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

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BACKGROUND

In order to describe the incidence and predictors of virological failure to second line cART in EuroSIDA.

OBJECTIVES

RESULTS

In an appreciable 14% of patients all drug(s) that were switched to at baseline was (were) drug(s) for which there was no previous virological failure on a certain drug if there was a single viral load >400 copies/mL after >6 months from CVF of 1st regimen and calendar year of baseline. The most frequent type of 1st cART was a nucleoside pair including zidovudine and lamivudine and a NNRTI (nelfinavir or efavirenz) or a single PI (indinavir and nelfinavir) (Table 3). In contrast, the 2nd cART 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 6). In most cases, if the 2nd cART was PI-based then the 3rd cART was also PI-based but the majority who were on a NNRTI-based 1st cART switched to a PI or PI/r based regimen (Table 8). Overall, 3% started a single new drug class, 12% two new classes, 5% two new drugs within the same class and for 86% none of the drugs were new. The median date of initiation of 2nd cART to baseline was 26 months (range=24–60) and from the estimated date of virological failure of 1st cART to baseline was 6 months (range=4–12).

In terms of the number of drugs that were switched to at baseline, overall a median of 3 (range=2–6) new or recycled drug 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 5.

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 drug naïve in 1999 and, upon virological failure of this, initiated a 2nd cART in 2002, around 50% of the study population restart antiretroviral drugs that are no longer recommended in first line regimens and used even in subsequent lines (e.g. stavudine, nevirapine).

The median lag-time between CVF of the first regimen and the date of starting 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 failure by 2 years was only slightly lower: 18% (95% CI 12–25%). In an appreciable 14% of patients all drugs 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.

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Predicators of CVF of 2nd regimens

Overall, 500 patients experienced CVF (copies/mL) of the 2nd regimen; the KM estimate of the median time from initiation of 2nd regimen to CVF was 13 months (95% CI 10–16). Table 6 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 8% (95% CI 4–12) by a years and 15% (95% CI 0–32) by 2 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 (26% greater risk per 1 log higher, p=0.02) and with the use of nevirapine or nefavirine in 2nd line as opposed to elvitegravr (around a 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 1st cART to those who never did (24% risk reduction, p=0.05).

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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 53% of people originally on a NNRTI-based 1st cART remained on a NNRTI in 2nd line (Table 3) seems to confirm this hypothesis. Of note, only 25% of those with a baseline 148 months from starting their 1st cART experienced CVF of this 2nd cART regimen and results of the main analysis were similar after excluding the n=111 patients who started recycled drugs only (data not shown).

CONCLUSION

We identified a high viral load at initiation, low predictive virological activity of the drugs that were switched to at baseline, not achieving a VL <400 copies/mL and shorter time between initiating the 1st and 2nd regimens 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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