Protease inhibitor-sparing simplified maintenance therapy: a need for perspective

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Body fat changes and metabolic abnormalities such as hyperlipidaemia and diabetes have been increasingly reported following the successful introduction of highly active antiretroviral therapy (HAART). These side effects were attributed initially to the use of protease inhibitors (PIs). As a consequence, a series of trials were conducted where patients with well-controlled HIV viraemia either continued on PIs or were switched to a simplified maintenance therapy (SMT) without PIs. Evidence from these trials is still insufficient to show that switching from PIs to either abacavir, nevirapine or efavirenz is safe. However, patients with suboptimal pre-HAART treatment are at increased risk of virological failure if switched to an SMT. Patients switched from PI regimens tend to stay longer on an SMT and those switched to abacavir show a reduction in total cholesterol, but there is no evidence of any additional benefit from non-PI-based SMT. There is a clear need for a better understanding of HAART-related lipodystrophy and metabolic toxicity, and pharmacogenetic tests to identify those patients most at risk. The advent of simpler formulations for all drug classes, and new PIs with less metabolic toxicity, is likely to reshape completely the role of SMT.

Keywords: antiretroviral therapy, metabolic toxicity, treatment failure

Introduction

Highly active antiretroviral therapy (HAART) has led to a dramatic improvement in the survival of HIV-infected individuals in resource-rich countries. In these countries, issues of chronic disease management and long-term drug toxicity have become the central focus of clinicians caring for those with HIV. Five years ago, changes in body fat and lipid metabolism, now commonly known as lipodystrophy, were first described in patients receiving protease inhibitors (PIs).1 These changes are characterized by facial or peripheral lipoatrophy and central lipohyper trophy, metabolic disorders with increases in cholesterol and triglycerides, increased lactate and blood glucose and increased insulin resistance.

An association between stavudine and lipoatrophy has been found in several clinical trials and in one well-designed prospective cohort study.2-3 PI-based regimens have been associated with increased blood lipids in cross-sectional studies.4 However, because of study-design limitations (cross-sectional or retrospective cohort studies), inconsistencies in the definition of lipodystrophy, and the number of possible antiretroviral drugs and drug combinations, so far it has been impossible to give a more definitive hierarchy of responsible drugs or drug classes in a causal pathway leading to lipodystrophy.

PIs may promote lipodystrophy when they bind to the catalytic site used by HIV protease, by inhibiting lipid and adipocyte regulatory proteins that also partially use this site.5 In addition, in vitro studies have shown that PIs can inhibit the differentiation of premature adipocytes, which may in turn lead to decreased storage of triglycerides, insulin resistance and apoptosis. PIs have been associated with elevated blood lipids and insulin resistance.6 For example, ritonavir use for 2 weeks in volunteers without HIV led to increases in cholesterol and triglycerides.6 There is increasing evidence that nucleoside analogue reverse transcriptase inhibitors (NRTIs) lead to mitochondrial toxicity and this may be associated with some types of lipoatrophy. NRTIs may inhibit adipogenesis and stimulate lipolysis; and in vitro studies show that they may have synergistic effects with PIs.6 In addition, NRTI use is associated with a variety of other side effects of mitochondrial toxicity, such as hyperflectaemia, liver steatosis, myopathy and peripheral neuropathy.

Rationale of PI-sparing simplified maintenance therapy (SMT)

Concerns about the long-term risk of cardiovascular disease from these metabolic disorders have been confirmed by the DAD.
Effect of SMT on HIV-1 viral suppression

In a meta-analysis of randomized controlled trials, we identified nine trials that compared continued PIs versus a switch to an SMT, using either abacavir (three trials), efavirenz (three trials) or nevirapine (two trials). In an additional trial, individuals were randomly switched from PIs to either efavirenz or nevirapine. Three trials were conducted in patients with lipodystrophy at baseline. The analysis included 833 individuals treated with an SMT and 616 individuals treated with continued PI-based therapy. Compared with continued PIs, the risk ratio for virological failure in abacavir trials was 2.56 (95% CI 1.17–5.64), in efavirenz trials 0.83 (95% CI 0.36–1.91) and in nevirapine trials 0.54 (95% CI 0.29–1.02). In a post-hoc subgroup analysis of trials with abacavir, we were unable to show or rule out that the increased risk of virological failure under SMT with abacavir was associated with prior suboptimal mono or dual NRTI therapy. In two abacavir trials with information on baseline resistance testing, there was no clear pattern to suggest that patients with virological failure had genotypic resistance at the time of switching. No difference in the mean change in CD4 cells was found for SMT with any of the three drugs compared with continued PIs (−17 CD4 cells/mm³, 95% CI −46 to 11). However, treatment discontinuation for any reason other than drug failure was much less likely with SMT (risk ratio 0.61; 95% CI 0.48–0.77). Convenience and a better tolerance of SMT were the main reasons for the lower discontinuation rate.

These findings are in line with a trial by Martinez et al., where all patients on PIs were switched to either abacavir, efavirenz or nevirapine. There was no difference between the three groups in the rate of progression to virological failure, AIDS or death. In a post-hoc subgroup analysis, the hazard rate for virological failure in patients with prior suboptimal mono or dual NRTI therapy was 3.76 (95% CI 1.53–9.23), with the highest failure rate in the abacavir group.

The available evidence from clinical trials is insufficient to show that switching to SMT is safe, but there are indications of an increased risk of virological failure for patients with prior suboptimal NRTI therapy. This risk seems to be highest for patients on SMT with abacavir. For this reason, a switch to abacavir should be reserved for patients with a known drug history who have not undergone prior mono or dual NRTI therapy. Preliminary data from the Eurosidia cohort suggest a higher risk of virological failure in patients with prior suboptimal NRTI therapy taking abacavir or nevirapine compared with those taking efavirenz: patients taking abacavir are at higher risk than those taking nevirapine. However, in pre-HAART naive patients, there was no difference among the three drugs.

Effect of SMT on metabolic parameters

In our meta-analysis, the difference in absolute mean cholesterol for SMT compared with continued PIs was −0.15 mmol/L (95% CI −0.40 to 0.09), suggesting a trend towards lower cholesterol levels in patients taking SMT. In planned subgroup analyses, the difference in cholesterol for SMT with abacavir was −0.51 mmol/L (95% CI −0.70 to −0.33), with efavirenz 0.22 mmol/L (95% CI 0 to 0.43) and with nevirapine −0.19 mmol/L (95% CI −0.48 to 0.09) compared with continued PIs. The difference in absolute mean triglycerides for SMT compared with PIs was −0.38 mmol/L (95% CI −0.57 to −0.18).

Trials using different switch protocols have confirmed a moderate cholesterol reduction when switching from PIs to abacavir. The reduction in cholesterol seen with abacavir is clinically important and is particularly relevant for HIV-infected patients with established coronary heart disease or multiple cardiovascular risk factors.

Effect of SMT on lipodystrophy

Several trials have used dual X-ray absorptiometry (DEXA) to compare changes in peripheral and central body fat distribution between continued PI-based regimens and a switch to an SMT. In two trials, no difference in fat distribution was seen after switching to nevirapine or efavirenz. Two additional trials investigated switches from PIs to a combination of abacavir, nevirapine, adeovir and hydroxyurea or to abacavir. Patients switching showed a decrease in limb, subcutaneous abdominal and intra-abdominal fat mass in one trial, and a moderate increase in leg and arm fat in the other trial. Given the different protocols, open trial design possibly without blinded outcome assessment of DEXA, and the short follow-up time, these trials do not provide convincing evidence that switching from PIs to SMT is associated with a clinically relevant improvement in the redistribution of body fat. And two trials switching antiretroviral drugs because of lipodystrophy failed to show any improvement in body fat redistribution that was considered relevant by patients.

The future of SMT

Continued advances in therapy over the last decade have justified the initial optimism for second- and third-generation antiretroviral drugs. Recent potent PIs, such as boosted lopinavir or saquinavir, are effective even against medium-resistant isolates. Even more potent drugs are desirable, but the potency of drugs is already fairly high in patients naive to therapy, especially when adherence is optimal. Therefore, the focus of antiretroviral drug development may shift towards drugs with fewer side effects and towards drugs that are easier to take. With the advent of additional antiretroviral drugs and drug classes, individualized antiretroviral therapy to optimize tolerance and adherence should become standard. The introduction of new drug compounds and boosted PI regimens should allow PIs to be used with a lower pill burden in once-daily regimens and with lower risk of metabolic toxicity. Therefore, convenience and metabolic toxicity will be less of an issue in the decision to switch PIs in the future.
As yet, there is little evidence from clinical trials on the efficacy and safety of PI and non-PI once-daily regimens. Further clinical trials are needed to address this question, and in particular in patients with known adherence problems. Significant progress has been made in understanding the pathogenesis of lipodystrophy and its associated metabolic disorders. However, basic research, pharmacogenetics and long-term prospective cohort studies are needed to understand better the role of different drugs and drug classes in the development of lipodystrophy and to define better those individuals most at risk. Given the potency of some boosted PIs and the potential to identify patients with a genetic predisposition towards lipodystrophy, PI monotherapy may be a valid option in the future for some patients. Such potent monotherapies could have lower toxicity—meanwhile keeping other therapy options in reserve in case of drug resistance. The spread of resistant viral strains will re-emphasize the importance of very potent simple regimens and of the need to think carefully about future therapy options for our patients.

Conclusions

The decision to switch patients with well-controlled HIV-1 viraemia from a PI to a non-PI regimen should be individualized based on issues of tolerance, risk for cardiovascular disease and convenience. Future therapy options should always be borne in mind when switching therapy. The introduction of new PIs with less metabolic toxicity and a low pill burden will further reduce the need to switch PIs. Current evidence suggests that switching from PIs to an SMT may be safe, more convenient and may reduce future therapy changes. However, switching from PIs to abacavir should be reserved for patients with a known drug history and no prior suboptimal mono or dual NRTI therapy; otherwise the risk of viral rebound is increased. Switching to abacavir leads to a clinically relevant reduction of hypercholesterolaemia and can be considered in patients at substantial risk of coronary heart disease (e.g. 20% 10 year risk or higher of a coronary event). For patients with well-controlled HIV viraemia, there is little evidence of any further advantage that would justify a switch from a PI to a non-PI regimen.

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