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The use of and response to second combination antiretroviral therapy regimens in EuroSIDA

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BACKGROUND

Relatively little is known about the response to second line combined antiretroviral therapy (cART), despite the fact that newly emerging therapies are likely to be initially aimed at this patient group.

OBJECTIVES

This study aims to describe the incidence and predictors of virological failure to second line cART in EuroSIDA.

PATIENTS AND METHODS

All patients in EuroSIDA who started cART (≥3 drugs-containing regimen) from ART-naïve, experienced confirmed virological failure (CVF) to this first regimen and subsequently started a 2nd cART regimen were included. The time of starting ≥1 new or recycled drug as part of cART after a CVF of the 1st regimen (e.g. when VL was >400 copies/mL) was defined as the date of starting the 2nd regimen (baseline, see **Chart 1** for an example for one patient). The date of CVF was defined as the time of the first of two consecutive viral loads >400 copies/mL ≥6 months after starting cART (same definition was used for both the 1st and 2nd regimen). Drug switches that occurred in patients without evidence of previous CVF did not define the start of a 2nd regimen. Thus, in the example in **Chart 1**, the substitution of 3TC with FTC while viral load was <400 copies/mL does not define the date of starting a 2nd regimen. A patient was defined to have experienced virological failure on a certain drug if there was a single viral load >400 copies/mL after >6 months from starting the drug and he/she had continuously used the drug for >6 months. Using this definition we calculated how many drugs of those that were switched to at baseline had already been previously failed virologically (i.e. a virologically active score [VAS] for the 2nd regimen).

Statistical Analysis

We estimated the time from baseline to CVF of the second regimen using the Kaplan-Meier (K-M) method; the follow-up of patients who had no evidence of CVF to 2nd regimen was censored at the date of last available viral load. We used proportional hazards Cox regression (stratified by centre) to identify independent predictors of CVF. We considered all the variables listed in **Table 4** as potential predictors.

RESULTS

Baseline characteristics

Overall, 695 patients starting a 2nd line regimen were eligible for inclusion in the analysis. Of these, 157 (23%) were females, 289 (42%) acquired HIV via homosexual contacts, 150 (22%) via injecting drug use and 216 (31%) via heterosexual contacts.

Table 1 and 2 show the characteristics of the patients at the time of initiation of 1st and 2nd regimen, respectively. The most frequent type of 1st cART was a nucleoside pair including zidovudine and lamivudine and a NNRTI (nevirapine or efavirenz) or a single PI (indinavir and nelfinavir) (**Table 1**). In contrast, the 2nd regimen contained a wider range of nucleoside pairs (including lamivudine/tenofovir and emtricitabine/tenofovir) and a larger proportion of patients were treated with ritonavir-boosted PI based regimens (**Table 2**). In most cases, if the 1st cART was PI-based then the 2nd regimen was also PI-based but the majority who were on a NNRTI-based 1st cART switched to a PI o PI/r based regimen (**Table 3**). Overall, 31% started a single new drug class, 1% two new classes, 53% ≥1 new drug within the same class and for 16% none of the drugs were new. The median from the date of initiation of the 1st cART to baseline was 26 months (range:7-164) and from the estimated date of virological failure of 1st regimen to baseline was 6 months (range:0-18).

Drugs that were switched to at baseline

In terms of the number of drugs that were switched to at baseline, overall a median of 3 (range:1-6) new or recycled drugs were started, 2 of which were nucleosides (range:0-5); In 95 patients (14%) all of these drugs were recycled and had previously failed virologically; the complete distribution of patients according to the number of new or recycled (but not previously failed) drugs started at baseline (i.e. the virologically active score – VAS) is shown in **Table 3**.

Chart 1

Design of the analysis (definition of baseline)

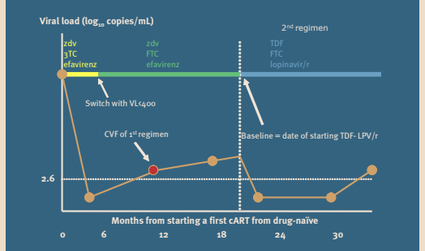

Table 1

Characteristics of the n=695 patients at initiation of 1st regimen

Age, median (range) Years	38 (18-79)
CD4 count, median (IQR) Cells/µl	195 (88-321)
Viral load, median (IQR) Log10 copies/mL	4.94 (4.27-5.46)
Calendar year, median (range)	1998 (1996-2005)
Antiretrovirals most frequently started, n(%)	
d4T/3tc	90 (13%)
d4t/ddl	65 (9%)
Zdv/3tc	350 (50%)
Zdv/ddl	31 (5%)
Abacavir	17 (3%)
Efavirenz	60 (9%)
Nevirapine	68 (10%)
Lopinavir/r	19 (3%)
Indinavir	181 (26%)
Nelfinavir	114 (16%)

Table 2

Characteristics of the patients at initiation of 2nd regimen

CD4 count, median (IQR) Cells/µl	275 (165-417)
Viral load, median (IQR) Log10 copies/mL	4.25 (3.54-4.89)
Calendar year, median (range)	2001 (1996-2007)
Antiretrovirals in regimen, n(%)	
d4T/3tc	107 (15%)
d4t/ddl	88 (13%)
zdv/3tc	214 (21%)
zdv/ddl	31 (4%)
FTC/tdf	30 (4%)
3TC/ddl	44 (6%)
3tc/tdf	34 (5%)
Abacavir	26 (4%)
Efavirenz	112 (16%)
Nevirapine	93 (14%)
Lopinavir/r	103 (15%)
Indinavir	68 (10%)
Nelfinavir	96 (14%)
Indinavir/r	29 (4%)
Saquinavir/r	30 (4%)
Atazanavir/r	34 (5%)

Predictors of CVF of 2nd regimen

Overall, 310 patients experienced CVF>400 copies/mL of the 2nd regimen; the KM estimate of the median time from initiation of 2nd regimen to CVF was 39 months (95% CI:25-48).

Table 4 shows the Kaplan-Meier estimates of the proportion of patients with virological failure according to a number of factors. In the subset of patients whose baseline was within 3 months of the date of CVF of their 1st regimen the proportions of patients with CVF of the 2nd regimen were 48% (41-55) by 2 years and 55% (47-63) by 4 years.

All factors shown in **Table 4** were found to be independently associated with the risk of virological failure as shown by the Cox regression model analysis (**Table 5**). In terms of the magnitude of the effect, the largest increase in risk of CVF seemed to be associated with a higher VL at baseline (20% greater risk per 1 log10 higher, p=0.02) and with the use of nevirapine or nelfinavir in 2nd-line as opposed to efavirenz (around 2-fold and 80% risk increase, respectively). The largest decrease in the risk of CVF was observed comparing patients who achieved a VL<400 at least in one occasion on first cART to those who never did (24% risk reduction, p=0.05).

DISCUSSION

The overall incidence of virological failure to a 2nd cART regimen was high (55% by 2 years of starting the 2nd regimen, **Table 4**) in our study population of patients who, on average, started their 1st cART from drug-naïve in 1998 and, upon virological failure of this, initiated a 2nd cART in 2001. Around 30% of the study population started antiretroviral drugs that are no longer recommended in first line regimens and seldom used in subsequent lines (e.g. stavudine, nelfinavir). The median lag between CVF of the first regimen and the date of starting of the 2nd regimen was 6 months, confirming that extremely prompt drug switches upon discovery of virological failure are less common in European clinical practice than might have been presumed. In the subset of patients who had a drug switch within 3 months of CVF the probability of 2nd failure by 2 years was only slightly lower: 48% (95% CI:41-55).

In an appreciable 14% of patients all drug(s) that were switched to at baseline was (were) drug(s) for which there was evidence that had previously failed virologically. Only 32% of patients started a new (i.e. never experienced before) class of drugs in the 2nd regimen.

A limitation of this study is that, although our definition of 2nd regimen implied that the switch had occurred when VL was >400 copies/mL, in some cases it is possible that the new regimen was considered by clinicians as a change due to toxicity or it was a restart of a drug that was temporarily suspended. The fact that a high percentage of the drugs that were switched to was a nucleoside and that 31% of people originally on NNRTI-cART remained on a NNRTI in 2nd line (**Table 3**) seems to confirm this hypothesis. Of note, only 20% of those with a baseline >48 months from starting their 1st regimen experienced CVF of this 2nd regimen (**Table 4**) and results of the main analysis were similar after excluding the n=111 patients who started recycled drugs only (data not shown).

CONCLUSION

Our study identified a high viral load at initiation, low predicted virological activity of the drugs that were switched to at baseline, not achieving a VL ≤400 on first cART and shorter time between initiating the 1st and 2nd regimen as independently associated with a higher risk of CVF of 2nd cART. The latter two factors may reflect the fact that non adherent patients failed quickly both regimens, though the role of adherence and drug resistance warrants further investigation.

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Table 3

Distribution of type of 2nd cART according to type of 1st cART

Type of 1st cART	Type of 2nd cART: Single-PI	NNRTI	PI/r	Abacavir	>3 drugs
			n (row %)		
Single PI	142 (31%)	114 (25%)	103 (22%)	17 (4%)	87 (19%)
NNRTI	12 (10%)	38 (32%)	43 (36%)	4 (3%)	21 (18%)
PI/r	9 (18%)	10 (19%)	21 (41%)	4 (8%)	7 (14%)
Abacavir	0 (0%)	10 (37%)	8 (30%)	1 (4%)	8 (30%)
>3 drugs	6 (17%)	8 (22%)	13 (36%)	0 (0%)	9 (25%)
Total	169 (24%)	180 (26%)	188 (27%)	26 (4%)	132 (19%)

Distribution of the number of drugs started at time of switch (n, %)

	All	Nucleosides	NNRTI	PI	VAS
0	-	135 (19%)	449 (65%)	276 (40%)	95 (14%)
1	128 (18%)	161 (23%)	242 (35%)	315 (45%)	199 (29%)
2	146 (21%)	358 (52%)	4 (1%)	100 (14%)	193 (28%)
3	329 (47%)	38 (5%)	-	4 (1%)	167 (24%)
>3	92 (13.%)	3 (0.3%)	-	-	41 (6%)

Table 4

K-M estimates of the % of patients with CVF >400 copies/mL by time from starting the 2nd regimen according to a number of factors

Factor	Proportion (95% CI) with CVF by 2 years	4 years	log-rank p-value
Baseline VL			0.05
501-10K	40% (34-46)	49% (43-55)	
10k-100k	50% (42-58)	64% (56-72)	
>100k	46% (36-56)	55% (45-65)	
Months from 1st to 2nd			0.0001
7-24	54% (42-66)	64% (52-76)	
24-48	49% (43-55)	60% (54-66)	
>48	20% (12-28)	25% (15-35)	
3rd drug in 2nd cART			0.0001
Efavirenz	29% (19-39)	46% (32-60)	
Nevirapine	61% (49-73)	70% (58-82)	
Nelfinavir	58% (48-68)	66% (56-76)	
VAS			0.79
0	43% (30-56)	55% (40-70)	
1	49% (41-57)	53% (45-61)	
2	42% (34-50)	56% (46-66)	
≥3	45% (37-53)	54% (44-64)	
Ever <400 on 1st cART			0.0001
No	53% (47-59)	63% (57-69)	
Yes	32% (26-38)	42% (34-50)	

Table 5

Relative hazard of virological failure >400 copies/mL from fitting a Cox regression model

	Crude RH (95% CI)	Adjusted RH (95% CI)
Baseline VL (per log10 higher)	1.13 (1.00-1.20) p=0.05	1.20 (1.04-1.40) p=0.02
Months from 1st to 2nd cART (per 6 months longer)	0.91 (0.87-0.94) p=0.0001	0.94 (0.89-0.99) p=0.04
Efavirenz in 2nd cART	1.00	
Nevirapine in 2nd cART	2.15 (1.40-3.30) p=0.0004	2.19 (1.38-3.50) p=0.001
Nelfinavir in 2nd cART	2.17 (1.44-3.29) p=0.0002	1.80 (1.13-2.87) p=0.01
VAS (per 1 unit higher)	1.00 (0.90-1.10) p=0.99	0.90 (0.80-1.00) p=0.05
Ever VL<400 cps/mL on 1st cART		
No	1.00	1.00
Yes	0.59 (0.46-0.75) p=0.0001	0.76 (0.57-1.00) p=0.05

Adjusted for: age, gender, mode of HIV transmission, ethnicity, HBV/HCV status, viral load and CD4 count at initiation of 1st cART, lag-time between CVF of 1st cART and baseline, type of 1st cART regimen (single PI, NNRTI, PI/r, abacavir, other) nucleoside pair in 2nd regimen and calendar year of baseline

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