Predictors of having a resistance test following at least one episode of viral load (VL) failure of cART: data from EuroSIDA

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BACKGROUND:

- The emergence of resistance to an antiretroviral drug (ARV) in a combination antiretroviral therapy (cART) regimen can compromise the effectiveness of treatment
- Current guidelines suggest that patients who are failing cART with a viral load (VL) >1000 copies/ml should have a resistance test, but not all patients get tested
- Genotypic resistance testing was more common after 1996 and as a result there were increases in the detection of drug resistance mutations between 1996 and 2003. However, since 2003 there have been declines in the prevalence of drug resistance mutations among patients with virological failure (VL-failure)
- This decline could be attributed to improvements in access to genotyping (i.e. more patients get tested), improved treatment strategies and the prompt detection and management of VL-failure

OBJECTIVES:

We propose to 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 rates of resistance mutations in patients with a test

METHODS:

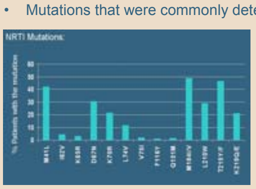
- EuroSIDA is an ongoing, observational cohort study that includes more than 16500 HIV infected patients from 32 European countries, Israel and Argentina
- All patients who started cART with ≥3 drugs after 2000 were considered for inclusion in this analysis
- A patient was defined as having an indication for a resistance test (i.e. VL-failure) if they had a viral load >1000 copies/ml after at least 4 months continuous use of any one drug
- In these patients, the date of the next resistance test was identified (if available) and factors predicting the availability of a resistance test were explored using Cox proportional hazards analysis. Stepwise regression was used to identify variables for inclusion in the multivariable analysis
- Resistance tests in the four months preceding VL-failure were categorised as pre-failure tests
- 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%
- We focussed on prospectively collected resistance tests in order to study resistance testing in clinical practice

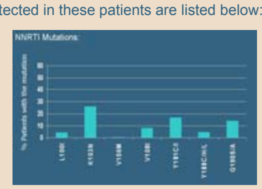
RESULTS:

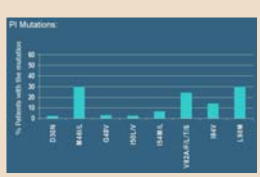
- A total of 2479 patients had VL-failure after 2000. Of these, a total of 1523 (61.2%) patients had reached a viral load <500 copies/ml on the regimen prior to VL-failure and in 1058 (69.5%) cases this value was confirmed. This illustrates that the majority of patients had managed to achieve complete and durable viral suppression on their regimen prior to VL-failure
- At VL-failure, patients had been on the same regimen for a median (IQR) of 10.0 (6.0-22.5) months and were followed for a median (IQR) 3.3 (1.8-5.1) years after VL-failure. The last follow-up visit occurred in April 2008
- There were 775 (31.3%) patients with a resistance test after VL-failure and 74 patients (3.0%) with a pre-failure test (Table 1)
- Using Kaplan-Meier estimates (Figure 1), the probability of having a resistance test was 18.5% by 1-year, 26.2% by 2-years, 32.0% by 3-years, 36.5% by 4-years, 39.9% by 5-years, 41.5% by 6-years and 43.3% by 7-years. Among those with a resistance test, the median (IQR) time from VL-failure to the resistance test was 9.4 months (2.1-22.2 months)
- In unadjusted analysis, fixed predictors of having a resistance test included gender (Relative Hazard (RH): 0.86; 95% CI: 0.73-1.01 for female versus male), race (RH: 1.58; 95% CI: 1.03-2.44 for Asian versus White) and region of Europe (RH: 1.73; 95% CI: 1.45-2.07 for North versus South) (Table 2A).
- Resistance testing was also more likely with increasing calendar year, among patients who had failed more regimens and among patients who had an indication of poor adherence. Patients who had spent longer with a VL>1000 copies/ml were less likely to have a resistance test (Table 2B).
- In multivariable analysis (excluding adherence due to the small number of patients who had an adherence measurement), predictors of having a resistance test included region of Europe, calendar year, current use of cART, the number of regimens failed and the time spent with a VL>1000 copies/ml (Table 2A and 2B).

Resistance patterns among patients who underwent resistance testing

- A total of 720 (92.9%) patients had information on mutations that were detected at the time of the resistance test. For the other 55 patients either sequencing was not possible or the resistance records are still awaiting approval
- There were a total of 542 (75.3%) patients in whom NRTI mutations were detected, 351 (48.8%) patients in whom NNRTI mutations were detected and 348 (48.3%) patients in whom PI mutations were detected
- Overall, mutations were detected to at least two classes of drugs in 581 (80.7%) patients
- Mutations that were commonly detected in these patients are listed below:







SUMMARY AND CONCLUSIONS:

- In EuroSIDA, resistance tests were reported for 43.3% of patients who had VL-failure up to 7yrs after VL-failure
- The probability of having a resistance test was lowest after 2007, which could be attributed to a delay in reporting
- Certain populations are more likely to undergo resistance testing, including those in Northern Europe, those who are not currently on cART and those who have failed more regimens previously
- Even though we have adjusted for region, this may reflect different attitudes towards performing and reporting the results of resistance tests in different centres
- The most common NRTI mutations that were detected were M184I/V (48.8%), T215Y/F (46.7%) and M41L (42.1%), the K103N NNRTI mutation was detected in 25.8% patients and for PIs the M46I/L (29.7%) and L90M (30%) were most frequently detected

Table 1: Characteristics of patients at the time of the viral load measurement

	All N=2479	Patients without a resistance test (N=1704)	Patients with a resistance test (N=775)
Gender (# Male, %)	1826 (73.7%)	1231 (72.3%)	594 (76.7%)
Race; (#, %)			
White	2166 (88.4%)	1506 (89.4%)	660 (86.3%)
Asian	47 (1.9%)	26 (1.5%)	21 (2.8%)
Black	172 (7.0%)	112 (6.7%)	60 (7.8%)
Other/Unknown	65 (2.7%)	41 (2.4%)	24 (3.1%)
Risk group; (#, %)			
MSM	974 (39.7%)	662 (39.2%)	312 (40.7%)
IDU	579 (23.6%)	417 (24.7%)	162 (21.2%)
Heterosexual	736 (30.0%)	497 (29.4%)	238 (31.1%)
Other/Unknown	166 (6.8%)	112 (6.6%)	54 (7.1%)
Year of failure; (#, %)			
2000	204 (8.2%)	122 (7.2%)	82 (10.6%)
2001	419 (16.9%)	240 (14.1%)	179 (23.1%)
2002	479 (19.3%)	332 (19.5%)	147 (19.0%)
2003	344 (13.9%)	221 (13.0%)	123 (15.9%)
2004	353 (14.2%)	244 (14.3%)	109 (14.1%)
2005	339 (13.7%)	249 (14.6%)	90 (11.6%)
≥2006	341 (13.8%)	296 (17.4%)	45 (5.8%)
cART use prior to 2000; (# Yes, %)	1768 (71.3%)	1151 (67.6%)	617 (79.6%)
Pre-failure resistance test; (# Yes, %)	74 (3.0%)	36 (2.1%)	38 (4.9%)
Age (median, IQR)	40.8 (36.1, 47.3)	40.9 (36.2, 47.5)	40.7 (36.0, 46.7)
Log_{10} VL at VL-Failure (med, IQR)	3.9 (3.4, 4.7)	3.9 (3.4, 4.7)	3.9 (3.4, 4.6)
CD4 count at VL-Failure (med, IQR)	323 (187, 491)	322 (187, 496)	326 (187, 484)

Figure 1: Kaplan Meier: Time to resistance test following a viral load >1000 copies/mL

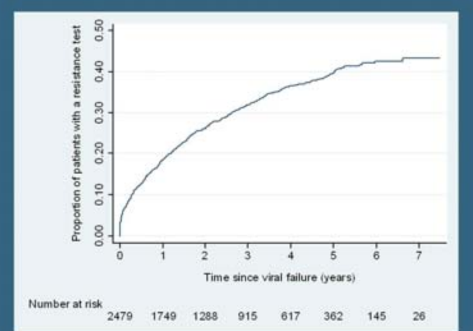


Table 2A: Cox proportional hazard models: Fixed variables

	Unadjusted analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Fixed variables:				
Gender (Female vs Male)	0.86 (0.73, 1.01)	0.07	-	-
Race;		0.05	-	-
White	Ref			
Asian	1.58 (1.03, 2.44)			
Black	1.29 (0.99, 1.68)			
Other/Unknown	1.30 (0.86, 1.95)			
Risk group;		0.34	-	-
MSM	Ref			
IDU	0.87 (0.72, 1.05)			
Heterosexual	1.03 (0.87, 1.22)			
Other/Unknown	1.04 (0.78, 1.39)			
Region of Europe;		<0.0001		<0.0001
South	Ref		Ref	
Central	1.24 (1.03, 1.50)		1.11 (0.92, 1.35)	
North	1.73 (1.45, 2.07)		1.59 (1.33, 1.90)	
East	0.81 (0.63, 1.03)		0.91 (0.70, 1.17)	
Argentina	0.69 (0.42, 1.13)		0.85 (0.52, 1.40)	
Age at viral failure (per 10 years older)	1.04 (0.97, 1.12)	0.28	-	-
Viral load at failure (per log_{10} increase)	1.02 (0.94, 1.12)	0.60	-	-

Table 2B: Cox proportional hazard models: Time updated variables

	Unadjusted analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Time updated variables:				
Calendar year:		<0.0001		<0.0001
2000	Ref		Ref	
2001	1.73 (0.96, 3.12)		1.87 (1.04, 3.39)	
2002	1.58 (0.88, 2.82)		1.83 (1.02, 3.27)	
2003	1.83 (1.03, 3.28)		2.10 (1.17, 3.76)	
2004	2.29 (1.29, 4.07)		2.65 (1.49, 4.71)	
2005	2.28 (1.28, 4.05)		2.60 (1.46, 4.64)	
2006	1.51 (0.84, 2.73)		1.70 (0.93, 3.08)	
≥2007	0.65 (0.33, 1.30)		0.69 (0.34, 1.37)	
Currently on cART (Yes vs No)	0.87 (0.62, 1.23)	0.45	0.70 (0.49, 0.99)	0.04
# regimens failed (per additional regimen failed)	1.10 (1.06, 1.14)	<0.0001	1.11 (1.07, 1.15)	<0.0001
Adherence (N=852):		<0.0001	-	-
Perfect (>95%)	Ref			
Intermediate (70-95%)	1.81 (1.06, 3.09)			
Poor (<70%)	2.55 (1.52, 4.29)			
Time with VL>1000 copies/ml (per 6 months longer)	0.83 (0.80, 0.86)	<0.0001	0.82 (0.79, 0.85)	<0.0001

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