Fatal and non-fatal AIDS and non-AIDS events in HIV-1 infected patients with high CD4 counts according to viral load strata

J Reekie, J Gatell, I Yust, E Bakowska, A Rachmanova, M Losso, M Krasnov, P Francioli, J Kowalska, A Mocroft
for the EuroSIDA study group
Background

• Some non-AIDS defining illnesses associated with low CD4 count

• The development of both AIDS and non-AIDS defining illnesses in patients who are not immune compromised has not been fully investigated

• Uncontrolled HIV replication may be an independent risk factor associated with the occurrence of non-AIDS events
Aim

• In people with current CD4 count >350cells/mm³, to compare between viral load strata the incidence of fatal and non-fatal AIDS and non-AIDS events
EuroSIDA is a large prospective cohort with 16,597 patients from 33 European countries, Israel and Argentina.

AIDS defining events

Non-AIDS defining events

- Cardiovascular events
- Chronic Liver disease
- Pancreatitis
- End stage renal disease
- Non-AIDS defining malignancies (NADM)
Methods

A patient contributed person years at risk if their most recent CD4 count was $>350$ cells/mm$^3$ in addition to a viral load measured in previous 6 months.

Patients were eligible to contribute person years at risk from:

- 1/1/1997 for AIDS events
- 1/1/2001 for non-AIDS events

Person years were split into three different viral load strata:

- $<500$ copies/ml
- 500-10000 copies/ml
- $\geq10000$ copies/ml
Methods

• All fatal and non-fatal AIDS and non-AIDS events, occurring during the follow-up time were recorded
• Recurrences of the same diagnosis were excluded
• Incidence rates calculated per 100 PYFU
• Poisson regression analysis was used to investigate the relationship between viral load and clinical events after adjustment for confounding variables
• Possible confounding variables:
  gender, ethnic origin, age, HIV exposure group, region of Europe, hepatitis B & C status, smoking status, hypertension, year of follow-up, on cART, prior AIDS, CD4 count
## Follow-up characteristics

<table>
<thead>
<tr>
<th>Fatal and non-fatal AIDS events (Total 43,524 PYFU)</th>
<th>Viral load categories (% of follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;500</td>
</tr>
<tr>
<td>Total PYFU (% of total)</td>
<td>34676 (80%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>77%</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>86%</td>
</tr>
<tr>
<td>HIV exposure group</td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>48%</td>
</tr>
<tr>
<td>IDU</td>
<td>17%</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>28%</td>
</tr>
<tr>
<td>On cART*</td>
<td></td>
</tr>
<tr>
<td>91%</td>
<td>62%</td>
</tr>
<tr>
<td>CD4 count</td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>34%</td>
</tr>
<tr>
<td>500-750</td>
<td>41%</td>
</tr>
<tr>
<td>&gt;750</td>
<td>25%</td>
</tr>
</tbody>
</table>

*on cART defined as currently taking ≥3 antiretrovirals

EuroSIDA
AIDS results

43,524 PYFU

379 AIDS events occurred

- 54 Pulmonary Tuberculosis
- 49 Oesophageal Candidiasis
- 46 Cervical Carcinoma
- 38 Non-Hodgkin's lymphoma
- 31 Herpes Simplex
- 27 Extra pulmonary Tuberculosis
- 26 Kaposi’s Sarcoma
- 21 Pneumonia
- 14 Deaths
Non-AIDS results

35,252 person years of follow-up
- 83% <500 copies/ml
- 10% 500-10000 copies/ml
- 7% ≥10000 copies/ml

476 non-AIDS events
- 176 Cardiovascular events
- 163 Non-AIDS defining malignancies
- 32 Liver related events
- 28 Pancreatitis
- 15 End stage renal disease
- 62 Deaths
**Crude incidence rate per 100 PYFU**

- **AIDS events**
  - <500: 0.2 (0.1-0.3)
  - 500-10000: 1.5 (1.3-1.7)
  - ≥10000: 2.5 (2.3-2.7)

- **Non-AIDS events**
  - <500: 1.0 (0.8-1.2)
  - 500-10000: 1.5 (1.3-1.7)
  - ≥10000: 2.0 (1.8-2.2)

**Viral load (copies/ml)**

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>AIDS Events</th>
<th>Non-AIDS Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500</td>
<td>239</td>
<td>56</td>
</tr>
<tr>
<td>500-10000</td>
<td>56</td>
<td>84</td>
</tr>
<tr>
<td>≥10000</td>
<td>84</td>
<td>411</td>
</tr>
<tr>
<td>&lt;500</td>
<td>411</td>
<td>52</td>
</tr>
<tr>
<td>500-10000</td>
<td>52</td>
<td>35</td>
</tr>
<tr>
<td>≥10000</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

**EuroSIDA**
Univariate and multivariate incidence rate ratios

IRR (95% CI)

Univariate and Multivariate

Viral load categories (copies/ml)

AIDS events

<500 500-10000 ≥10000

non-AIDS events

<500 500-10000 ≥10000

EuroSIDA
Univariate and multivariate incidence rate ratios for specific non-AIDS events

N Events | 150 | 19 | 7 | 138 | 15 | 10 | 22 | 4 | 6
---|---|---|---|---|---|---|---|---|---

Viral load categories (copies/ml)

Cardiovascular events

Non-AIDS Malignancies

Liver events

EuroSIDA
Conclusion

In patients with a CD4 count > 350 cells/mm³

- An increased incidence of AIDS events was found in patients with uncontrolled viral replication

- A slightly increased incidence of non-AIDS events was found with high viral replication

  - No difference observed between moderate and high viral replication
  - Despite adjustment, there could remain confounding in the association between viral load and outcome
  - Non-AIDS events are a very heterogeneous group
  - Limited number of other specific non-AIDS events to form clear conclusions
The EuroSIDA Study Group

The multi-centre study group of EuroSIDA (national coordinators in parentheses).

Argentina: (M Losso), C Elias, Hospital JM Ramos Mejia, Buenos Aires. Austria: (N Vetter), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck. Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk. VM Mitsura, Gomel State Medical University, Gomel; O Suetnol, Regional AIDS Centre, Svetlogorsk. Belgium: (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Brussel, Brussels; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Arche, Nice; F Dabis, D Neau, Université INSERM, Bordeaux. Bulgaria: (K Kostov), Infectious Diseases Hospital, Sofia. Croatia: (J Beograd), University Hospital of Infectious Diseases Zagreb, Central Croatia: (B Strinibar), Hrvatska Klinicka Biblioteka, Zagreb. Denmark: (J Nielsen), G Kronborg, T Benfield, M Larsen, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, O D Larsen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus. Estonia: (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, 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; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Arche, Nice; F Dabis, D Neau, Université INSERM, Bordeaux. Germany: (J Rockstroh), Universitätsspitzen Bonn, R Schmidt, Medizinische Hochschule Hannover, J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stelbrink, IPM Study Center, Hamburg; S Staszewski, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. Greece: (J Kosmidis), P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital, Athens. Ireland: (F Mulcahy), St. James's Hospital, Dublin. Israel: (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa; S Maayan, Hadassah University Hospital, Jerusalem. Italy: (A Chiesi), Istituto Superiore di Sanità, Rome; R Esposito, I Mazzu, Mussini, Università Modena, Modena; C Arci, Ospedale Riuniti, Bergamo; A Mocroft, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, F Iacomi, G Narciso, M Zacarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L Sacco, Milan; A d'Arminio Montforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan. Latvia: (B Rozentals), I Zeltina, Infectology Centre of Latvia, Riga. Lithuania: (S Chaplinskas), Lithuanian AIDS Centre, Vilnius. Luxembourg: (R Hemmer), T Staub, Centre Hospitalier, Luxembourg. Netherlands: (P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. Norway: (V Ormaasen), A Maeland, J Bruun, Ullevål University Hospital, Oslo. Poland: (B Knysz) J Gasiorski, Medical Academy Botkin Hospital, St Petersburg; E Vinogradova, St Petersburg AIDS Centre, St Petersburg; S Buzunova, Novgorod Centre for AIDS, Novgorod. Serbia: (J Djevovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovakia: (M Mokraš), D Staneková, Deér Hospital, Bratislava. Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. Spain: (J González-López), V Soriano, P Labarga, J Medrano, Hospital Carlos III, Madrid; S Moreno, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona. Sweden: (A Karisson), Vänersborg-Sodersjukhuset, Stockholm; L Flammol, Malmö University Hospital, Malmö. Switzerland: (F Ledergerber), R Weber, University Hospital, Zürich; P Francioni, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Genève, Genève; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel. Ukraine: (E Kravchenko), N Chentsov, Kiev. Centre for AIDS, Kiev; G Kutsyna, Luhansk State Medical University, Luhansk; S Servitskiy, Odesa Region AIDS Centre, Odesa; M Krasnov, Kharkov State Medical University, Kharkov. United Kingdom: (S Barton), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; A Phillips, A Rakhmanova, P Reiss (Vice-Chair), J Rockstroh

Steering Committee: P Reiss (Chair), B Clotet, D Duiculescu, J Gatell, B Gazzard, A Horban, K Hostetter, J Kjær, L Peters, J Reekie, J Kowalska.