The rise and fall of triple nucleoside reverse transcriptase inhibitor (NRTI) regimens

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Triple nucleoside reverse transcriptase inhibitor (NRTI) regimens have attracted much interest due to their potential to (1) simplify dosing, with potential gains in adherence to treatment, and (2) reduce or even reverse dyslipidaemia associated with protease inhibitor (PI) therapy. A variety of triple NRTI combinations have been investigated, in both antiretroviral-naive and antiretroviral-experienced HIV-infected patients. Many of these trials have generated disappointing results, and some have been prematurely discontinued due to poor efficacy. This article reviews the background to the development of triple NRTI regimens, and the mounting evidence that this approach is suboptimal for antiretroviral-naive patients. Indeed, some triple NRTI regimens should never be used in this population. A role for triple NRTI combinations as a simplification strategy in treatment-experienced patients whose HIV is well controlled has been suggested, but emerging evidence indicates that such an approach can, under adequate selection pressure, lead to the emergence of mutations and viral load rebound. This commentary discusses the factors that appear to influence patients’ responses to triple NRTI therapy, and their implications for patient selection.

Keywords: clinical trials, genetic barrier, HAART, HIV, simplification strategies

The ultimate goal of antiretroviral treatment in patients infected with human immunodeficiency virus (HIV) is to prolong survival while maintaining an acceptable quality of life. Antiretroviral therapy has dramatically improved survival for people with HIV infection and acquired immunodeficiency syndrome (AIDS),\(^4,5\) as a result, quality of life and long-term consequences of treatment are attracting growing attention. Adherence to therapy is an important factor influencing the efficacy of triple antiretroviral regimens;\(^3\) there is evidence that convenient dosing regimens can improve adherence to treatment, and that adherence may in turn influence patient outcomes.\(^3,4\) These considerations have led to the development of simplified regimens based on three nucleoside reverse transcriptase inhibitors (NRTIs).

Advantages of triple NRTI regimens

Triple NRTI regimens potentially afford important advantages for long-term therapy. Dosing is simpler than for protease-inhibitor (PI)-based highly active antiretroviral therapy (HAART). Patients on triple NRTI regimens generally have a reduced pill burden, rendering triple NRTI therapy more attractive to patients who wish to maintain as normal a lifestyle as possible. Furthermore, dosing can be independent of food intake, and NRTIs have relatively few serious drug–drug interactions.

Furthermore, a triple NRTI strategy spares other antiretroviral drug classes, i.e. non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). This allows these other drug classes to be kept in reserve for later intensification or rescue regimens, if required, while limiting the adverse events associated with antiretroviral treatment. The potentially increased risk of cardiovascular disease linked with long-term PI therapy has attracted particular concern;\(^5\) PI-containing regimens have been linked with a significant increase in dyslipidaemia and insulin resistance.\(^10,11\) However, HIV infection itself is associated with an increased prevalence of decreased high-density lipoproteins, hypertriglyceridaemia, hypercoagulability, endothelial dysfunction and abnormal coronary artery pathology, and it is hence difficult to determine the differential effects of disease and therapy.\(^12,13\) Current guidelines stress that viral suppression should remain the prescriber’s prime consideration.\(^14\)

Clinical trials in antiretroviral-naive patients

Data are beginning to emerge from clinical trials comparing triple NRTI regimens with NRTI/PI and NRTI/NNRTI regimens in the treatment of antiretroviral-naive patients with HIV infection (Figure 1). These studies have confirmed that triple NRTI therapy is associated with more favourable lipid profiles than PI-containing regimens; however, this advantage appears to be offset by a decrease in antiviral efficacy.
In the Atlantic study, a triple NRTI regimen of didanosine (ddI), stavudine (d4T) and lamivudine (3TC) proved less effective at reducing viral load than both a PI-containing regimen (ddI, d4T and indinavir) and an NNRTI-containing regimen [ddI, d4T and nevirapine (NVP)] (Table 1). At 48 weeks, there was a significant difference in the on-treatment (OT) analysis, and a non-significant trend in the intention-to-treat (ITT) analysis; at 96 weeks, the difference was significant in both analyses.

In the CLASS study (ESS40001), at 48 weeks’ follow-up, a triple NRTI regimen of abacavir (ABC), 3TC and d4T proved as effective as a regimen of ABC/3TC plus PI [amprenavir (APV)/ritonavir (RTV)] (73% of patients achieved plasma HIV titres <50 copies/mL in both groups), but inferior to a regimen of ABC/3TC plus the NNRTI efavirenz (EFV) (on which 93% of patients achieved plasma HIV titres <50 copies/mL; \(P = 0.047\) by ITT analysis; \(P = 0.008\) by OT analysis). A triple NRTI regimen of ABC/d4T/ddI has been shown to have poor efficacy and to be associated with an unacceptably high level of adverse events. In this study, only 43% of patients in the triple NRTI group achieved plasma HIV RNA titres <20 copies/mL, compared with 69% of patients receiving nelfinavir (NFV) plus NVP, and 62% of patients receiving RTV plus saquinavir (SQV). The ABC/d4T/ddI arm was also associated with a significant increase in neuropathy (27% \(P < 0.001\) versus other treatment groups), suspected hypersensitivity (12%) and symptomatic hyperlactaemia (8%). Possible hypersensitivity reactions to ABC have also been reported in 5% of patients receiving NRTI therapy using an ABC/3TC/ZDV combination.

These results indicate that patients initiating triple NRTI therapy in 21% of patients receiving the triple NRTI regimen (ZDV/3TC/ABC) compared with 11% of patients in the other two study arms. The time to virological failure was also significantly shorter in the ZDV/3TC/ABC treatment group, irrespective of whether baseline viral titres were higher or lower than 100 000 copies/mL. (\(P < 0.001\)). As a result, the triple NRTI treatment arm was discontinued, and the US Department of Health and Human Services issued a Notice to Physicians (March 10, 2003, taken from http://www.nlm.nih.gov/databases/alerts/hiv.html).

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### Table 1. Percentage of patients with a treatment success in the Atlantic Study (ITT analysis)

<table>
<thead>
<tr>
<th>Treatment success definition</th>
<th>Week 48</th>
<th></th>
<th>Week 96</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>response rate (%) [95% CI]</td>
<td>(P) value</td>
<td>response rate (%) [95% CI]</td>
</tr>
<tr>
<td>(&lt;500) copies/mL (ddI/d4T/IDV)</td>
<td>100</td>
<td>55.0 [45.2–64.8]</td>
<td>0.353</td>
<td>44.0 [34.1–54.2]</td>
</tr>
<tr>
<td>(&lt;500) copies/mL (ddI/d4T/NVP)</td>
<td>89</td>
<td>53.9 [43.6–64.3]</td>
<td></td>
<td>55.1 [44.2–65.7]</td>
</tr>
<tr>
<td>(&lt;500) copies/mL (ddI/d4T/3TC)</td>
<td>109</td>
<td>45.9 [36.5–55.2]</td>
<td></td>
<td>28.4 [20.2–37.8]</td>
</tr>
</tbody>
</table>

CI, confidence interval; \(ddI\), didanosine; \(d4T\), stavudine; IDV, indinavir; NVP, nevirapine; 3TC, lamivudine.

Adapted from Ref. 15.
that includes ABC should be monitored closely for the development of hypersensitivity.

The ESS30009 study compared ABC/3TC/tenofovir (TDF) with ABC/3TC/EFV, with a planned follow-up of 48 weeks. Early observations of poor treatment responses, however, prompted an unplanned interim analysis (including at least 8 weeks follow-up for 194 patients) that revealed a dramatically high treatment failure rate in the TDF group (49% versus 5.4% in the EFV group). At 16 weeks, 69% of ABC/3TC/TDF-treated patients demonstrated a ≥2-log decrease in HIV titres by polymerase chain reaction (PCR) assay (compared with 97% in the ABC/3TC/EFV group), and only 29% achieved <50 HIV RNA copies/mL (compared with 95% in the ABC/3TC/EFV group). A 1 log rebound from nadir HIV levels by PCR was recorded in 8% of triple NRTI-treated patients compared with 0% on the EFV-containing regimen. A pilot study of this combination was also stopped early (at 16 weeks) due to a high incidence of virological failure. Although this was a small study, these results alone would raise concerns about the clinical potential of this regimen. Mean viral titres were 67 483 copies/mL at 4 weeks and 74 162 copies/mL at 8 weeks, from a baseline mean value of 82 381 copies/mL. In addition, 52% (9/17) of patients demonstrated a rebound of HIV titres during 16 weeks of treatment.

The combination of ABC/3TC/TDF was also evaluated in the Tonus study. Virological failure was defined as patients who never reached undetectable viral load of <400 copies/mL or who exhibited viral load rebound above 0.7 log10 copies/mL from nadir. The trial was prematurely interrupted after an unplanned interim analysis. Virological failure was observed in 12/36 patients. Genotypes available from the patients with virological failure revealed the presence of both K65R and M184V mutations in 11 of the 12, with the remaining sample having just the M184V mutation.

The triple nucleoside regimen of ddI/3TC/TDF has been associated with a disastrous efficacy outcome. A small cohort study of 24 antiretroviral-naive patients who received ddI/3TC/TDF had to be prematurely stopped due to a failure rate of 91% (defined as a <2 log reduction in HIV RNA plasma levels). Given these results, it is clear that this combination should not be used under any circumstances.

Although it is clear that some triple nucleoside regimens should never be used, data indicate that virological failure is substantially lower with the combination of ABC/ZDV/3TC (Trizivir) than with other triple nucleoside regimens. Although patients in the ACTG5095 study who were randomized to ABC/ZDV/3TC had significantly higher virological failure rates than patients receiving the EFV-based combinations (21% versus 11%), the efficacy rate of the triple nucleoside arm (74% with <200 copies/mL at 48 weeks) was within the range of other HAART regimens. Based on these results, it is possible to consider ABC/ZDV/3TC as initial therapy in a selected number of patients who, for other reasons, are not candidates for more potent regimens.

**Why have triple NRTI regimens underperformed in clinical trials of antiretroviral-naive patients?**

Until recently, triple NRTI regimens seemed an attractive option to simplify lifelong treatment and avoid any increased cardiovascular risk associated with PIs. Individually, these drugs have shown valuable activity as part of HAART regimens, so why have triple NRTI regimens underperformed in clinical trials of antiretroviral-naive patients? A number of factors are likely to have contributed:

**Insufficient potency**

The trial data reported to date suggest that triple NRTI regimens may have lower antiviral potency than PI- or NNRTI-containing HAART regimens. Suboptimal virological responses seem to be a characteristic of all the triple NRTI regimens tested (Figure 1), and this has serious implications for long-term treatment outcomes. In the CNAAB3005 study, significantly fewer patients with baseline viral titres above 100 000 copies/mL achieved levels <50 copies/mL on ABC/3TC/ZDV therapy than on IDV/3TC/ZDV (31% versus 45%). Several studies have identified nadir viral titres as an important determinant of long-term outcomes, and suggested that the best outcomes follow nadir HIV levels of <20 copies/mL, or below the limit of detection using standard HIV kits. Some investigators have also proposed that initial therapy offers the best chance of achieving a good long-term response, so it seems that the ideal approach to treating antiretroviral-naive patients is to select the most potent HAART regimen possible, and then consider simplification strategies at a later date. The potential for antiretroviral therapy to achieve a very low HIV nadir appears to be even more important than adherence to treatment in reducing the risk of virological failure.

**Suboptimal pharmacokinetics**

Once-daily dosing of triple NRTI combinations could potentially be limited by these agents’ relatively short plasma half-lives (about 2.5 h for ABC, for example)—although it should be borne in mind that the relationship between plasma half-life and intracellular half-life is complex. With respect to ABC, a recent study suggests that once-daily ABC may be effective in combination with 3TC and EFV. Furthermore, there are pharmacological data that support the idea that ABC may be suitable for once-daily dosing. In this study by Piliero et al., although the plasma half-life of ABC was shown to be only 2.59 h, the intracellular half-life of its metabolite, carbovir triphosphate, was shown to be 20.64 h, making ABC theoretically appropriate for once-daily dosing. These results have to be confirmed in larger studies in order to exclude interpatient variability.

A detrimental intra- or extracellular interaction between TDF and ABC has been suggested as a possible explanation for the poor performance of the ABC/3TC/TDF combination. However, this negative interaction has not been convincingly proven so far. In the Tonus study, at month 1, 32/37 patients had an adequate Cmin for all the three drugs, and the other five had at least one Cmin below the limit of detection for TDF (5), ABC (3), and 3TC (3). The data indicate that most of the patients who experienced virological failure had adequate plasma drug exposure. With regard to an intracellular interaction, two recent studies, one of which was carried out in healthy volunteers and the other in HIV-infected patients, have not found evidence of an intracellular interaction between TDF and ABC.
Review

Low genetic barrier

The very poor virological responses observed in studies using ABC/3TC/TDF or ddI/3TC/TDF might be explained by the selection of a pre-existing viral population resistant to one or more drugs included in the regimen. Genotypic analysis of HIV isolates obtained after failure of ABC/3TC/TDF or ddI/3TC/TDF show a very high prevalence of isolates with single (M184V/I) or double (M184V/I and K65R) reverse transcriptase mutations (Table 2). If pre-existing double mutants are the main reason for failure of the ABC/3TC/TDF and ddI/3TC/TDF combinations, it is somewhat difficult to explain why a number of isolates obtained after virological failure only contain M184V/I without K65R. This discrepancy might be related to factors that can diminish the sensitivity of genotypic testing, such as minority viral populations, analytical methods and fitness of the mutant viruses.

It appears that pathways to resistance to triple nucleoside regimens seem to be very different for regimens that include a thymidine analogue. In the ACTG5095 study,31 none of the 81 samples taken from patients who experienced virological failure after treatment with ABC/ZDV/3TC contained the K65R mutation, while 36–92% of samples in patients failing ABC/3TC/TDF or ddI/3TC/TDF were positive for K65R (Table 2). Interestingly, while thymidine analogue mutations (TAMs) were seen in 12% of patients failing ABC/ZDV/3TC therapy in the ACTG5095 study, TAMs were almost never seen in patients failing ABC/3TC/TDF or ddI/3TC/TDF regimens (Table 2).

A recent study of the ABC/3TC/TDF and ZDV combination further supports the notion of antagonism between TAMs and the K65R mutation. The COL40263 study was a pilot, open-label, multicentre study evaluating the efficacy and safety of the K65R mutation. The COL40263 study was a pilot, open-label, multicentre study evaluating the efficacy and safety of ddI/3TC/TDF and TDF, tenofovir; ZDV, zidovudine.

Is there a role for triple NRTI regimens in simplification strategies?

In the light of recent evidence, it is becoming clear that triple NRTI regimens are a suboptimal choice for the majority of antiretroviral-naive patients. The remaining question is whether these regimens might still prove useful in simplification strategies for antiretroviral-experienced patients. Evidence from the NEFA simplification trial suggests that, if so, these patients should be carefully selected to minimize the risk of virological failure.35

In the NEFA simplification trial, virological failure occurred in 16% of patients receiving ABC as a substitute for a PI, compared with 9.7% of patients switched to NVP, and 7.7% of patients who received EFV in place of a PI.35 The overall virological failure rate was 11%. Patients who had previously received suboptimal antiretroviral therapy using one or two NRTIs alone were at an increased risk of virological failure compared with patients who had received HAART throughout their treatment history. Virological failure in patients who switched to ABC was about three times more common following NRTI monotherapy or dual therapy than consistent HAART use (Table 3). It seems clear from these data that using intensive antiretroviral regimens from the start—rather than trying suboptimal regimens such as NRTI-only monotherapy or dual therapy—reduces the risk of virological failure following a switch to simplification therapy.35

Some support for the use of triple NRTI regimens has come from the Atlantic and the CNA30017 studies. In these studies, data showed that triple NRTI regimens can improve lipid profiles compared with standard PI-containing HAART.36,37 There is thus a strong argument to suggest that it may be clinically feasible to select and monitor patients who may benefit from PI-sparing therapy to reduce their cardiovascular risk. However,

<table>
<thead>
<tr>
<th>Study (nucleosides)</th>
<th>Failure rate</th>
<th>Patients with K65R</th>
<th>Patients with M184VI</th>
<th>Patients with TAMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS30009 (ABC/3TC/TDF)</td>
<td>50/102 (49%)</td>
<td>23/36 (64%)</td>
<td>36/36 (100%)</td>
<td>0/36 (0%)</td>
</tr>
<tr>
<td>Farthing (ABC/3TC/TDF)</td>
<td>11/19 (58%)</td>
<td>4/11 (36%)</td>
<td>5/11 (45%)</td>
<td>0/11 (0%)</td>
</tr>
<tr>
<td>Tonus (ABC/3TC/TDF)</td>
<td>12/36 (33%)</td>
<td>11/12 (92%)</td>
<td>12/12 (100%)</td>
<td>1/11 (9%)</td>
</tr>
<tr>
<td>Jemsek (ddI/3TC/TDF)</td>
<td>20/22 (91%)</td>
<td>10/20 (50%)</td>
<td>20/20 (100%)</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td>COL40263 (ABC/ZDV/3TC/TDF)</td>
<td>8/54 (15%)</td>
<td>1/8 (12.5%)</td>
<td>3/8 (37.5%)</td>
<td>5/8 (62.5%)</td>
</tr>
<tr>
<td>ACTG5095 (ABC/ZDV/3TC)</td>
<td>82/382 (21%)</td>
<td>0/81 (0%)</td>
<td>37/81 (46%)</td>
<td>10/81 (12%)</td>
</tr>
</tbody>
</table>

3TC, lamivudine; ABC, abacavir; ddI, didanosine; TDF, tenofovir; ZDV, zidovudine.
NRTI regimens as simplification strategies will need careful evaluation.

**Conclusion**

The past year has brought a substantial weight of evidence against the use of triple NRTI regimens in antiretroviral-naive patients. Two combinations (ABC/3TC/TDF and ddI/3TC/TDF) should never be prescribed. However, the ABC/ZDV/3TC combination might still have a role in treatment-naive patients in whom other more potent regimens cannot be used. Although triple NRTIs may still have a role to play in dose simplification strategies in treatment-experienced patients, any such use will require careful monitoring.

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