milan; A D'Arminio Montforte, A D'Arminio Montforte, Università degli Studi di Milano, Milan. Latvia: (I Chibisova) D Balodzis, I Laboratory of the Aids Centre, Jelgava. Lithuania: (S Chaplinskas) Lithuanian AIDS Centre, Vilnius. Luxembourg: (F Kieffer) CHU de Luxembourg, Luxembourg. Netherlands: (P Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam; A Boron, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, A Wiercinska-Drapalo, Medical University, Bialystok; A Boron-Kaczmarska, M Pyka, Medical University, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Gdansk. Portugal: (F Antunes) E Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; P Melo, Hospital Curry Cabral, Lisbon. Romania: (D Duiculescu) Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucharest. Russia: (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; E Vinogradova, St Petersburg AIDS Centre, St Petersburg; S Buzunova, Novgorod Centre for AIDS, Novgorod. Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovakia: (M Mokras) D Stanekova, Dérer Hospital, Bratislava. Spain: (J González-Lahoz) V Soriano, L Martin-Carbonero, P Labarga, Hospital Carlos III, Madrid; B Clotet, A Jou, J Conejero, C Tural, Hospital Sant Pau, Barcelona. Sweden: (A Karlsson), Karolinska University Hospital, Stockholm; PO Persson, Karolinska University Hospital, Huddinge; L Flammol, Malmö University Hospital, Malmö. Switzerland: (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Corthier, Hospital Cantonal Universitaire de Genève, Geneva; H Furrer, Inselspital Bern, Bern; M Battegay, J Elzi, University Hospital Basel. Ukraine: (E Kravchenko) N Chentsova, Kiev Centre for AIDS, Kiev. United Kingdom: (S Barton) St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College Medical School London, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; R Bignardi, Western General Hospital, Edinburgh. Virology group: B Clotet (Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study. Steering Committee: F Antunes, B Clotet, D Duiculescu, J Gatell, B Gazzard, A Horban, A Karlsson, C Katlama, B Ledergerber (Chair), A D'Arminio Montforte, A Phillips, A Rakhmanova, P Reich (Vice-Chair), J Rockstroh Coordinating Centre Staff: J Lundgren (project leader), O Kirke, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, C Holmken Olsen, J Kjaer, L Peters, J Reekie