Switch strategies in patients on effective HAART

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To provide the best possible long-term outcomes for patients, a number of strategies have been proposed based on the possibility to switch from a successful protease inhibitor (PI)-based highly active antiretroviral therapy (HAART) to another antiretroviral regimen. The available evidence from clinical trials in virologically controlled patients demonstrates that switching the PI-based HAART to a simplified regimen is safe. However, abacavir-based simplified therapies should be limited to patients with a known drug history who have not undergone prior mono or dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) therapy. Triple NRTI regimens that do not include a thymidine analogue have not been adequately tested so far and are not recommended. The switch strategy may enhance long-term adherence and induce a moderate reduction in cholesterol or amelioration of the total/high-density lipoprotein (HDL) cholesterol ratio that might be particularly relevant for patients presenting other risks for coronary heart disease. Simplified regimens are not associated with a clinically relevant improvement in the redistribution of body fat. Thus, if such a therapeutic strategy is considered, it should be preferably implemented to prevent or delay lipodystrophy. As the therapeutic scenario is significantly changing, in the future, convenience and metabolic alterations will be less of an issue in the decision to use a PI-switch strategy. Future switch strategies may involve NRTIs. Among NRTIs, thymidine analogues and particularly stavudine appear to be most associated with lipoatrophy. NRTI switches may also be beneficial in reducing the risk of lactate level elevation, mitochondrial toxicity, insufficient immunological response to HAART and of selecting class-inducing resistance mutations.

Keywords: HIV, HAART simplification, protease inhibitors, NRTIs, NNRTIs, switch therapy

Introduction

In developed countries the widespread use of antiretroviral agents has made HIV infection a chronic disease. Clinicians caring for patients with HIV must therefore face new problems related to the long-term management of the disease and of a chronic therapy.

The first choice of highly active antiretroviral therapy (HAART) usually consists of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) associated with a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Some PI-based regimens offer potent initial treatment options, but adherence to many of these regimens may be limited because of dietary restrictions, pill burden, adverse events and increased relative risk of morphological change and metabolic disorders.

To provide the best possible long-term outcomes for patients and ensure the three cornerstones of successful antiviral therapy (safety, efficacy and adherence), a number of strategies have been proposed based on the possibility to switch from a successful PI-based HAART to another antiretroviral regimen.

PI substitution and efficacy

A number of comparative clinical studies have explored the effectiveness of switching to a PI-sparing regimen. The ATHENA study group followed 446 patients that either continued an ongoing PI-based therapy or switched the PI to nevirapine. Patients in the nevirapine group had, over a 48 week period, a 5-fold lower risk of failing treatment either because of virological rebound or therapy discontinuation. A second randomized trial studied the possibility to switch an ongoing PI-based therapy to either efavirenz or abacavir. In this case, the follow-up was prolonged to 104 weeks. Virological failure occurred in 10.1% of patients switched to abacavir, in only 2.9% of those in the efavirenz group and in 5.7% of those continuing the PI-based therapy. Although differences were not statistically significant, in the abacavir group, the risk was greater and was explained by the higher failure rate in patients with previous suboptimal exposure to both thymidine analogues and/or lamivudine.

More recently, a meta-analysis of nine randomized controlled studies has confirmed these data. The analysis included a total...
of 833 patients who switched their PI with abacavir, efavirenz or nevirapine. The control group included 616 individuals who continued the PI-based HAART. When compared with this last group, the risk ratio for virological failure was 2.56 (95% CI 1.17–5.64) for abacavir and dropped to 0.83 (95% CI 0.36–1.91) for efavirenz or to 0.54 (95% CI 0.29–1.02) for nevirapine.

The available evidence indicates that the risk of virological failure is increased in patients switched to abacavir who had been exposed to a prior monotherapy or dual therapy with NRTIs.

A virological advantage with NNRTI switch strategies has not been demonstrated although simplified regimens with any of the three studied drugs reduced the risk of discontinuation of therapy for reasons other than virological failure.

**PI substitution and safety**

One of the driving forces that led to the exploration of switch strategies was the need to manage actual or potential adverse events, especially dyslipidaemia, insulin resistance and morphological changes.

As far as the impact on lipid blood levels is concerned, most trials have shown a general beneficial impact, although the effective results could be influenced by the implemented switch strategies.2-6

The NEFA study,7 which compared the substitution of nevirapine, efavirenz or abacavir for a PI in 400 patients with virological suppression, may offer a definitive answer. The proportion of patients with fasting lipid levels requiring lipid-lowering agents was significantly lower in the abacavir group; median fasting total cholesterol levels at each follow-up point were significantly lower in the abacavir group and were significantly less likely to be greater than 240 mg/dL (6.2 mmol/L), when compared with either other group. Despite this, somewhat more favourable effects on high-density lipoprotein (HDL) cholesterol were observed in patients switched to nevirapine or efavirenz.

The impact on triglyceride levels was modest and the median fasting levels did not differ among groups over the follow-up period,7 however, when compared with a continuing PI-based therapy, the mean reduction in triglycerides obtained with switch strategies was significant (−33.62 mg/dL, 95% CI −50.44 to −15.92; −0.38 mmol/L, 95% CI −0.57 to −0.18).3

Switch studies have failed to show significant benefits on lipaccumulation2,5,7 or have obtained contrasting results.6,8 Most studies addressing the problem of fat maldistribution reported a progression of fat loss after switching to non-PI-based regimens.6,8

Considering the whole range of drug-related adverse events that could lead to treatment discontinuation or change, all studies demonstrated how maintaining the PI-based HAART was a greater risk. The relative risk for patients continuing a PI-based therapy compared with those switched to efavirenz was 2.21 (95% CI 1.10–4.39) and was 2.71 (95% CI 1.29–5.66) if compared with patients switched to abacavir.3 In the NEFA study,7 the discontinuation rate due to adverse events was similar (17%) for patients switched to efavirenz or nevirapine and was significantly higher than that observed in patients receiving abacavir (6%).

**Switching for simplicity**

The idea of simplification is naturally correlated with switch strategies that explored the change from non-boosted PI-based HAART to any NNRTI combination or to triple NRTI regimens. In general, the aim was to reduce tablet load to a minimum, remove food restrictions and establish simple once- or twice-daily dosing. All studies based on the simple switch from a PI to an NNRTI or to abacavir without any change of the ongoing NRTI backbone induced de facto a simplification of the therapeutic regimen. Simplification was generally consistent as far as the daily pill burden is concerned and much less pronounced in terms of daily doses.

Two studies8,10 explored the possibility to switch to a single class fixed combination of drugs (zidovudine/lamivudine/abacavir) modifying both the NRTI backbone and the third agent of the ongoing therapy. In both studies, the regimen’s third agent was abacavir and the results both in terms of efficacy and tolerability were similar to those of previously described trials on abacavir simplification not involving a change of the NRTI backbone.

More recently, a once-daily regimen with didanosine, emtricitabine and efavirenz was evaluated.11 The Alize study enrolled 355 patients who were followed for 48 weeks. Results demonstrated a significantly higher virological efficacy of the switch arm and a similar tolerability outcome. Results highlighted how switching therapy also had potential benefits with regard to supporting adherence. Self-reported adherence rates (defined as 100% adherence) were significantly higher in the once-daily group (82%) compared with the PI control group (63%). These data confirm previously reported observations on how the lower number of pills in the regimen and a compact dosing schedule could enhance adherence.2,11

**Where are we now?**

The available evidence from clinical trials in virologically controlled patients demonstrates that switching the PI-based HAART to a simplified regimen is safe, but there are strong indications of an increased risk of virological failure for patients with previous exposure to suboptimal NRTI therapy. This risk seems to be particularly relevant for patients switching therapy to abacavir. Therefore abacavir-based simplified therapies (three NRTIs including a thymidine analogue) should be limited to patients with a known drug history who have not undergone prior mono or dual NRTI therapy.

Triple NRTI regimens that do not include a thymidine analogue have not been adequately tested, so far, as switch alternatives. Moreover they have shown particularly poor efficacy as first-line therapy. Thus they should not be recommended.

The switch strategy may induce a moderate reduction in cholesterol or amelioration of the total/HDL cholesterol ratio that might be particularly relevant for patients presenting other risk factors for coronary heart disease.

Available trials do not provide convincing evidence that switching from a PI to a simplified regimen is associated with a clinically relevant improvement in the redistribution of body fat. Thus, if such a therapeutic strategy is considered, it should be preferably implemented to prevent or delay lipodystrophy.

Indications exist that seeking simplicity may enhance long-term adherence of patients to HAART.
Future perspectives

The introduction of new compounds and the use of PIs according to boosted schedules have lowered pill burden of PIs and, in some cases, have allowed once-daily regimens and lowered the risk of metabolic toxicity. The therapeutic scenario is significantly changing and in the future, convenience and metabolic alterations will be less of an issue in the decision to use a PI-switch strategy.

Progress in understanding the pathogenesis of metabolic complications, including lipodystrophy, has led to the recognition of the aetiological effect of some NRTIs. Among NRTIs, thymidine analogues and particularly stavudine appear to be most associated with lipodystrophy. Substitution of thymidine analogues with abacavir induced limb fat gain and increments in arm, leg and trunk fat between 12% and 35%, with no significant effect on viral load, fasting lipid profile, or glucose or lactate levels.

NRTI switches may also be beneficial in reducing the risk of lactate level elevation and, potentially, lactic acidosis as data are accumulating suggesting that not all NRTIs or NRTI combinations influence mitochondrial activity to the same extent.

NRTI switches could also be considered in the case of insufficient immunological response to HAART if preliminary data are confirmed indicating a more pronounced immune recovery in the absence of thymidine analogues.

A careful sequencing and switch strategy within the NRTI class could finally be used to minimize the risk of selecting class-inducing resistance mutations. As more compact once-daily formulations of agents of this class become available, it is likely that an inter-class switching approach will become more widespread.

Conclusions

With the advent of additional new antiretroviral drugs and drug classes, individualized HAART to optimize tolerance, efficacy and adherence should become standard. The regimen choice will remain a constant effort to balance risks and benefits. Simple regimens best fitting patients’ needs and requests will be a relevant part of the therapeutic armamentarium as well as simplifying switch strategies that will, however, probably not be limited to PI-switch alone.

The chronic management of antiretroviral therapy will include regular and frequent fine-tuning through regimen modification.

References


