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Predictors of Virologic Response to etravirine-based cART Regimens in a Large European Cohort of HIV-infected Patients

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BACKGROUND

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Unlike other currently available agents in the class such as efavirenz and nevirapine, resistance to other NNRTIs seem to confer limited resistance to etravirine and the number of etravirine-associated mutations seems to be the major determinant of virological success on etravirine.

The understanding of the true potency of etravirine when used as part of a second-line regimen in patients who failed a first line regimen with NNRTI has implications both in the resource-rich and –in the future potentially- also in limited settings for patients who cannot afford or tolerate PI. Most of the expert-based interpretation systems (IS) are based on the etravirine-mutations identified in the DUET trials with little cross-validation of these rules in other settings. Therefore, which and how many NNRTI mutations are sufficient to substantially reduce the virological response to etravirine-cART regimens remains to be better established.

OBJECTIVE

The primary objective of this analysis was to estimate the prevalence of NNRTI-resistance accumulated up to the time of starting an etravirine-based regimen in EuroSIDA and to assess the long-term risk of virologic failure to etravirine-based ART regimens according to detected resistance and other factors.

METHODS

Study population

The EuroSIDA study is a prospective, observational, open cohort of 16,599 HIV-1 infected patients in 102 centres across 31 European countries, Israel and Argentina. The study is described in detail at www.cphiv.dk. EuroSIDA also requests plasma samples from patients to be collected prospectively every six months and stored in a central repository. Retrospective genotypic sequencing has been carried out on samples identified for specific projects. HIV-1 RNA is isolated from patient blood plasma using QIAamp kit (Qiagen, Barcelona, Spain) and sequence analysis of HIV-1 RT and PR reading frames is performed using the Trugene HIV-1 genotyping Kit and OpenGene DNA Sequencing System according to the manufacturer's recommendations (Bayer, Barcelona, Spain).
In this analysis, we included patients in EuroSIDA who started an etravirine-based cART regimen (containing at least 2 other antiretrovirals besides etravirine which was started as new) at any point in time after January 1, 2001. The date of starting etravirine as part of cART was defined as baseline. An additional inclusion criterion was an available measure of viral load before baseline (only n=3 patients were excluded because of this criterion).

Statistical analysis

The prevalence of etravirine-associated mutations and NNRTI-resistance based on all genotypic resistance tests (GRT) performed prior to the time of starting etravirine was described. Etravirine- and NNRTI-resistance mutations were defined according to the IAS-USA list of December 2009. Etravirine activity was estimated using current versions of the 3 most frequently used expert based interpretation systems (ANRS, Stanford and Rega) as well as two etravirine-specific scores: the Tibotec (TBT) weighted genotypic score and the Monogram (MGR) score. The activity of the background regimen (including all drugs received at the time of starting etravirine, besides etravirine) was estimated using the Rega system.

Time to virological failure was defined as the time of a single HIV-1 RNA >400 copies/mL after >6 months of starting the etravirine-containing regimen. If baseline viral load was ≤400 copies/mL, the definition was the same but there was no requirement for > 6 months to have elapsed to declare a rebound. Standard survival analysis by means of Kaplan-Meier curves and Cox proportional hazards regression model, stratified by year of starting etravirine, was employed. Statistical analyses were performed using SAS (Version 9.2). All reported p-values are two-sided.

Tabel 1

Characteristics	Viral load <=400	Viral load>400	Total	p-value
	N= 93	N= 123	N= 216	
Age, years				0.006
Median (IQR)	50 (44, 57)	46 (41, 54)	48 (42, 55)	
Viral load, copies/mL				<.001
Median (IQR)	49 (39, 109)	6700 (1610, 61200)	874 (49, 11049)	
Gender, n(%)				0.010
Female	8 (8.6%)	26 (21.1%)	34 (15.7%)	
Ethnicity, n(%)				<.001
White	89 (96%)	92 (75%)	181 (84%)	
Asian	0 (0%)	2 (2%)	2 (1%)	
Black	2 (2%)	21 (17%)	23 (11%)	
Other/unknown	2 (2%)	7 (6%)	9 (4%)	
Mode of HIV transmission, n(%)				0.051
Homosexual contacts	15 (16%)	40 (33%)	55 (25%)	
Heterosexual contacts	9 (10%)	9 (7%)	18 (8%)	
IDU	9 (10%)	15 (12%)	24 (11%)	
Other/unknown	15 (16%)	40 (33%)	55 (25%)	
Geographical region, n(%)				0.419
Argentina	0 (0%)	0 (0%)	0 (0%)	
Belgium	5 (5%)	19 (15%)	24 (11%)	
Central East Europe	1 (1%)	5 (4%)	6 (3%)	
South East Europe	0 (0%)	1 (1%)	1 (0%)	
France	16 (17%)	18 (15%)	34 (16%)	
Germany	4 (4%)	9 (7%)	13 (6%)	
Greece	2 (2%)	2 (2%)	4 (2%)	
Spain	5 (5%)	1 (1%)	6 (3%)	
Israel	7 (8%)	18 (15%)	25 (12%)	
Italy	11 (12%)	14 (11%)	25 (12%)	
Scandinavia	27 (29%)	27 (22%)	54 (25%)	
Switzerland	0 (0%)	0 (0%)	0 (0%)	
United Kingdom	15 (16%)	9 (7%)	24 (11%)	
CD4 count, cells/mm³				<.001
Median (IQR)	433 (262, 587)	267 (165, 460)	327 (194, 503)	
AIDS diagnosis, n(%)				0.982
Yes	44 (47%)	58 (47%)	102 (47%)	
Hepatitis co-infection, n(%)				0.689
No	72 (77%)	98 (80%)	170 (79%)	
Yes	20 (22%)	23 (19%)	43 (20%)	
Unknown	1 (1%)	2 (2%)	3 (1%)	

Table 2a

Antiretroviral treatment and HIV drug resistance				
Factors	Viral load <=400	Viral load>400	Total	p-value
	N=137	N=183	N= 320	
Prior exposure to NNRTI, n(%)				
No	15 (11%)	13 (7%)	28 (9%)	0.014
Efavirenz	58 (42%)	58 (32%)	116 (36%)	
Nevirapine	27 (20%)	46 (25%)	73 (23%)	
Both	37 (27%)	66 (36%)	103 (32%)	
No. of nucleosides previously failed				
Median (range)	4 (0, 7)	5 (0, 7)	4 (0, 7)	<.001
No. of NNRTI previously failed				
Median (range)	1 (0, 2)	1 (0, 2)	1 (0, 2)	<.001
No. of PI previously failed				
Median (range)	2 (0, 7)	3 (0, 8)	3 (0, 8)	<.001
No. of fusion/integrease inhibitors previously failed				
Median (range)	0 (0, 2)	0 (0, 2)	0 (0, 2)	<.001
No. of total drugs previously failed				
Median (range)	6 (0, 17)	9 (0, 18)	8 (0, 18)	<.001
Nucleosides newly started besides etravirine				
zidovudine	3 (2%)	12 (7%)	15 (5%)	0.056
didanosine	0 (0%)	15 (8%)	15 (5%)	<.001
stavudine	0 (0%)	6 (3%)	6 (2%)	0.009
lamivudine	6 (4%)	30 (16%)	36 (11%)	<.001
emtricitabine	4 (3%)	8 (4%)	12 (4%)	0.494
abacavir	1 (1%)	7 (4%)	8 (3%)	0.059
tenofovir	7 (5%)	17 (9%)	24 (8%)	0.152
PI newly started besides etravirine				
saquinavir	0 (0%)	1 (1%)	1 (0%)	0.290
indinavir	0 (0%)	2 (1%)	2 (1%)	0.134
ritonavir (boost)	27 (20%)	52 (28%)	79 (25%)	0.072
amprenavir	1 (1%)	3 (2%)	4 (1%)	0.455
lopinavir	1 (1%)	13 (7%)	14 (4%)	0.002
atazanavir	1 (1%)	2 (1%)	3 (1%)	0.736
tipranavir	0 (0%)	1 (1%)	1 (0%)	0.290
darunavir	51 (37%)	97 (53%)	148 (46%)	0.005
Other drugs newly started besides etravirine				
T20	2 (1%)	17 (9%)	19 (6%)	0.001
maraviroc	3 (2%)	14 (8%)	17 (5%)	0.023
raltegravir	48 (35%)	80 (44%)	128 (40%)	0.116
No. of new drugs started				
Median (IQR)	2 (1, 3)	3 (2, 4)	3 (2, 3)	<.001
No. of active drugs in background regimen-Rega (n=216)				
Median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.390
Duration of previous exposure to failing efavirenz, months (n=292)				
Mean (SD)	3.8 (9.4)	5.5 (11.4)	4.8 (10.6)	0.011
Duration of previous exposure to failing nevirapine, months (n=292)				
Mean (SD)	4.9 (12.1)	7.2 (14.5)	6.2 (13.6)	0.031
Time from last use of NNRTI, months				
Median (IQR)	50 (9, 79)	50 (20, 70)	50 (16, 74)	0.885

Table 2b

Antiretroviral treatment and HIV drug resistance				
Factors	Viral load <=400	Viral load>400	Total	p-value
	N= 93	N= 123	N= 216	
Predicted etrvirine activity				
Rega				0.179
Sensitive	73 (78%)	88 (72%)	161 (75%)	
Intermediate	17 (18%)	27 (22%)	44 (20%)	
Resistant	3 (3%)	8 (7%)	11 (5%)	
HIVDB				0.059
Sensitive	69 (74%)	80 (65%)	149 (69%)	
Intermediate	21 (23%)	31 (25%)	52 (24%)	
Resistant	3 (3%)	12 (10%)	15 (7%)	
ANRS				0.242
Sensitive	89 (96%)	111 (90%)	200 (93%)	
Intermediate	2 (2%)	9 (7%)	11 (5%)	
Resistant	2 (2%)	3 (2%)	5 (2%)	
TBT score				0.069
Sensitive	72 (77%)	88 (72%)	160 (74%)	
Intermediate	17 (18%)	17 (14%)	34 (16%)	
Resistant	4 (4%)	18 (15%)	22 (10%)	
MGR score				0.366
Sensitive	73 (78%)	90 (73%)	163 (75%)	
Resistant	20 (22%)	33 (27%)	53 (25%)	

Figure 1a

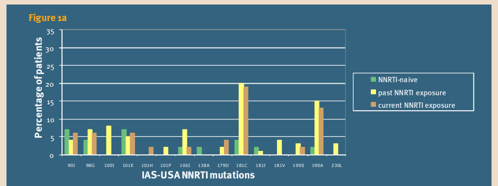
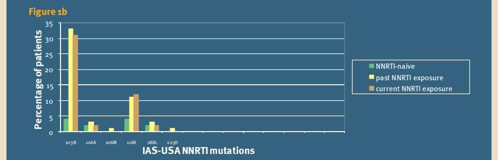


Figure 1b



RESULTS

Study population

We identified 320 patients who started etravirine as part of cART between May 2001 and October 2009 (median Feb 2008). **Table 1** shows the main characteristics of the study population according to whether they started etravirine with a suppressed or unsuppressed viral load for the subset of 216 patients (68%) with at least one genotypic test prior to etravirine initiation. **Table 2a/b** compares the same two groups with respect to factors measuring antiretroviral treatment and HIV drug resistance.

NNRTI resistance at time of etravirine initiation and at time of failure

For 154 (71%) of the 216 with >=1 GRT, the date of the most recent test was after the estimated date of virological failure of ≥1 drugs in the NNRTI class. Considering all 216, the median time between the test and the date of starting etravirine was 37 months (range:1-176) and 32 (1-141) months when restricting to the 154 tested after failure. The prevalence of patients with ≥1 IAS-USA NNRTI detected up to the most recent test before starting etravirine was 43% overall, 24% in patients never previously exposed to NNRTI (mainly due to detection of polymorphisms 90I, 98G and 101E), 48% in those exposed in the past but not receiving a NNRTI at the time of the last test and 46% in those last tested when receiving a NNRTI. The prevalence of etravirine specific mutations was 34% (95% CI:28-41) overall and 24% (12-39), 38% (29-47) and 35% (22-49) in the same subgroups. **Figure 1a/b** shows the distribution of specific IAS-USA NNRTI-associated mutations according to NNRTI exposure prior to last test. Thirty-seven patients (30% of those who showed no NNRTI-resistance up to the time of their last test) started nevirapine or efavirenz between the date of this test and the date of starting etravirine. **Figure 2** shows the percentage of patients who at the time of their last GRT were estimated to have a virus which was susceptible to etravirine according to system used and predicted activity of the background regimen.

Virological response to the etravirine-based cART and its predictors

Over a total of 399 person years of follow-up we observed 42 cases of virological failure (incidence rate=10.5 per 100 person years, 95% CI:7.7-14.0), of which only one was a rebound from a patient who started etravirine with a viral load suppressed ≤400 copies/mL. Virological failure was declared a median of 9 months from starting etravirine in those who experienced failure. **Table 3** shows the associations between predicted etravirine activity (based on all tests performed an average 37 months before start etravirine), specific etravirine mutations and virological response from fitting a Cox proportional hazards regression model. The ANRS score was the only IS showing a significant association with the risk of virological failure for increased levels of resistance. In addition, an increased risk of virological failure was seen in patients carrying mutations 101E. Interestingly, detection of mutation 103N was independently associated with a significantly reduced risk of subsequent virological failure. Results were similar when we performed sensitivity analyses: i) after restricting to tests performed within 1 year of starting ETR - RH=13.2 for ANRS intermediate vs. ANRS sensitive, p=0.04; 373.5 for ANRS resistance vs. ANRS sensitive, p=0.008 and RH=0.01 for patients in which K103N was detected (p=0.05) and ii) after excluding patients who started a NNRTI between the date of the last test and the date of commencing etravirine - RH=8.5 for ANRS intermediate vs. ANRS sensitive, p=0.01; 44.3 for ANRS resistance vs. ANRS sensitive, p=0.001 and RH=0.15 for patients in which K103N was detected (p=0.002).
Calendar year of starting ETR (RH=0.66 per more recent year, p=0.001) was the only other independent predictor of virological failure (**Table 4** – analysis performed also on all 320 patients, not just those with >=1 GRT). Results were similar when we used two consecutive viral loads>400 copies/mL to define virological failure (34 events, data not shown).

CONCLUSIONS

Uncertainty regarding predictions of antiviral activity for etravirine in NNRTI-treated patients in clinical practice remains high. Analysis of this database after the accumulation of additional patients starting etravirine as well as analyses of other datasets are needed to further investigate the role of 103N in determining etravirine hypersensitivity.

Figure 2

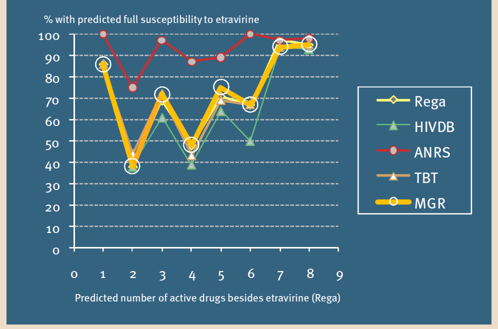


Table 3

N=216 patients >= 1 GRT before starting ETR	Crude and adjusted relative hazards of virological failure			
Factors*	Crude RH (95% CI)	p-value	Adjusted** RH (95% CI)	p-value
Predicted etrvirine activity				
Rega				
Sensitive	1.00		1.00	
Intermediate	1.47 (0.74, 2.92)	0.268	1.18 (0.50, 2.78)	0.708
Resistant	1.85 (0.65, 5.33)	0.252	1.64 (0.42, 6.43)	0.474
HIVDB				
Sensitive	1.00		1.00	
Intermediate	1.59 (0.82, 3.09)	0.174	1.13 (0.44, 2.90)	0.792
Resistant	1.88 (0.72, 4.96)	0.200	1.26 (0.38, 4.18)	0.701
ANRS				
Sensitive	1.00		1.00	
Intermediate	4.17 (1.84, 9.43)	<.001	3.33 (1.03, 10.80)	0.045
Resistant	4.50 (1.07, 18.90)	0.040	8.72 (1.56, 48.77)	0.014
TBT score				
Sensitive	1.00		1.00	
Intermediate	0.98 (0.40, 2.39)	0.965	0.77 (0.26, 2.28)	0.636
Resistant	3.35 (1.65, 6.82)	<.001	3.08 (1.08, 8.76)	0.035
MGR score				
Sensitive	1.00		1.00	
Resistant	1.89 (1.02, 3.50)	0.043	1.45 (0.61, 3.44)	0.396
IAS-USA NNRTI mutations				
103N	0.22 (0.09, 0.58)	0.002	0.21 (0.07, 0.58)	0.003
188L	1.33 (0.17, 10.13)	0.785		
90I	2.37 (0.69, 8.14)	0.171		
98G	1.42 (0.46, 4.39)	0.543		
101E	5.20 (1.86, 14.49)	0.002	5.95 (1.76, 20.10)	0.004
181C	1.53 (0.64, 3.63)	0.337	1.65 (0.62, 4.38)	0.318
190A	1.79 (0.64, 4.99)	0.269		
230L	3.65 (0.48, 27.88)	0.212	1.71 (0.10, 28.41)	0.710

*A separate model for each of these
**Adjusted for gender, mode of HIV transmission, race, hepatitis co-infection status, year of baseline, age, baseline cd4 count and viral load, prior history to exposure to NNRTI, total number of drugs previously failed, no. of new drugs started, no. of active drugs in background regimen,duration of previous exposure to efavirenz, duration of previous exposure to nevirapineand time from last exposure to a NNRTI

Table 4

All patients (N=320)	Crude and adjusted relative hazards of virological failure					
Factors*	Crude RH (95% CI)	p-value	Adjusted** RH (95% CI) All patients (n=320)	p-value	Adjusted** RH (95% CI) Patients with genotype (n=216)	p-value
Prior exposure to NNRTI, n(%)						
No	1.00		1.00		1.00	
Efavirenz	0.78 (0.42, 1.44)	0.425	0.81 (0.40, 1.67)	0.573	0.75 (0.29, 1.93)	0.548
Nevirapine	0.97 (0.52, 1.80)	0.916	0.84 (0.38, 1.84)	0.657	0.85 (0.31, 2.32)	0.750
No. of total drugs previously failed per one additional	1.05 (0.98, 1.12)	0.135	1.01 (0.93, 1.10)	0.831	1.06 (0.95, 1.18)	0.327
No. of new drugs started per one additional	1.16 (0.96, 1.39)	0.115	1.01 (0.82, 1.25)	0.890	1.16 (0.92, 1.47)	0.218
No. of active drugs in background regimen-Rega per one additional	1.03 (0.82, 1.28)	0.808			1.18 (0.89, 1.56)	0.245
Duration of previous exposure to failing efavirenz, months per year longer	1.01 (0.77, 1.33)	0.938	1.08 (0.77, 1.51)	0.663	1.24 (0.82, 1.85)	0.308
Duration of previous exposure to failing nevirapine, months per year longer	1.04 (0.86, 1.27)	0.660	1.10 (0.84, 1.43)	0.492	0.93 (0.64, 1.34)	0.687
Time from last use of NNRTI, months per year longer	0.99 (0.90, 1.08)	0.759	1.04 (0.92, 1.18)	0.546	1.02 (0.87, 1.21)	0.780
Viral load at baseline per log_{10} higher	1.35 (1.10, 1.65)	0.004	1.25 (0.96, 1.62)	0.093	1.20 (0.87, 1.65)	0.258
Calendar year of baseline per more recent	0.75 (0.65, 0.87)	<.001	0.79 (0.65, 0.97)	0.021	0.66 (0.51, 0.85)	0.001

**Adjusted for gender, mode of HIV transmission, race, hepatitis co-infection status, age, and baseline cd4 count, none of which showed an association with the risk of virological failure

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