Benefits and concerns of simplification strategies in HIV-infected patients

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Highly active antiretroviral therapies (HAART) provide sustained viral control in most patients, but many of these regimens are restricted by complex dosing, drug–drug interactions and toxicities. Numerous strategies of simplified treatment have been explored in order to improve patient quality of life and adherence to treatment, as well as to manage drug-related toxicities while maintaining viral suppression. The first simplification strategy involved switching from protease inhibitors (PIs) to non-nucleoside reverse transcriptase inhibitors (NNRTIs), with an additional benefit on lipid metabolism. The development of once-daily drugs or co-formulated combinations has successfully been used to further simplify treatment. However, studies assessing triple nucleoside regimens have shown a higher frequency of viral failure in comparison with standard HAART, mainly in patients with previous sequential suboptimal treatments. Finally, NRTI-sparing approaches, consisting of NNRTI + PI combinations or monotherapies with boosted PIs, are alternatives to avoid NRTI-related mitochondrial toxicities. An accurate analysis of each patient’s history will be necessary in each case to determine whether a simplification strategy is appropriate.

Keywords: HIV-infection, antiretroviral therapy, simplification strategies, efficacy, safety

Introduction

The chronic nature of HIV-infection usually requires lifelong therapy, and the benefit of treatment is closely related to high drug adherence.1,2 However, high pill burden, dietary restrictions and treatment-related toxicities are factors that are likely to compromise long-term adherence.

As a result, numerous strategies of simplified treatment have been explored in order to improve patient quality of life and adherence to treatment, as well as to manage drug-related toxicities while maintaining viral suppression.

The first strategy developed to simplify these regimens was to switch protease inhibitors (PIs) to non-nucleoside reverse transcriptase inhibitors (NNRTIs), offering a substantial reduction in the number of pills per day, as well as an improvement in PI-related metabolic alterations.

A secondary step was the development of once-a-day strategies thanks to the availability of once-daily antiretroviral drugs.

Finally, the introduction of co-formulated, fixed-dose nucleoside combinations such as abacavir/lamivudine/zidovudine (Trizivir®), lamivudine/zidovudine (Combivir®) or the new abacavir/lamivudine (Epzicom®, Kivexa®) and emtricitabine/tenofovir (Truvada®) has increased the options for easy dosing. More recently, some triple nucleoside combinations have been used alone as PI- and NNRTI-sparing regimens.

NRTI-sparing regimens such as PI plus NNRTI combinations or PI-boosted monotherapies (lopinavir/ritonavir) could reduce the incidence of mitochondrial-related toxicities, although such approaches do not always reduce the number of pills or daily doses.

We describe the results of some of the most relevant simplified studies carried out since the introduction of highly active antiretroviral therapy (HAART).

1. Simplification from PI approaches (Table 1)

The principal goal of PI-sparing approaches is the maintenance of viral suppression with simpler regimens, reducing the number of pills and increasing patient quality of life. Additionally, many of these combinations are able to reduce drug-related toxicities, such as lipodystrophy and cardiovascular risk factors, which is especially important in the current HIV-infected population, whose life expectancy is rising.

At the end of the 1990s, many studies were conducted to assess these issues. In this section, we describe in more detail the results from some of the most relevant trials, either because of the large sample size or the long follow-up period, as well as our own experience in this field. Other trials are summarized in Table 1.

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Leading article

Table 1. Simplification from PIs to NNRTIs

<table>
<thead>
<tr>
<th>Author</th>
<th>Study treatment</th>
<th>Study design</th>
<th>Study population (n)</th>
<th>Follow-up (weeks)</th>
<th>Viral rebound (%)</th>
<th>Cholesterol levels</th>
<th>Triglyceride levels</th>
<th>Body shape</th>
<th>QoL</th>
</tr>
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<tr>
<td>Becker</td>
<td>EFV or PI</td>
<td>rand.</td>
<td>EFV: 226, PI: 120</td>
<td>48</td>
<td>EFV: 3 / PI: 10</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Raffi</td>
<td>NVP or EFV</td>
<td>observ.</td>
<td>NVP: 63, EFV: 10</td>
<td>82</td>
<td>13.7 (global)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Ruiz</td>
<td>NVP or PI</td>
<td>rand.</td>
<td>NVP: 52, PI: 54</td>
<td>48</td>
<td>NVP: 9.6 / PI: 5.5</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Negredo</td>
<td>NVP, EFV or PI</td>
<td>rand.</td>
<td>NVP: 26, EFV: 25, PI: 26</td>
<td>48</td>
<td>NVP: 4 / EFV: 8</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

NVP, nevirapine; EFV, efavirenz; ABC, abacavir; PI, protease inhibitor; QoL, quality of life; rand., randomized; observ., observational; ↓, unchanged; ↑, increased; ↓, decreased.

(i) One of the switching trials published with a large sample is the NEFA study. A total of 498 PI-treated patients were randomly assigned to replace the PI with efavirenz, nevirapine or abacavir. Results at 48 weeks of follow-up showed a greater proportion of viral rebound in the abacavir arm (7%, 5% and 14%, respectively; P = 0.003). However, despite the virological differences among groups, similar results in the ITT analyses were detected since adverse events were less frequent in the abacavir arm (P = 0.006). In the multivariate analyses, viral rebound was related to a suboptimal previous mono or dual therapy with NRTIs. The proportion of patients with abnormal triglyceride and cholesterol levels was lower in the abacavir group (P = 0.05 and P < 0.001, respectively), but no changes in lipodystrophy were detected at 48 weeks of follow-up.

(ii) The DMP266-049 study investigated the efficacy of efavirenz-based regimens, comparing patients who switched from PI to efavirenz (n = 226), with others who continued their PI strategy (n = 120). Final results at 48 weeks of follow-up showed that 84% of patients in the efavirenz arm maintained viral suppression with respect to 73% in the PI arm (P = 0.026).

(iii) Results from the Maintavir study showed similar antiviral efficacy even after a longer follow-up (a median of 82 weeks) in the same patient setting. In this trial, 63 patients switched the PI-containing therapy to nevirapine-based approaches and 10 to efavirenz. Viral rebound was detected in 13.8% of the patients at 72 weeks of follow-up. Regarding lipid profile, triglyceride levels significantly improved in both groups (from 2.6 to 1.7 mmol/L at 24 weeks; P = 0.03).

(iv) Our group carried out a prospective, randomized, controlled study including patients with viral suppression and lipodystrophy who were randomized to maintain the same PI regimen (n = 54) or to switch to a nevirapine-containing approach (n = 52). Results at 48 weeks of follow-up showed a similar antiviral potency between both arms (79% in the nevirapine group versus 77% in the control group) and an amelioration of lipid abnormalities in the nevirapine arm (P < 0.05). Nevertheless, no improvement in body-shape composition was detected after the switch. In addition, subjects in the nevirapine arm reported a better quality of life index than controls (P < 0.001).

(v) Another simplification study conducted by our team compared the continuation of PI-based regimens with a switch to either a nevirapine or an efavirenz combination. A similar antiviral potency was observed among groups at week 48 but an improvement in lipid profile was seen only in NNRTI-containing arms. However, it must be noted that these strategies are not free of adverse events, specifically liver toxicities and CNS symptoms, although all studies showed a low incidence of severe toxicities.

In summary, these and other studies have been able to establish the non-inferiority of NNRTIs (nevirapine or efavirenz) with respect to PIs in terms of antiviral potency, as a component of simplification therapy. Additionally, most of them showed an improvement in lipid profile, especially with the use of nevirapine. However, no changes in lipodystrophy were seen in those studies that included subjective or objective body composition evaluations.

2. Once-daily strategies (Table 2)

Currently, many antiretroviral drugs are licensed for once-daily use; four NRTIs (didanosine, lamivudine, emtricitabine and tenofovir), the NNRTI efavirenz and two boosted PIs (atazanavir and fosamprenavir). Likewise, pharmacokinetic or clinical studies also support the use of once-daily abacavir, nevirapine, lopinavir/ritonavir, indinavir and saquinavir.

These consistent results have led investigators to assess the clinical efficacy and safety of different once-daily combinations. Although these regimens initially included NNRTIs, other trials have more recently demonstrated the efficacy of some ritonavir-boosted PIs used in once-daily-based regimens, mainly atazanavir but also fosamprenavir or lopinavir/ritonavir.

(i) Molina et al. performed a once-daily combination study of 48 weeks of follow-up. A total of 355 HIV-1-infected adults with suppressed viral load were randomly assigned...
to maintain the PI regimen \((n = 177)\) or switch to emtricitabine, didanosine and efavirenz \((n = 178)\). At the end of the study, the proportion of patients with a viral load of <50 copies/mL was higher in the once-daily group \((87\%)\) than in the PI group \((79\%), \text{ } \(P < 0.05\)). The number of patients who suffered adverse events was similar between groups \((10\% \text{ as compared with } 9\%, \text{ respectively; } P = 0.8)\), although the once-daily arm showed a better lipid profile with respect to HDL-cholesterol levels compared with the PI group \((P < 0.0001)\).

(ii) Similarly, our group observed comparable antiviral potency at 48 weeks in the once-daily study\(^{17}\) when comparing a once-daily regimen \((\text{didanosine, tenofovir and nevirapine, } n = 85)\) with twice-daily regimens \((n = 84)\). All patients who continued the same twice-daily regimen maintained viral suppression in comparison with 97% of those who switched to the once-daily regimen \((P = 0.497)\). Nonetheless, more patients from the once-daily arm discontinued therapy due to adverse events, especially hepatotoxicity \((P = 0.03)\). In contrast, this group showed a decline in the prevalence of hyperglycemia during follow-up, from 37.6% of patients at baseline to 20.6% at 24 weeks \((P = 0.012)\) and to 24.6% at 48 weeks \((P = 0.097)\).

(iii) Nevertheless, a paradoxical decrease in CD4+ cell counts was seen in patients who received full doses of didanosine, tenofovir and nevirapine despite the maintenance of viral suppression.\(^{18,19}\) This finding has been explained by the lymphotoxicity caused by the pharmacokinetic interaction between didanosine and tenofovir. It is important to keep these data in mind since this nucleoside combination could be an excellent option as part of a once-daily regimen. Thus, the use of both drugs in combination \(\text{(always at recommended reduced doses of didanosine) should be always carefully considered and only used when other alternative combinations are not available.}\)

(iv) The Swan study\(^{14}\) is one of the first studies that has evaluated the efficacy of a PI, atazanavir, as part of a simplification regimen. Subjects with an undetectable viral load and stable boosted PI-containing strategies were allocated to remain on the same therapy \((n = 133)\) or to switch to atazanavir/ritonavir \((n = 274)\). Results at 48 weeks of follow-up demonstrated a lower rate of viral rebound in the atazanavir arm with respect to the control arm \((7\% \text{ versus } 16\%; \text{ } P < 0.01)\). In addition, non-HDL-cholesterol levels improved significantly in the atazanavir group \((\text{a decrease of } 18\% \text{ versus } 3\%, \text{ } P < 0.0001)\).

3. Triple NRTI approaches (NNRTI/PI-sparing regimens) (Table 3)

New PI- and NNRTI-sparing strategies aim to decrease metabolic disturbances and other PI- and NNRTI-related toxicities, as well as to improve adherence and reduce the economic cost of antiretroviral treatment. We describe some of the most relevant published clinical studies. Other studies are also summarized in Table 3.

3.1 Simplification to ABC-containing regimens\(^{12,20-25}\)

(i) The ESS40013 study\(^{20}\) was a multicentre, open-label trial that involved 40 hospitals and 448 antiretroviral-naive patients. Participants started antiretroviral treatment with three NRTIs, including abacavir, plus efavirenz, and after 48 weeks were randomized to continue receiving the same treatment or to discontinue efavirenz. Results at 96 weeks of follow-up \((48 \text{ weeks from the simplification of treatment})\) demonstrated the non-inferior antiviral efficacy of triple nucleoside treatment versus quadruple therapy including efavirenz \((77\% \text{ versus } 79\% \text{ of viral suppression}; \text{ } P = 0.697)\), without differences regarding time to treatment failure, and with a similar continuous immunological recovery.

(ii) The SimplifiHAART study\(^{21}\) randomly allocated virologically suppressed patients on a first PI- or NNRTI-containing treatment to switch to Trizivir\(^{b} \text{ ( } n = 68 \text{ ) or to Combivir}^{b} \text{ plus nevirapine ( } n = 66 \text{ ). Results at 48 weeks of follow-up showed equal viral control in both arms (71\% versus 73\%; } P = 0.783)\). Both groups achieved a significant improvement in lipid profiles, but with a higher increment of HDL-cholesterol levels in those subjects who changed to Combivir\(^{b} \text{ ( } P = 0.023)\). In addition, the effort to take medication index was also better in the Trizivir\(^{b} \text{ group with respect to the nevirapine arm ( } P < 0.001).\)

(iii) The Trizal study\(^{22}\) was a simplification study involving 209 patients who were randomized to maintain their PI- or NNRTI-containing strategy, or to switch to Trizivir\(^{b} \text{. At 48 weeks of follow-up, } 22\% \text{ of patients in each group suffered viral rebound. The number of adverse events was similar between groups (35\% in the switch arm and 29\% in the control arm). Once again, patients on Trizivir\(^{b} \text{ therapy showed an additional metabolic benefit, with a significant decrease in triglyceride levels ( } P = 0.006) \text{ and total cholesterol ( } P < 0.001).\)
on efavirenz- or nevirapine-containing strategies. Viral rebound was correlated with previous suboptimal sequential NRTI treatments, as Martinez et al.3 also concluded in the NEFA study.

3.2 Simplification to other NRTIs/N(t)RTI backbone

Other triple nucleoside combinations, mainly containing didanosine and tenofovir but not abacavir, have been used as simplification strategies. However, recent studies have demonstrated an early virological failure with some of these nucleoside combinations in antiretroviral-naive patients.26–30

(i) One of these trials is a pilot study26 that included 22 antiretroviral-naive patients with a median plasma viral load at baseline of 4.91 log10 and 133 cells/mm3 CD4+ count, who initiated a once-daily combination consisting of tenofovir, didanosine and lamivudine. At week 12, 20 patients (91%) discontinued treatment due to incomplete viral suppression. The median time of viral failure was 16 weeks (range: 7–23). Resistance testing showed the emergence of the M184V/I mutation in all of them (100%), and K65R in 10 (50%).

(ii) A second study,30 also in naive patients, confirmed these results but in this case the antiretroviral combination included an NNRTI. This study, which compared two once-daily combinations (efavirenz, didanosine and lamivudine or tenofovir) in 77 patients, was discontinued at 12 weeks of follow-up due to a significant increase in viral failure in the tenofovir arm [5 out of 41 patients from the tenofovir group (12.2%) compared with 0 out of 36 in the lamivudine group]. Patients with viral failure had baseline CD4 cell counts fewer than 200 cells/mm3, baseline viral load greater than 100 000 copies/mL and had developed early NNRTI-related resistance mutations.

Simultaneously, similar results have been observed with triple nucleoside combinations as simplification approaches.

(i) An observational, retrospective study31 included 55 virologically suppressed patients who switched from a HAART regimen to two NRTIs plus tenofovir. The main reason...
for switching was toxicity. Sixty-five percent of patients had previously received suboptimal, sequential NRTI therapies or had failed with a lamivudine-based strategy. After 24 weeks of follow-up, only 31% of the patients continued exhibiting viral suppression. The poorest viral response was associated with didanosine [only 1 out of 21 patients receiving didanosine (5%) maintained viral suppression, as compared with 16 out of 34 without didanosine (47.1%); \( P = 0.001 \)], and the best viral control was associated with zidovudine (75% versus 27%, respectively; \( P = 0.083 \)), followed by stavudine and lamivudine, although few patients were included in these study arms. Multivariate analyses confirmed that the didanosine plus tenofovir combination was the only variable associated with a high probability of viral failure (odds ratio: 17.7; 95% confidence interval: 2.1–147; \( P = 0.007 \)).

In conclusion, triple nucleoside combinations including abacavir seem to be good alternatives as simplification strategies, but only in patients with no previous suboptimal nucleoside exposure or previous failure with these nucleosides. On the other hand, other triple NRTI combinations have been associated with poor virological response, especially when didanosine and tenofovir are used in combination.

4. Other strategies: NRTI-sparing approaches (Table 4)

Although NRTI-sparing strategies are not always simplification strategies, we wanted to highlight the possible benefits of these regimens in terms of reducing mitochondrial-related toxicity associated with NRTIs.

Table 4. Simplification to NRTI-sparing approaches

<table>
<thead>
<tr>
<th>Author</th>
<th>Study treatment</th>
<th>Study design</th>
<th>Study population (n)</th>
<th>Follow-up (weeks)</th>
<th>Viral rebound (%)</th>
<th>Cholesterol levels</th>
<th>Triglyceride levels</th>
<th>Body shape</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negredo32</td>
<td>LPV/rtv + NVP or LPV/rtv + NRTIs</td>
<td>rand.</td>
<td>LPV/rtv + NVP: 16</td>
<td>48</td>
<td>LPV/rtv + NVP: 0</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>–</td>
</tr>
<tr>
<td>Allavena33</td>
<td>LPV/rtv + EFV + NRTIs</td>
<td>cohort</td>
<td>LPV/rtv + NRTIs: 15</td>
<td>48</td>
<td>LPV/rtv + NRTIs: 0</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>–</td>
</tr>
<tr>
<td>López-Cortes34</td>
<td>SQV/rtv + EVF</td>
<td>open label</td>
<td>42</td>
<td>60</td>
<td>29%</td>
<td>HDL-cholesterol ↑</td>
<td>– subjective ↑</td>
<td>↓</td>
<td>–</td>
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<td>Arribas11</td>
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<td>LPV/rtv: 21</td>
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<td>↓</td>
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<tr>
<td>Vernazza35</td>
<td>ATZ monotherapy pilot</td>
<td>control arm: 0</td>
<td>LPV/rtv + NRTIs: 21</td>
<td>24</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

LPV/rtv, lopinavir/ritonavir; SQV/rtv, saquinavir/ritonavir; NVP, nevirapine; NRTIs, nucleoside reverse transcriptase inhibitors; EFV, efavirenz; ATZ, atazanavir; rand., randomized; ↓, unchanged; ↑, increased; ↓, decreased.
atazanavir/ritonavir monotherapy, only one patient suffered viral rebound after 24 weeks from change.

Conclusions

The ideal candidate

The ideal candidate for simplification of antiretroviral therapy would be the patient on a HAART regimen who presents viral suppression, mainly those subjects receiving highly complex combinations, or those presenting antiretroviral-associated toxicities, factors that can diminish antiretroviral adherence and patient quality of life. Many simplification studies have demonstrated an increase in quality of life after the simplification of patients' drug regimens.6,17,21

Additionally, NNRTI-based strategies should be only offered to patients without NNRTI-related mutations, excluding those with previous viral failure or poor drug adherence during an NNRTI-containing regimen. Similarly, simplification to a triple nucleoside approach (Trizivir6) would not be recommended for patients with a history of suboptimal nucleoside combinations, intolerance or resistance to any of the components of the regimen.

The ideal scenario

Candidates for simplification strategies must have good drug adherence since these combinations frequently include antiretroviral drugs with a low genetic barrier, like NNRTIs or some NRTIs. This is especially important when the combination includes antiretrovirals with a short half-life and, even more, when these drugs are combined in a once-daily regimen. In these cases, the loss of a dose probably means suboptimal drug plasma concentrations.

For these reasons, this consideration must be extensively analysed prior to the recommendation of one of these approaches, considering the socio-psychological characteristics of the patient, as well as schedule, employment or other factors that may have a negative impact on treatment adherence. Counselling, preceding the antiretroviral switch, and a regular follow-up of adherence and drug tolerance thereafter will favour successful therapy. It is important to remember that intolerance or toxicity of antiretroviral drugs is one of the most frequent causes of inadequate adherence.

On the other hand, simplified strategies would be also a recommendable approach when close control of drug intake is necessary (directly observed therapy; DOT).

The ideal antiretroviral combination

Considering all of the data reported about strategies of simplification, a simplified antiretroviral combination requires careful selection of drugs. It is necessary to consider the patient's previous antiretroviral treatment, the intrinsic potency of the drugs, toxicity and drug–drug interactions. Moreover, the ideal combination should take into consideration the future salvage therapies in case of viral rebound. Thus, an antiretroviral combination must be selected individually for each patient since a unique ideal combination does not exist.

Regarding antiviral efficacy, multiple studies have shown the non-inferiority of NNRTI approaches with respect to PI regimens in terms of antiviral potency in a simplification setting.6-7 However, a disadvantage of NNRTIs are their low genetic barrier that requires patients to achieve high adherence levels as well as to carefully take this drug with a potent non-resistant NRTI backbone.69 Conversely, triple nucleoside combinations, sparing PIs and NNRTIs, are associated with a 2-fold higher risk of viral failure in subjects in whom mutations pre-exist in the reverse transcriptase gene.23 Only Trizivir6 may be an alternative, but just for those patients who had never received suboptimal nucleoside combinations or without history of viral failure with the use of NRTIs.21,22 Triple NRTI approaches including didanosine and tenofovir have been correlated with a high risk of viral rebound, in the context of previous suboptimal treatments or in antiretroviral-naive patients.26-31

Regarding antiretroviral-related toxicity, the interruption of a PI-based regimen and the introduction of an NNRTI-containing regimen frequently lead to a significant amelioration of metabolic abnormalities. On the contrary, most of the studies agree with the lack of benefit of this strategy in lipodystrophy,6 probably due to the maintenance of NRTIs, the short follow-up that may not be enough to permit changes in body-shape composition, in case of reversibility, and/or the multifactorial aetiology of the syndrome.

But NNRTIs are not exempt from specific toxicities. Liver damage is the most common nevirapine-associated toxicity, being more frequent in patients co-infected with hepatitis B and/or C viruses, subjects carrying the HLA-DRB1*0101 haplotype and women with CD4+ counts above 250 cells/mm³, due to a hypersensitivity syndrome.37 Cutaneous reactions and severe liver toxicity typically occur during the first weeks of therapy and may be more likely to take place in patients with low CD4+ counts and more advanced stages of HIV infection.38 On the other hand, efavirenz use could be discouraged in patients with previous or current psychiatric disease or drug or alcohol abuse because of the CNS disturbances linked to efavirenz.39

With respect to NRTI-based strategies, despite the fact that these drugs do not require any dietary restrictions and exhibit an easy dosage, they are not free from disadvantages. For example, hypersensitivity reactions associated with abacavir in patients presenting the HLA-B*5701 genotype led to its discontinuation.40 Certain combinations including stavudine and didanosine are associated with a higher risk of lipatrophy, and a drug–drug interaction has been demonstrated between didanosine and tenofovir, which are associated with a higher toxicity including lymphocyte toxicity and CD4+ count decrease,4,7-10 and with a high rate of viral failure.26,30,31 Considering all these data, some of the safest alternative combinations could be lamivudine or emtricitabine plus abacavir, didanosine or tenofovir, or abacavir plus didanosine, as part of a once-daily regimen, or combinations including zidovudine or stavudine for regimens administered twice a day.

The new PI incorporations to the therapeutic arsenal enhance the options of switching to easier combinations with lower toxicity, such as atazanavir or fosamprenavir since both may be used once daily and are associated with a good lipid profile.14,15

In conclusion, simplified strategies should offer combinations with a similar antiviral potency to standard HAART regimens, but with more favourable dosing and reduced long-term toxicity. However, clinicians should be cautious when recommending a treatment simplification. Special attention must be paid to select the appropriate strategy and drugs, while considering the patient and the drug characteristics that sometimes contraindicate the switch.
Transparency declarations

The authors declare no conflict of interest in connection with this article.

References


