Predictors of Hepatitis C RNA Levels in HIV Co-infected Individuals in a Prospective Cohort Study

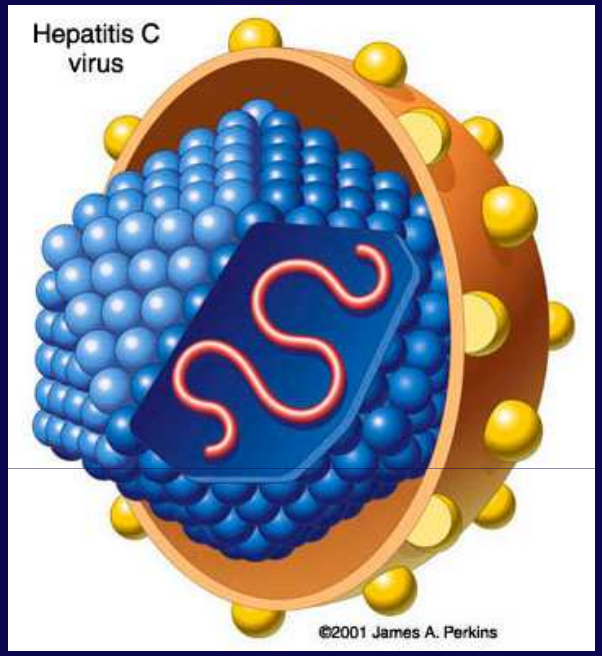
D. Grint, J. Reekie, V. Soriano, O. Kirk, B. Knysz, O. Suetnov, A. Lazzarin, B. Ledergerber, J. K. Rockstroh, A. Mocroft and L. Peters for EuroSIDA in EuroCoord

EACS 2011, Belgrade Serbia
14th October

Background

- Infection with hepatitis C virus (HCV) is a major cause of chronic liver disease[1]

- High levels of HCV-RNA have been associated with a poor response to treatment for HCV[2]



www.hepcni.net/

- HCV-RNA reported to stay relatively stable in mono-infected individuals, while the course of HCV-RNA is less well characterised in HIV/HCV co-infected individuals[3]

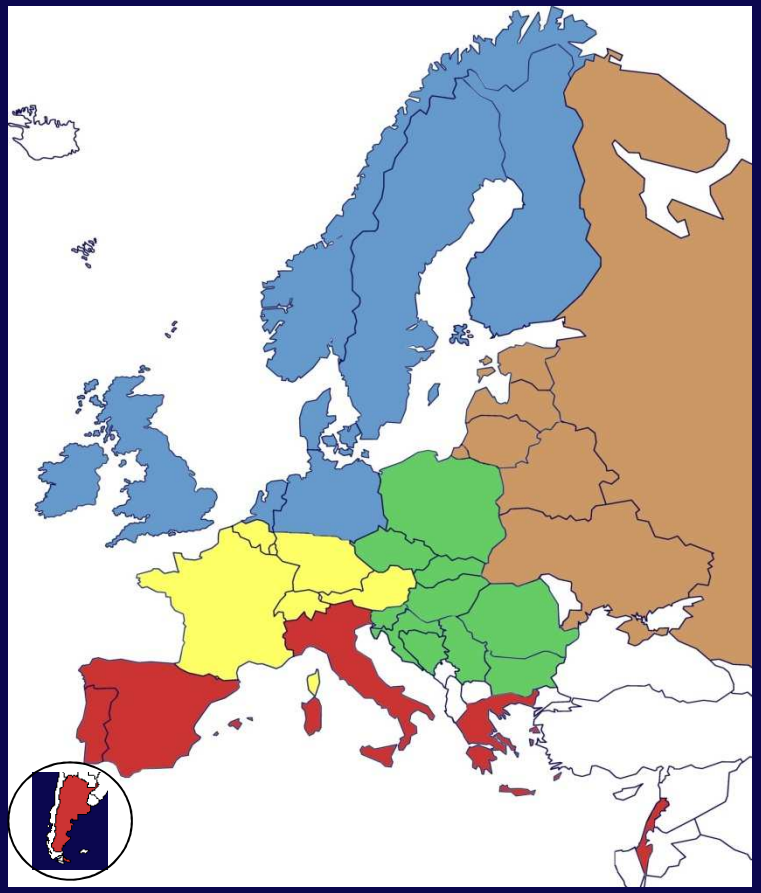
[1]Rockstroh JK, JID 2005
[2]Torriani FJ, N Engl J Med 2004
[3]Fishbein DA, JAIDS 2006

Aims

- Examine the change over time in HCV-RNA levels in chronic HCV/HIV co-infected individuals
- Estimate the effect of genotype on the natural history of HCV-RNA levels
- Determine whether any other factors affect the natural history of HCV-RNA levels

EuroSIDA

EuroSIDA is a large prospective cohort with 16597 patients from 33 European countries, Israel and Argentina

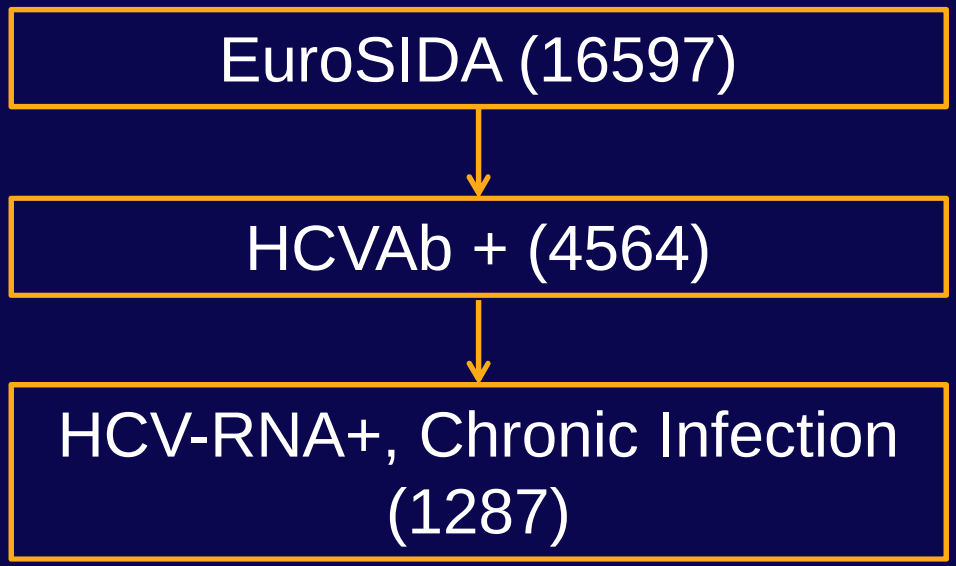


EuroSIDA

- HCV antibody
- HCV-RNA and genotype
- Hepatitis B (HBV) surface antigen
- HBV-DNA and genotype
- Demographics
- CD4 counts, HIV viral loads

Inclusion Criteria

- Inclusion Criteria
  - Chronic HCV with quantitative HCV-RNA measured
  - HCV-RNA measurements taken after initiation of HCV treatment were not included



Methods

- Statistical Methods
  - Baseline defined as the date of each individual's first HCV-RNA measurement
  - Multivariable mixed models were used to model HCV-RNA levels adjusting for:
    - Age/Gender/Race
    - Region of Europe
    - HIV-RNA/CD4 cell count*
    - HCV genotype + assay
    - Hepatitis B status*
    - HIV risk group
    - cART initiation status*
    - Date of HCV infection

*Time updated

Baseline Characteristics

		No. Participants (%)
Total		1287 (100)
HCV Genotype	1	676 (52.5)
	2	37 (2.9)
	3	391 (30.4)
	4	183 (14.2)
Baseline HBsAg Status	Positive	71 (5.5)
	Negative	1031 (80.1)
	Unknown	185 (14.4)
HIV Exposure Group	IDU	952 (74.0)
	MSM	105 (8.2)
	Heterosexual	148 (11.5)
	Other	82 (6.3)
Baseline HCV-RNA (log10)	Median (IQR)	5.87 (5.36 – 6.31) IU/ml

HCV-RNA Measurements

- Median number of HCV-RNA measurements per individual = 2 (IQR: 1 – 3, Range: 1 - 10)
- Median total follow-up time = 4.1 years (IQR: 2.0 – 7.3)
- Median time between HCV-RNA measurements = 2 years (IQR: 0.9 – 4.1)

Results: Change in Time

Multivariate Model*

Variable	Estimate (log10)	95% CI	p-value
Time from baseline (years) [SLOPE]	0.024	(0.0042, 0.043)	0.017

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.

Results: Change in Time

Multivariate Model*

Variable	Estimate (log10)	95% CI	p-value
Time from baseline (years) [SLOPE]	0.024	(0.0042, 0.043)	0.017

- HCV-RNA increased 5.7% (95% CI: 1.0% - 10.4%) per year
- Rate of increase in HCV-RNA constant across all other subgroups
- Although limited power to detect differences in the rate of change in HCV-RNA

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.

Results: Genotype

Multivariate Model*

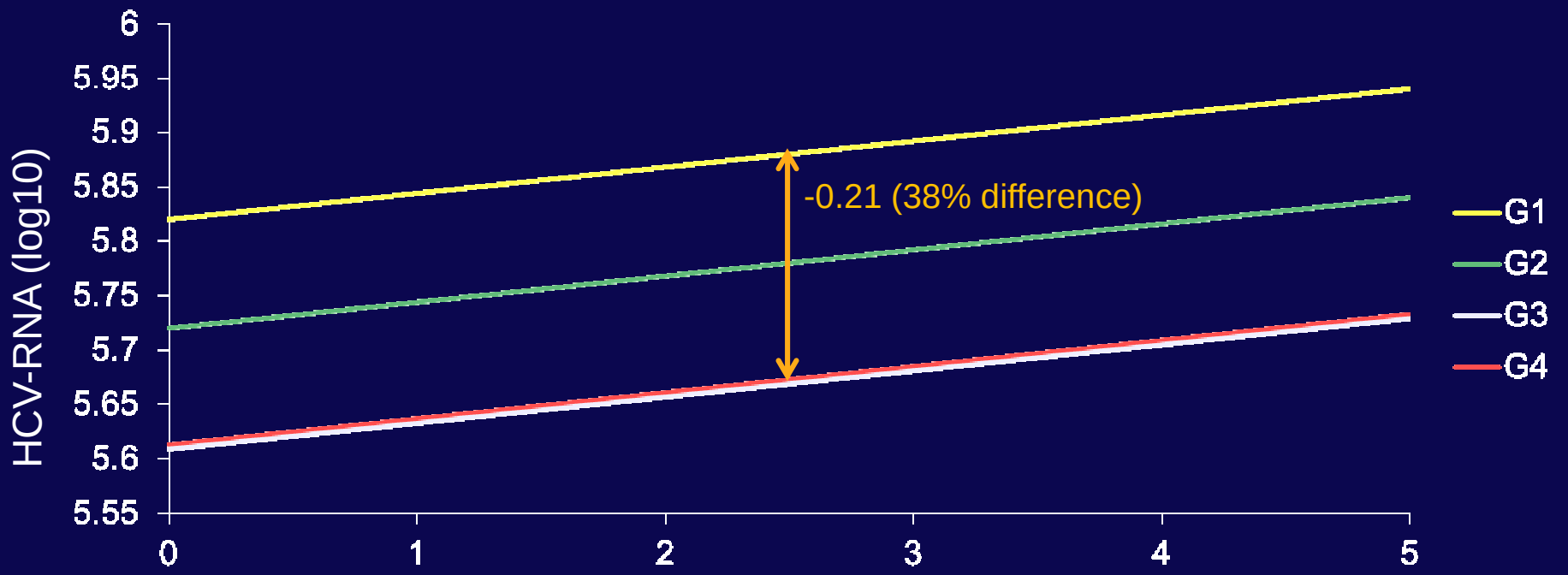
Variable	Estimate (log10)	95% CI	p-value
Time from baseline (years) [SLOPE]	0.024	(0.0042, 0.043)	0.017
HCV Genotype			
1	0		
2	-0.10	(-0.35, 0.15)	0.42
3	-0.21	(-0.31, -0.12)	<0.0001
4	-0.21	(-0.34, -0.084)	0.0012

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.

Results: Genotype

Multivariate Model*

Variable	Estimate (log10)	95% CI	p-value
Time from baseline (years) [SLOPE]	0.024	(0.0042, 0.043)	0.017
HCV Genotype			
1	0		
2	-0.10	(-0.35, 0.15)	0.42
3	-0.21	(-0.31, -0.12)	<0.0001
4	-0.21	(-0.34, -0.084)	0.0012



EuroSIDA

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.

Results: HIV Risk Group

Multivariate Model*

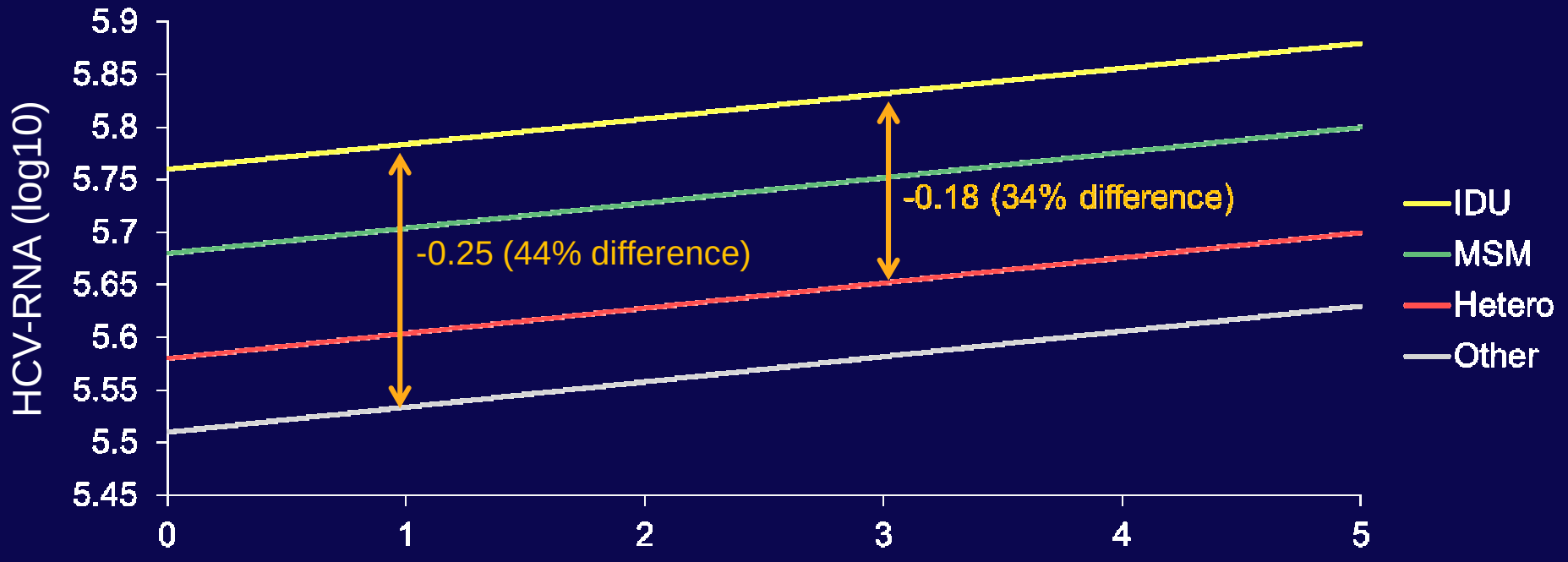
Variable	Estimate (log10)	95% CI	p-value
Time from baseline (years) [SLOPE]	0.024	(0.0042, 0.043)	0.017
HIV Risk Group			
Injection Drug User	0		
MSM	-0.084	(-0.25, 0.077)	0.31
Heterosexual	-0.18	(-0.31, -0.039)	0.012
Other	-0.25	(-0.42, 0.081)	0.0039

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.

Results: HIV Risk Group

Multivariate Model*

Variable	Estimate (log10)	95% CI	p-value
Time from baseline (years) [SLOPE]	0.024	(0.0042, 0.043)	0.017
HIV Risk Group			
Injection Drug User	0		
MSM	-0.084	(-0.25, 0.077)	0.31
Heterosexual	-0.18	(-0.31, -0.039)	0.012
Other	-0.25	(-0.42, 0.081)	0.0039



EuroSIDA

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.

Results: Current HIV-RNA

Multivariate Model*

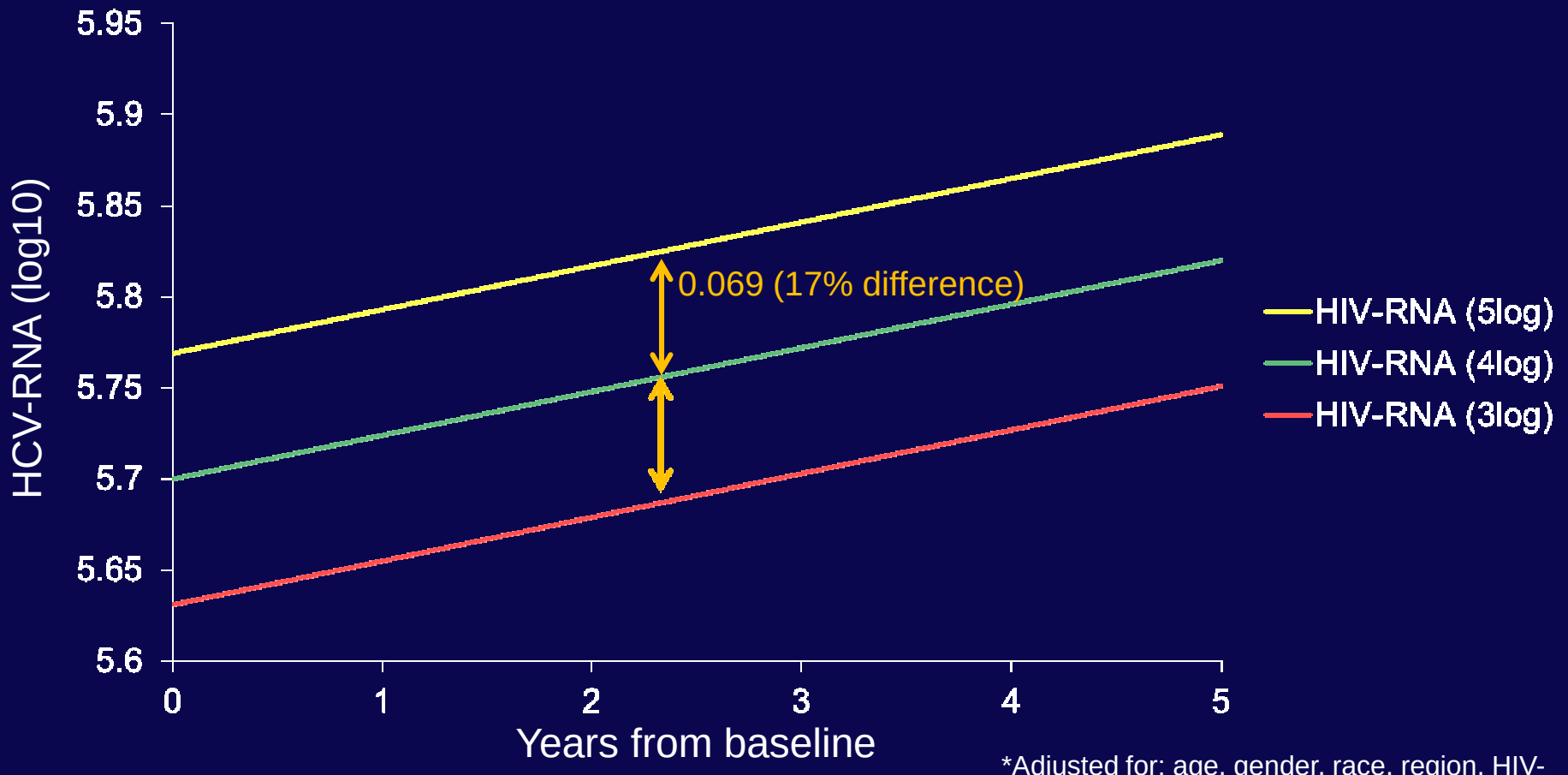
Variable	Estimate (log10)	95% CI	p-value
Time from baseline (years) [SLOPE]	0.024	(0.0042, 0.043)	0.017
HIV-RNA (per log10 increase)	0.069	(0.035, 0.10)	<0.0001

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.

Results: Current HIV-RNA

Multivariate Model*

Variable	Estimate (log10)	95% CI	p-value
Time from baseline (years) [SLOPE]	0.024	(0.0042, 0.043)	0.017
HIV-RNA (per log10 increase)	0.069	(0.035, 0.10)	<0.0001



EuroSIDA

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.

Limitations

- Median number of HCV-RNA measurements = 2 (IQR: 1 – 3)
- 250 individuals with at least 3 HCV-RNA measurements
- Sensitivity analysis in these 250 individuals:

Limitations

- Median number of HCV-RNA measurements = 2 (IQR: 1 – 3)
- 250 individuals with at least 3 HCV-RNA measurements
- Sensitivity analysis in these 250 individuals:
    - 6.6% increase in HCV-RNA per year, p=0.08
    - Effects of genotype, HIV risk group and HIV-RNA consistent with previous results

Conclusions

- HCV genotype 1 carried 38% higher baseline levels of HCV-RNA than genotypes 3 and 4
- IDUs carried 34% and 44% higher baseline levels of HCV-RNA compared to heterosexuals and those in the ‘other’ HIV risk group, respectively
- A 1 log increase in HIV-RNA associated with a 17% increase in HCV-RNA

Conclusions

- HCV-RNA levels increased at a rate of 5.7% per year with no evidence of a difference according to subgroups
- Deferral of HCV treatment increases HCV-RNA levels little in the short term, whereas controlling HIV viral load with cART may improve the likelihood of sustained viral response (SVR) indirectly by lowering HCV-RNA levels

The EuroSIDA Study Group

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

The multi-centre study group o-n EuroSIDA (national coordinators in parenthesis).
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 Suetnov, 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 Gent, Gent. **Bosnia-Herzegovina:** (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo. **Bulgaria:** (K Kostov), Infectious Diseases Hospital, Sofia. **Croatia:** (J Begovac), University Hospital of Infectious Diseases, Zagreb. **Czech Republic:** (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **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, 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-Salpétière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, D Neau, 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 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; H Sambatakou, Ippokration Genereal Hospital, Athens. **Hungary:** (D Banhegyi), Szent Lásló Hospital, Budapest. **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:** (S Vella), Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, M Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, A Testa, P Narciso, C Vlassi, M Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan; A d'Arminio Monforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan. **Latvia:** (B Rozentale), 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 Hospital, Oslo. **Poland:** (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; A Grzeszczuk, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, M Parczewski, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk; E Jablonowska, E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz. **Portugal:** (F Antunes), M Doroana, L Caldeira, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. **Romania:** (D Duiculescu), Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest. **Russia:** (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; N Zakharova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod. **Serbia:** (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. **Slovakia:** (M Mokráš), D Staneková, Dérer Hospital, Bratislava. **Slovenia:** (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. **Spain:** (J González-Lahoz), V Soriano, P Labarga, J Medrano, Hospital Carlos III, Madrid; S Moreno, J. M. Rodriguez, 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 Karlsson), Venhaelsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö. **Switzerland:** (B Ledergerber), R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel. **Ukraine:** (E Kravchenko), N Chentsova, Kiev Centre for AIDS, Kiev; V Frolov, G Kutsyna, Luhansk State Medical University; Luhansk; S Servitskiy, Odessa Region AIDS Center, Odessa; M Krasnov, Kharkov State Medical University, Kharkov. **United Kingdom:** (S Barton), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, 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; C Leen, Western General Hospital, Edinburgh.

Steering Committee: J Gatell, B Gazzard, A Horban, J Lundgren, I Karpov, B Ledergerber, M Losso, A D'Arminio Monforte, C Pedersen, , A Phillips, A Rakhmanova, M Ristola, P Reiss, J Rockstroh (Chair), S De Wit (Vice-Chair)

Coordinating Centre Staff: O Kirk, A Mocroft, A Cozzi-Lepri, D Grint, M Ellefson, D Podlekareva, J Kjær, L Peters, J Reekie, J Kowalska, J Nielsen, J Tverland, A H Fischer

EuroSIDA representatives to EuroCoord: O. Kirk, A. Mocroft, J. Grarup, S. deWitt, P. Reiss, A. Cozzi-Lepri, R. Thiebaut, J. Rockstroh, D. Burger, R. Paredes, J. Kjær

Statement of Funding:
Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773), the 6th Framework (LSHP-CT-2006-018632), and the 7th Framework (FP7/2007-2013, EuroCoord n° 260694) programmes. Current support also includ es unrestricted grants by Gilead, Pfizer, and Merck and Co. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787).

EuroSIDA