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Genotypic resistance profile before initiation of combination antiretroviral therapy and association with virological and immunological outcome in EuroSIDA

WP Bannister[1], AN Phillips[1], B Clotet[2], P Reiss[3], B Ledergerber[4], A Lazzarin[5], C Katlama[6], A Cozzi-Lepri[1], L Ruiz[2], JD Lundgren[7] and the EuroSIDA study group

[1]Royal Free and University College Medical School, London, United Kingdom; [2]Hospital Germans Trias i Pujol, Badalona, Spain; [3]Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam, Netherlands; [4]University Hospital, Zürich, Switzerland; [5]Ospedale San Raffaele, Milan, Italy; [6]Hôpital de la Pitié-Salpétière, Paris, France; [7]Hvidovre Hospital, Copenhagen, Denmark

w.bannister@pcps.ucl.ac.uk

INTRODUCTION

- Resistance of HIV-1 to antiretroviral (ARV) drugs is associated with virological failure in patients undergoing treatment and limits subsequent therapy options
- Current European guidelines recommend the clinical use of resistance testing in ARV-naïve patients for those newly diagnosed with acute/recent HIV infection and for chronically infected patients starting therapy if the suspicion of resistance is high or the prevalence of resistance in the population exceeds 10%

OBJECTIVES

- To describe the change in prevalence of transmitted drug resistance (TDR) in EuroSIDA over calendar time
- To compare virological and immunological response to combination antiretroviral therapy (cART) in those with TDR to those without

METHODS

- Patients were included who had genotypic resistance test results available before starting any ARV therapy
- Sequence data were obtained by retrospectively performing a genotypic test on stored plasma samples in one of the central EuroSIDA laboratories or from clinical site reports
- For patients with multiple test results, the results closest to seroconversion were taken
- Logistic regression was used to analyse virological and immunological response at the first measurements 6-12 months after starting cART
- cART was defined as ≥ 3 drugs including a PI/NNRTI/ABC

RESULTS

- 561 patients had resistance test results available before starting ARV, of which 305 started cART.
- 18% had ≥ 1 NRTI, NNRTI or major PI resistance mutation according to IAS-USA October/November 2005 (Table 1) (12% of those who started cART).
- Over calendar time, the percentage of patients under follow-up who had NRTI, NNRTI or major PI resistance increased from 13% in 1996 to 36% in 2003-05, p=0.032 after adjustment for demographics, CD4 cell count and viral load at time of resistance test (Figure 1).

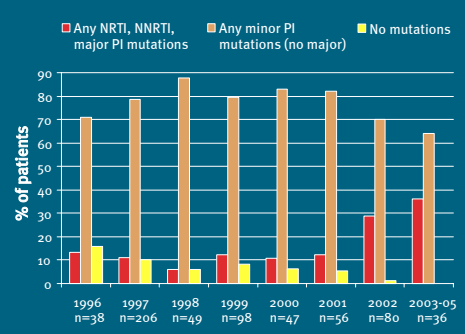
Table 1

Resistance profiles in ARV-naive patients

IAS-USA mutation	ARV-naïve	ARV-naïve and start cART
All, n (%)	561 (100.0)	305 (100.0)
Any NRTI, NNRTI, major PI	102 (18.2)	37 (12.1)
Any NRTI	85 (15.2)	27 (8.9)
M41L	30 (5.3)	7 (2.3)
D67N	20 (3.6)	3 (1.0)
K70R	17 (3.0)	10 (3.3)
L210W	32 (5.7)	6 (2.0)
T215Y/F	15 (2.7)	3 (1.0)
K219Q/E	27 (4.8)	4 (1.3)
Any NNRTI	11 (2.0)	4 (1.3)
Any major PI	29 (5.2)	9 (3.0)
Any minor PI	513 (91.4)	279 (91.5)

Figure 1

Resistance profiles in ARV-naive patients over calendar time



- Of 305 patients who started cART from ARV-naïve, 90% were sensitive to all of the drugs started ('active' group), with resistance interpreted using Rega algorithm, v6.4 (Table 2)
- 10% started a regimen with full or intermediate resistance to at least one drug ('resistant' group)
- Less patients started boosted PI regimens and more started single NNRTIs in the 'active' group (p<0.001). Patients also started cART later (p<0.001) in this group
- 270 patients with viral loads >500 copies/mL at time of starting cART were included in the virological response analysis. Counting missing values at 6-12 months after starting cART as virological failures, 75% achieved virological suppression (<=500 copies/mL) of 248 patients in the 'active' group, 50% of 22 in the 'resistant' group (Figure 2)
- Of 296 patients with baseline CD4 counts who were included in the immunological response analysis, 48% achieved a 100 cell/mm³ increase in CD4 count 6-12 months after cART of 267 in the 'active' group and 41% of 29 in the 'resistant' group.
- After adjustment for type of regimen, region, risk group, hepatitis B/C status, gender, race, prior AIDS diagnosis, year started cART, age, CD4 count, viral load and date of HIV diagnosis, there was no significant difference in virological response, OR: 0.47, 95% CI: (0.15-1.43), p=0.183 (Figure 3).
- There was also no significant difference in immunological response, adjusted OR: 0.64, 95% CI: (0.26-1.62), p=0.349.

CONCLUSIONS

- The relatively high prevalence of TDR observed in ARV-naïve EuroSIDA patients (18%) is due to a surprising upswing of TDR in 2002-2005, which may be due to an increase in selection bias.
- After adjustment for baseline viral load, CD4 count and demographics, there was a non-significant trend towards a worse virological and immunological response to cART in patients starting treatment with resistance to one or more drugs, however additional data are needed to increase power before a firm conclusion can be drawn.

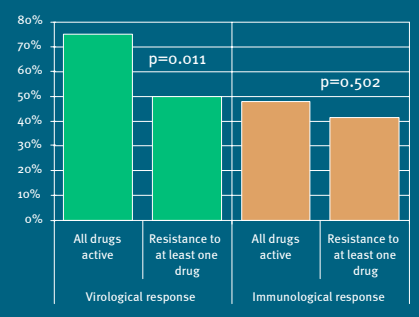
Table 2

Characteristics at start of cART regimen

	All drugs active	Resistance to at least one drug	p
All, n (%)	274 (90)	31 (10)	-
Male	209 (76)	28 (90)	0.075
MSM exposure	142 (52)	21 (68)	0.191
Previous AIDS diagnosis	32 (12)	4 (13)	0.217
cART regimen (incl >=2 NRTIs)			<0.001
Single PI	122 (45)	15 (48)	-
RTV-boosted PI	27 (10)	11 (36)	-
Single NNRTI	76 (28)	2 (7)	-
Other	49 (17)	3 (9)	-
Date started cART, median	Dec 99	Sep 97	<.001
Baseline CD4 count (cells/mm³)	249	246	0.836
Baseline viral load (log_{10}cps/mL)	4.9	5.0	0.678

Figure 2

% with virological[1] and immunological[2] response 6-12 months after starting cART

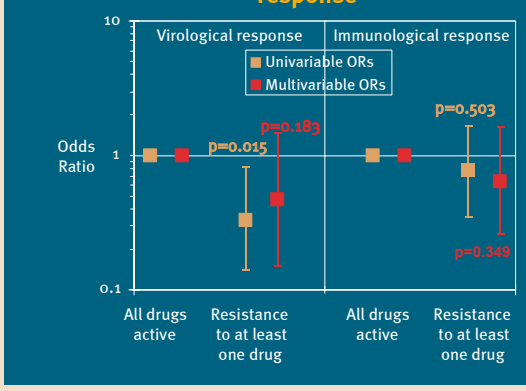


[1]Virological response: <500 copies/mL at first measurement 6-12 months after cART

[2]Immunological response: at least 100 cells/mm³ CD4 cell increase 6-12 months after cART

Figure 3

Odds ratios of virological[1] and immunological[2] response



The multicentre study group on EuroSIDA (national coordinators in parenthesis). **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. **Belgium:** (N Clumeck) S De Wit, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp. **Czech Republic** (L Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Pizen. **Denmark:** (J Nielsen) J Lundgren, T Benfield, O Kirk, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense. **Estonia:** (K Zilmer) West-Tallinn Central Hospital, Tallinn. **France:** (C Katlama) Hôpital de la Pitié-Salpêtière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; T Saint-Marc, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, Unité INSERM, Bordeaux. **Germany:** M Dietrich, C Manegold, Bernhard-Nocht-Institut for Tropical Medicine, Hamburg; J van Lunzen, H-J Stellbrink, Eppendorf Medizinische Kernkliník, Hamburg; S Staszewski, M Bickel, JW Goethe University Hospital, Frankfurt; F-D Goebel, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne; J Rockstroh, Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover. **Greece:** (J Kosmidis) P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital, Athens; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital, Athens. **Hungary:** (D Banhegyi) Szent László 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; Z Sthoeger, Kaplan Hospital, Rehovot; S Maayan, Hadassah University Hospital, Jerusalem. **Italy:** (A Chiesi) Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F. Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, Presidio Ospedaliero AD. Cotugno, Monaldi Hospital, Napoli; Antonucci, F Iacomi, Narciso, Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; A D'Arminio Monforte, Osp. L. Sacco, Milan. **Latvia:** (L Viksna) 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, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, A Wiercinska-Drapalo, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk. **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; A Streinu-Cercel, Institute of Infectious Diseases, Bucarest. **Russia:** E Vinogradova, St Petersburg AIDS Centre; A Rakhmanova, Medical Academy Botkin Hospital, St Petersburg. **Serbia & Montenegro:** (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. **Slovakia:** (M Mokráš) D Staneková, Dérer Hospital, Bratislava. **Spain:** (J González-Lahoz) M Sánchez-Conde, T Garcia-Benayas, L Martín-Carbonero, V Soriano, Hospital Carlos III, Madrid; B Clotet, A Jou, J Conejero, C Tural, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clínic i Provincial, Barcelona; P Domingo, MGutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona. **Sweden:** (A Blaxhult) Karolinska University Hospital, Solna; A Karlsson, Karolinska University Hospital, Stockholm; P Pehrson, Karolinska University Hospital, Huddinge. **Switzerland:** (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, A Telenti, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, V Soravia-Dunand, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern. **Ukraine:** (E Kravchenko) N Chentsova, Kyiv Centre for AIDS, Kyiv. **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; R Brettle, 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, 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), I Gjørup, O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, C Holkmann Olsen, J Kjær

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