Virological response and tolerability on a 2nd cART regimen is worse in patients switching initial cART because of early, compared to late toxicity.

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Introduction

The major reason for changing the initial combination antiretroviral therapy (cART) regimen in HIV-infected patients is toxicity. Although a subsequent new cART regimen may sustain viral replication below detection limits, we previously demonstrated an increased risk of recurrent toxicity in these patients. We now evaluated tolerability, virological response and clinical outcome in patients starting a second cART regimen, after having experienced early, medium-term or late toxicity on their first cART regimen.

Methods

Antiretroviral therapy naïve patients who had switched initial cART because of toxicity either within 3 months of starting (early toxicity), between 3 and 12 months (medium-term toxicity) or ≥1 year (late toxicity) and started a new cART regimen after 1/1/1998 were selected from the Netherlands ATHENA observational cohort. Logistic regression was used to model suppression of plasma HIV-RNA ≤50 copies/ml at 24 weeks after the switch (short-term success). Time from 9 months after the switch to HIV-RNA >500 copies/ml (virological failure), time to toxicity-driven switch on the second regimen, and time from start initial cART to death and new AIDS after the switch were modelled using Cox models. Left truncated models were used when modelling time to death/AIDS to allow for differences in timing of entry in the risk set. Multivariate analyses were adjusted for, amongst others, calendar year, CD4 count and HIV-RNA at the time of switch.

Results

Patients with an early toxicity-driven switch (n=753) were more likely to be male (p=0.0003), infected through heterosexual contact (p=0.003) and younger (p<0.0001) compared to patients with a medium-term (n=505) or late toxicity-driven switch (n=567). Patients with late toxicity were more likely to have plasma HIV-RNA ≤50 copies/ml at the switch (p<0.0001) and to switch without therapy interruption (p<0.0001). The most frequent reason for early and late toxicity-related switches were nausea (12.5%) and lipodystrophy (26.7%), respectively.

Within one year after starting the second regimen, 34.0%, 25.6% and 17.9% of patients with early, medium-term and late toxicity on initial cART, respectively, switched again for toxicity. The adjusted hazard ratio was 1.60 (95% CI 1.32-1.95, p<0.0001) for early vs. late toxicity and 1.18 (0.91-2.48, p=0.11) for medium-term vs. late toxicity.
The percentage of patients with short term virological success was 78.6%, 85.3% and 92.7% in patients switching because of early, medium-term and late toxicity, respectively (p<0.0001). Compared to late toxicity, the multivariate odds ratio for reaching plasma HIV-RNA <50 copies/ml was 0.37 (0.18-0.78, p=0.009) for early and 0.47 (0.23-0.96, p=0.04) for medium-term toxicity. The hazard ratio for virological failure ≥9 months after starting the second regimen for patients with early and medium-term toxicity combined compared to late was 1.53 (0.98-2.38, p=0.06). There were no significant differences in time to death and new AIDS.

Conclusion

Patients with an early toxicity-related switch on initial cART had a poorer virological response and a higher likelihood of a toxicity induced switch of their second cART regimen compared to patients switching because of longer-term toxicity. This did, however, not adversely affect their clinical outcome. These results stress the importance of selecting well tolerated initial cART regimens.