

# 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 ( $\geq 3$  drugs-containing regimen) from ART-naïve, experienced confirmed virological failure (CVF) to this first regimen and subsequently started a 2<sup>nd</sup> cART regimen were included. The time of starting  $\geq 1$  new or recycled drug as part of cART after a CVF of the 1<sup>st</sup> regimen (e.g. when VL was  $>400$  copies/mL) was defined as the date of starting the 2<sup>nd</sup> 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  $\geq 400$  copies/mL  $\geq 6$  months after starting cART (same definition was used for both the 1<sup>st</sup> and 2<sup>nd</sup> regimen). Drug switches that occurred in patients without evidence of previous CVF did not define the start of a 2<sup>nd</sup> 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 2<sup>nd</sup> 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 2<sup>nd</sup> 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 2<sup>nd</sup> 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

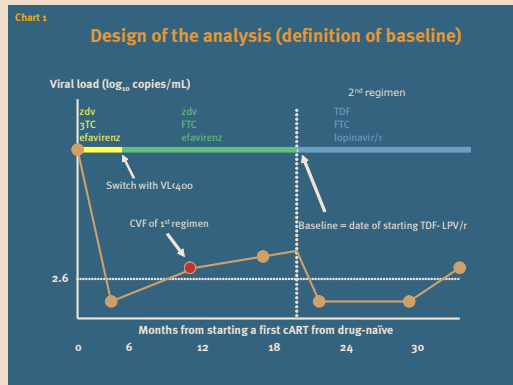
### Baseline characteristics

Overall, 695 patients starting a 2<sup>nd</sup> 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 1<sup>st</sup> and 2<sup>nd</sup> regimen, respectively. The most frequent type of 1<sup>st</sup> 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 2<sup>nd</sup> 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 1<sup>st</sup> cART was PI-based then the 2<sup>nd</sup> regimen was also PI-based but the majority who were on a NNRTI-based 1<sup>st</sup> cART switched to a PI or PI/r based regimen (**Table 3**). Overall, 31% started a single new drug class, 1% two new classes, 53%  $\geq 1$  new drug within the same class and for 16% none of the drugs were new. The median from the date of initiation of the 1<sup>st</sup> cART to baseline was 26 months (range:7-164) and from the estimated date of virological failure of 1<sup>st</sup> 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**.



**Table 1**  
**Characteristics of the n=695 patients at initiation of 1<sup>st</sup> regimen**

Age, median (range)	38 (18-79)
Years	
CD4 count, median (IQR)	195 (88-321)
Cells/ $\mu$ l	
Viral load, median (IQR)	4.94 (4.27-5.46)
Log <sub>10</sub> copies/mL	
Calendar year, median (range)	1998 (1996-2005)
Antiretrovirals most frequently started, n(%)	
d4T/3TC	90 (13%)
d4I/ddI	65 (9%)
ZdV/3TC	350 (50%)
ZdV/ddI	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 2<sup>nd</sup> regimen**

CD4 count, median (IQR)	
Cells/ $\mu$ l	275 (165-417)
Viral load, median (IQR)	
Log <sub>10</sub> copies/mL	4.25 (3.54-4.89)
Calendar year, median (range)	2001 (1996-2007)
Antiretrovirals in regimen, n(%)	
d4T/3TC	107 (15%)
d4I/ddI	88 (12%)
ZdV/3TC	214 (31%)
ZdV/ddI	31 (4%)
FTC/ddI	30 (4%)
3TC/ddI	44 (6%)
3TC/FTC	34 (5%)
Abacavir	26 (4%)
Efavirenz	112 (16%)
Nevirapine	93 (14%)
Lopinavir/r	103 (15%)
Indinavir	68 (10%)
Nelfinavir	96 (14%)
Indinavir/r	20 (3%)
Saqinavir/r	30 (4%)
Azatanavir/r	34 (5%)

## Predictors of CVF of 2<sup>nd</sup> regimen

Overall, 310 patients experienced CVF  $>400$  copies/mL of the 2<sup>nd</sup> regimen; the KM estimate of the median time from initiation of 2<sup>nd</sup> 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 1<sup>st</sup> regimen the proportions of patients with CVF of the 2<sup>nd</sup> 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 log<sub>10</sub> higher, p=0.02) and with the use of nevirapine or nelfinavir in 2<sup>nd</sup>-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 2<sup>nd</sup> cART regimen was high (55% by 2 years of starting the 2<sup>nd</sup> regimen, **Table 4**) in our study population of patients who, on average, started their 1<sup>st</sup> cART from drug-naïve in 1998 and, upon virological failure of this, initiated a 2<sup>nd</sup> 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 2<sup>nd</sup> 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 2<sup>nd</sup> 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 2<sup>nd</sup> regimen.

A limitation of this study is that, although our definition of 2<sup>nd</sup> 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 2<sup>nd</sup> line (**Table 3**) seems to confirm this hypothesis. Of note, only 20% of those with a baseline  $\geq 8$  months from starting their 1<sup>st</sup> regimen experienced CVF of this 2<sup>nd</sup> 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  $\leq 400$  on first cART and shorter time between initiating the 1<sup>st</sup> and 2<sup>nd</sup> regimen as independently associated with a higher risk of CVF of 2<sup>nd</sup> 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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