Predictors of Having a Resistance Test Following Viral Load (VL) Failure of cART: Data from EuroSIDA

ZV Fox[1,2], AN Phillips[2], A Cozzi-Lepri[2,3], A d'Arminio Monforte[4], A Karlsson[5], A Mocroft[2], G Kronborg[6], J Kjaer[1], B Clotet[7] and JD Lundgren[1] for EuroSIDA

[1]Copenhagen HIV Programme, Copenhagen, Denmark; [2]University College London Medical School, London, UK; [3]Division of Biostatistics, University of Minnesota, Minneapolis, USA; [4]Istituto di Malattie Infettive e Tropicali, Università di Milano, Milano, Italy; [5]Venhälsan, Södersjukhuset, Stockholm, Sweden; [6]Department of Infectious Diseases, Hvidovre Hospital, Copenhagen, Denmark; [7]University Hospital Germans Trias i Pujol, Badalona, Spain

z.fox@pcps.ucl.ac.uk

BACKGROUND:

- The emergence of resistance to an antiretroviral drug (ARV) in a combination antiretroviral therapy (cART) regimen can compromise the effectiveness of treatment
- Resistance testing guidelines recommend that, following viral load failure the result of a resistance test in combination with a patient's treatment history should be used to determine active drugs and make rapid changes to the regimen
- However, not all patients have a resistance test or undergo treatment changes following viral load failure
- Genotypic resistance testing became more common after 1996 and as a result there were increases in the detection of drug resistance mutations up to 2000
- However, recent studies have shown a decline in the rate of drug resistance mutations to all classes of drugs in ARV-experienced patients since 2000
- This decline could be attributed to improvements in access to genotyping (i.e. more patients get tested in order to provide reassurance, even when poor adherence is suspected) and the prompt detection and management of viral load failure

OBJECTIVES:

We use data from the EuroSIDA cohort study to:-

- Characterise the population of patients who undergo genotypic resistance testing
- Compare the characteristics of patients with a test to those without a test
- Describe the genotypic resistance profiles and prevalence of resistance mutations in patients with a test

METHODS:

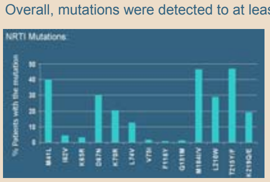
- EuroSIDA is an ongoing, observational cohort study that includes 16599 HIV infected patients from 33 European countries, Israel and Argentina
- Patients who started cART with ≥3 drugs from ≥2 different classes after 2002 were considered for inclusion in this analysis
- A patient was defined as having an indication for a resistance test (i.e. VL-failure) if they had a confirmed viral load (VL) >1000 copies/ml after at least 4 months continuous use of any one drug that was started as part of a ≥3 drug regimen
- The time of the first VL >1000 copies/ml was considered to be baseline (i.e. the time of VL-failure)
- In these patients, the date of the next resistance test was identified (if available) and factors predicting the availability of a resistance test in the year following VL-failure were explored using Cox proportional hazards analysis
- Resistance tests in the 4 months preceding VL-failure were categorised as pre-failure tests, taken at time zero
- Adherence levels for a subgroup of patients were estimated by the treating clinician and reported in the following categories: 1: >95%, 2: 70-95% or 3: <70%. All measures of adherence following VL-failure were averaged over time and if a patient had an average score >1.5 they were considered to have poor adherence. Adherence was only collected on a subgroup of patients.
- We focussed on prospectively collected resistance tests in order to study resistance testing in clinical practice

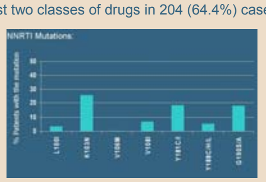
RESULTS:

- From the 16599 patients, 7356 (44.6%) started a new cART regimen after January 2002
- A total of 1128 (59.0%) patients experienced VL-failure after 2002 (i.e. a confirmed viral load (VL) >1000 copies/ml)
- From these 1128 patients, 564 (50.0%) patients reached a VL<500 copies/ml on the regimen prior to failure and in 335 (29.7%) cases this low VL recording was confirmed as low at the subsequent visit
- At VL-failure, patients had been on the same regimen for a median (IQR) of 8.1 (5.6 to 16.0) months and were followed for a median (IQR) 3.0 (1.6 to 4.5) yrs after VL-failure (ignoring regimen switches). The last follow-up visit occurred in July 2009.
- There were 69 (6.1%) patients with a pre-failure test and 528 (46.8%) patients with a test after VL-failure: overall, 547 (48.5%) patients had a resistance test (Table 1), but only 400 (35.4%) had a resistance test in the year following VL-failure
- Using Kaplan-Meier estimates (Figure 1), the probability of having a resistance test was 22.8% by 4 months, 31.5% by 8 months, and 37.0% at a year post VL-failure. Among those with a resistance test in the year following VL-failure, the median (IQR) time from VL-failure to the resistance test was 3.1 months (0.9 to 6.8 months)
- In unadjusted analysis, fixed-time predictors of having a resistance test include race (Relative hazard (RH): 2.21; 95% CI: 1.27 to 3.85 for Asian versus Whites), region of Europe (RH: 0.46; 95% CI: 0.25 to 0.85 for Eastern- versus Southern-Europe), prior use of cART (RH: 1.56; 95% CI: 1.19 to 2.04 for patients who are ARV-experienced), and age (RH: 1.09; 95% CI: 0.99 to 1.21 for each 10 years older) (Table 2).
- In unadjusted analysis for time dependent predictors, significant predictors were calendar year (RH: 1.64; 95% CI: 1.01 to 2.65 for 2004 versus 2002), number of regimens failed (RH: 1.07; 95% CI: 1.04 to 1.11 per additional regimen failed) and time spent with VL>1000 copies/ml (RH: 0.76; 95% CI: 0.74 to 0.78 for each 6 months longer) (Table 2).
- In multivariable analysis (excluding adherence due to the small number of patients with information), predictors of having a resistance test include race, region of Europe, VL at failure, calendar year, the number of regimens failed and the cumulative time spent with a VL>1000 copies/ml after VL-failure (Table 2).

Resistance patterns among patients who underwent resistance testing

- A total of 317 (79.3%) patients had information on mutations that were detected at the time of the resistance test. For the other 83 patients either sequencing was not possible or the resistance tests were done locally, but results were not submitted to CHIP
- There were a total of 229 (72.2%) resistance tests which showed NRTI mutations, 170 (53.6%) resistance tests which showed NNRTI mutations and 155 (48.9%) resistance tests which showed PI mutations
- Overall, mutations were detected to at least two classes of drugs in 204 (64.4%) cases.





SUMMARY AND CONCLUSIONS:

- In patients who had VL-failure after 4 months of continuous use of any one drug, resistance tests were reported for 37.0% up to 1 year after VL-failure (and could therefore be related to future episodes of VL-failure)
- Despite the recommendation of resistance testing as part of the management of VF, this has not yet become part of routine standard of care across the European continent
- The probability of having a resistance test was lowest after 2007, which could be attributed to a delay in reporting or to the availability of improved treatment strategies
- Certain populations are less likely to undergo resistance testing including patients in Eastern Europe, those who have failed fewer regimens previously and those with higher VLs at the time of failure (maybe because those with a higher VL are judged to be less adherent to ARVs). Those who spend longer with a VL >1000 cps/ml are less likely to undergo resistance testing, possibly another reflection of adherence or because they have fewer drug options available
- Asian patients are more likely to have a resistance test, this may be related to the health seeking behaviour of Asian patients who live in Europe
- The most common NRTI mutations detected were M184I/V (46.7%) and T215Y/F (47.0%), the K103N NNRTI mutation was detected in 25.6% cases and the M46I/L (31.6%) and V82A/F/L/T/S (31.6%) were the most frequently detected PI mutations

Table 1: Characteristics of patients at the time of VL-failure

	Patients without a resistance test N=581	Patients with a resistance test N=547	All N=1128
Gender (# Male, %)	409 (70.9%)	428 (78.2%)	837 (74.6%)
Race; (#, %)			
White	518 (89.9%)	477 (88.0%)	995 (89.0%)
Asian	7 (1.2%)	13 (2.4%)	20 (1.8%)
Black	38 (6.6%)	39 (7.2%)	77 (6.9%)
Other/Unknown	13 (2.3%)	13 (2.4%)	26 (2.3%)
Risk group; (#, %)			
MSM	197 (34.5%)	226 (41.9%)	423 (38.1%)
IDU	145 (25.4%)	98 (18.2%)	243 (21.9%)
Heterosexual	186 (32.6%)	169 (31.3%)	355 (32.0%)
Other/Unknown	43 (7.5%)	47 (8.7%)	90 (8.1%)
Year of failure; (#, %)			
2002	49 (8.4%)	85 (15.6%)	134 (11.9%)
2003	95 (16.4%)	153 (28.0%)	248 (22.0%)
2004	109 (18.8%)	138 (25.2%)	247 (21.9%)
2005	117 (20.1%)	87 (15.9%)	204 (18.1%)
2006	86 (14.8%)	56 (10.2%)	142 (12.6%)
≥2007	125 (21.5%)	28 (5.1%)	153 (13.6%)
cART use prior to 2002; (# Yes, %)	428 (73.7%)	460 (84.1%)	888 (78.7%)
Age (median, IQR)	41.2 (36.2, 47.4)	41.8 (37.2, 47.6)	41.5 (36.8, 47.5)
Log_{10} VL at VL-Failure (med, IQR)	4.2 (3.6, 4.8)	4.2 (3.6, 4.8)	4.2 (3.6, 4.8)
CD4 count at VL-Failure (med, IQR)	312 (170, 480)	254 (139, 437)	286 (154, 458)

Figure 1: Kaplan Meier: Time to resistance test following VL-failure

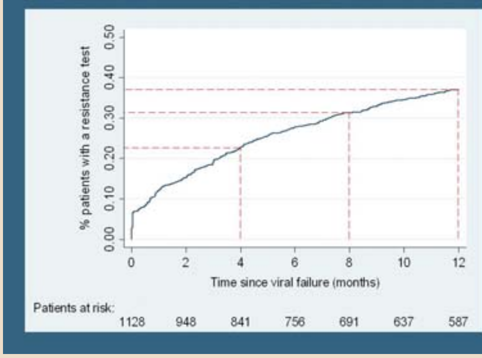


Table 2: Cox proportional hazard models investigating predictors of having a resistance test: fixed and time-updated variables

	Unadjusted analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Fixed variables:				
Gender (Female vs Male)	0.83 (0.65, 1.05)	0.11	0.87 (0.64, 1.19)	0.38
Race:		0.03		0.009
White	Ref		Ref	
Asian	2.21 (1.27, 3.85)		3.29 (1.81, 6.00)	
Black	1.38 (0.97, 1.96)		1.19 (0.78, 1.82)	
Other/Unknown	1.22 (0.65, 2.30)		0.95 (0.45, 2.00)	
Risk group:		0.18		0.08
MSM	Ref		Ref	
IDU	0.83 (0.63, 1.09)		1.14 (0.83, 1.56)	
Heterosexual	0.83 (0.66, 1.06)		1.32 (0.95, 1.85)	
Other/Unknown	1.15 (0.81, 1.65)		1.68 (1.14, 2.47)	
Region of Europe:		<0.0001		0.04
South	Ref		Ref	
Central West	1.10 (0.85, 1.42)		0.94 (0.69, 1.27)	
North	1.55 (1.21, 1.98)		1.27 (0.95, 1.69)	
Central East	0.62 (0.42, 0.92)		1.02 (0.65, 1.58)	
East	0.46 (0.25, 0.85)		0.47 (0.22, 0.98)	
Argentina	0.32 (0.13, 0.77)		0.49 (0.15, 1.55)	
Age at viral failure (per 10 years older)	1.09 (0.99, 1.21)	0.08	0.98 (0.87, 1.10)	0.76
Viral load at failure (per log_{10} increase)	0.98 (0.86, 1.11)	0.75	0.84 (0.72, 0.97)	0.02
CD4 at failure (per 100 cells/ml ↑)	0.97 (0.93, 1.02)	0.25	0.98 (0.93, 1.03)	0.36
Prior use of cART (Y/N)	1.56 (1.19, 2.04)	0.001	0.94 (0.67, 1.32)	0.73
Time updated variables:				
Calendar year:		<0.0001		<0.0001
2002	Ref		Ref	
2003	1.47 (0.91, 2.39)		2.13 (1.26, 3.59)	
2004	1.64 (1.01, 2.65)		2.88 (1.72, 4.84)	
2005	1.17 (0.71, 1.94)		1.79 (1.04, 3.09)	
2006	1.14 (0.67, 1.91)		1.33 (0.75, 2.38)	
≥2007	0.74 (0.43, 1.27)		0.69 (0.37, 1.28)	
Number of regimens failed (per additional regimen)	1.07 (1.04, 1.11)	<0.0001	1.05 (1.00, 1.10)	0.06
Adherence (N=650):		0.65	-	-
Perfect (>95%)	Ref			
Intermediate (70-95%)	0.80 (0.36, 1.82)			
Poor (<70%)	1.24 (0.56, 2.73)			
Time with VL>1000 copies/ml after VL-failure (per 6 months longer)	0.76 (0.74, 0.78)	<0.0001	0.75 (0.73, 0.76)	<0.0001

ACKNOWLEDGEMENTS: 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, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; (L Vandekerckhove) University Ziekenhuis Gent, Gent. Bosnia: (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) H Rozsypal, 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 Oestergaard, 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: (A Chiesi) 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, F Iacomi, P Narciso, C Vlassi, M Zaccarelli, 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 Monforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan. Latvia: (B Rozentale) P Aldins, 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: (J Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo. Poland: (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical University, 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) E Valadas, 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; E Vinogradova, 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, L Martin-Carbonero, P Labarga, 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 Karlsson), Karolinska University Hospital, Stockholm; PO Persson, Karolinska University Hospital, Huddinge; 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; (G Kutsyna) Luhansk AIDS Center, Luhansk; (S Servitskiy), Odessa Region AIDS Center, Odessa; (S Antoniak) Kiev; (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.

Virology group: B Clotet, R Paredes(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 Reiss (Vice-Chair), J Rockstroh
Coordinating Centre Staff: J Lundgren (project leader), O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, J Kjær, L Peters, J Reekie, J Kowalska

CHIP COPENHAGEN HIV PROGRAMME