Adherence to trizivir and tenofovir as a simplified salvage regimen is associated with suppression of viraemia and a decreased cholesterol

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Received 5 January 2005; returned 29 March 2005; revised 2 April 2005; accepted 19 April 2005

Background: Treatment failure during highly active antiretroviral therapy (HAART) is ultimately common and associated with the development of resistance mutations. Trizivir (zidovudine/lamivudine/abacavir) and tenofovir disoproxil fumarate may improve adherence and enhance virological suppression in individuals who have failed previous regimens.

Methods: Individuals were identified who had failed previous HAART and who were then prescribed trizivir and tenofovir. Viral load and genotypic information were obtained to assess virological response.

Results: One hundred and twenty-two individuals were identified from a database containing 5883 patients. In a last observation carried forward intention to treat analysis, 34% of individuals achieved an undetectable viral load of <50 copies/mL at 1 year. Of those who were able to remain on treatment for 1 year, 65% achieved undetectability. We observed no effect regarding previous regimens on viral outcome. Accumulation of TAMs (thymidine analogue mutations) was associated with a decrease in the number of patients achieving an undetectable viral load (with <2 TAMs present 38% of patients developed undetectable viral loads, ≥2 TAMs 17% undetectable; P = 0.03). Using the mean cell volume as a measure of compliance, those with higher values were more likely to achieve a viral load <50 copies/mL (P = 0.04). A beneficial effect on cholesterol was noted regardless of virological outcome.

Conclusions: In compliant heavily pre-treated individuals with less than 2 TAMs, salvage therapy with trizivir and tenofovir is associated with suppression of viraemia and an improved lipid profile.

Keywords: HAART, HIV/AIDS, thymidine analogue mutations, cholesterol

Introduction

In those for whom it is available, highly active antiretroviral therapy (HAART) has reduced mortality and increased quality of life by preventing opportunistic diseases. Despite the initial optimism concerning this selective targeting of the HIV reverse transcriptase and protease, HAART is not able to target the latent reservoir and it is associated with well known and described clinical side effects and toxicities. Virological failure may be associated with difficulties in adhering to complex regimens and in turn, it is specifically associated with the development of resistance mutations against the agents and associated antiretroviral classes, within received HAART regimens. As the number of drugs increases, quality of life and safety assume relatively greater importance and many studies demonstrate that discontinuation is higher in the arm where additional drugs are administered, whatever treatment is chosen for maximal suppression of viral replication.

The combination of trizivir (zidovudine/lamivudine/abacavir) (one tablet twice daily) and tenofovir (one tablet once daily) potentially offers an attractive and simple salvage regimen. Tenofovir disoproxil fumarate [R-9-(2-phosphonyl-methoxypropyl) adenine; tenofovir DF], the first nucleotide analogue reverse transcriptase inhibitor to be approved by the FDA, has been well tolerated and demonstrated efficacy in large clinical trials of naive and experienced patients, without evidence of long-term toxicity, including the mitochondrial toxicity that has been associated with some nucleoside analogue reverse transcriptase inhibitors. Whilst trizivir, a triple nucleoside-based regimen, is a useful therapy with a favourable lipid profile, one large study demonstrated that
it did not suppress viraemia as well as a non-nucleoside reverse transcriptase inhibitor based regimen.\textsuperscript{17}

We therefore studied the efficacy and safety of the tenofovir and trizivir combination in patients requiring salvage therapy. Such a combination spares the use of protease inhibitors and subsequent side effects, including an adverse effect on lipid profile, which in turn may cause premature cardiovascular disease.\textsuperscript{18–20} We therefore studied this profile and also investigated the use of resistance tests to establish patients who were more or less likely to respond to this regimen.

**Methods**

**Patients**

The Chelsea and Westminster HIV cohort is one of the largest in Europe. HIV-positive patients are seen at regular intervals for clinical assessment, trial follow-up, and immunological and virological assessments. We have routinely prescribed HAART since 1 January 1996, the date at which HAART became routinely available at our institution in accordance with published guidelines.\textsuperscript{21} We undertook a systematic search of our database in order to identify those individuals who had received and failed at least one prior antiretroviral regimen and then received trizivir and tenofovir. Antiretroviral histories were collated from the clinical database and patient notes, as well as any available resistance mutation information. Genotypic tests (Virco NV, Mechelen, Belgium), CD4 results (TetraOne antibodies on an Epics XL-MCL facscaliber, Beckman Coulter, High Wycombe, UK) and plasma viral load (Quantiplex HIV RNA 3.0, Chiron, Halstead, UK) were recorded from the database.

**Statistics**

Statistical analyses were performed in SAS version 8.0 using parametric tests. Where appropriate, data were log\textsubscript{10} transformed to stabilize the variance. MIXED procedure in SAS was used to calculate the difference in averages (DAVG), which represents the time weighted difference in viral load and CD4 count from baseline to each time point. On treatment and a last observation carried forward intention to treat analysis (ITT) was performed, firstly where the last observation (<50 copies/mL) was carried forward if data were unavailable at the time point and secondly, where any patient whose data were unavailable for any reason was assumed to have failed at the time of analysis. Fold changes from baseline were further calculated for viral load and CD4 count for each study time points and these have been presented as percentage change from baseline. Log rank $\chi^2$ tests were used for comparisons and all $P$ values presented are two-sided.

**Results**

A total of 5883 patients have been followed up at the Chelsea and Westminster Hospital during the HAART era. Of these, we identified 122 (2\%) HIV-1-infected individuals who received trizivir and tenofovir after failing at least one prior antiretroviral regimen. The median viral load at baseline measured 35 745 copies/mL and median CD4 count measured 164 cells/mm\textsuperscript{3} (Table 1). The number of patients achieving a viral load of <50 copies/mL after 1–6 months and at 1 year is demonstrated in Figure 1. Out of those who remained on treatment, 65\% achieved undetectability at 1 year versus 34\% in an intent to treat analysis.

Patients had a mean of 4 previous antiretroviral regimens (range 1–6). Out of these individuals, 87\% had previously received lamivudine (mean duration 22 months), 77\% zidovudine (mean 15 months), 55\% abacavir (mean 12 months) and 26\% tenofovir (mean 2 months). After 1 year of therapy with trizivir and tenofovir, there were 49 dropouts (15 virological failures, 16 lost to follow-up, 4 abacavir adverse drug reactions, 9 zidovudine adverse drug events related to myelosuppression, 1 tenofovir DF adverse drug event, 2 patient choice, 1 treatment simplification, 1 pregnancy).

The mean CD4 increase on treatment was 131 cells/mm\textsuperscript{3}, 66\% of patients (on treatment) achieved a one log drop in viral load and 65\% had an undetectable viral load (<50 copies/mL) at 1 year (Figure 1). Figure 1 demonstrates similar proportions of patients with undetectable viraemia on treatment at 6 months and at 1 year. The accumulation of TAMs was associated with a decrease in the number of patients achieving an undetectable viral load.

**Table 1.** Baseline characteristics of the 122 patients included in this analysis [median (IQR) and mean (SD)]

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median (IQR)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA copies/mL</td>
<td>35 745 (1535–161 979)</td>
<td></td>
</tr>
<tr>
<td>Mean cell volume (fL)</td>
<td>94.5 (9.3), range 75–123</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/mL)</td>
<td>4.6 (1.1), range 2.3–8.1</td>
<td></td>
</tr>
<tr>
<td>CD4 count (cells/mm\textsuperscript{3})</td>
<td>164 (94–282)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. The proportion of patients achieving a viral load <50 copies/mL.
Patients with fewer than 2 TAMs had significantly better virological outcomes compared with those with two or more TAMs (Table 2). Out of 15 patients with virological failure, 12 individuals had resistance tests available at baseline. One patient had 5 TAMs plus M184V, 2 had 3 TAMs plus M184V, 3 had 2 TAMs (2 plus M184V) and 2 had 1 TAM (1 plus M184V). At failure, only two patients had more TAMs than at baseline and none had acquired the M184V mutation. Only three patients had the K65R mutation conferring resistance to tenofovir. Of these, two experienced virological failure (one by 6 months and one by 1 year). However, the patient who failed at 1 year had 4 TAMs and the patient who failed at 6 months had 2 TAMs, thus the effect of K65R remains unclear.

A raised mean corpuscular volume (MCV) resulting from zidovudine therapy, was taken as a crude measure of adherence to the regimen. We have shown that more patients with a raised MCV (>100 fL) achieved an undetectable viral load (<50 copies/mL) than those with a ‘normal’ MCV (<100 fL) at each of the time points measured and this was statistically significant ($P = 0.04$).

In this analysis, we also investigated the effect on lipid profile (cholesterol), in those individuals who did and did not achieve an undetectable viral load. Figure 2, a DAVG analysis with 95% confidence intervals, demonstrates a statistically significant beneficial effect on cholesterol levels after 6 months of therapy that is maintained at 1 year, regardless of whether undetectability was achieved ($P < 0.05$). At 6 months, this was most evident in those who subsequently achieved undetectability although by 9 months to 1 year, all patients had significantly lower cholesterol levels than at the start of therapy.

### Table 2. Effect of thymidine analogue mutations on individuals achieving an undetectable viral load at 1 year

<table>
<thead>
<tr>
<th>Number of TAMs</th>
<th>Percentage affected</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 TAM versus ≥1 TAM</td>
<td>38% versus 23%</td>
<td>0.159</td>
</tr>
<tr>
<td>&lt;2 TAM versus ≥2 TAM</td>
<td>38% versus 17%</td>
<td>0.031</td>
</tr>
<tr>
<td>&lt;3 TAM versus ≥3 TAM</td>
<td>36% versus 15%</td>
<td>0.066</td>
</tr>
<tr>
<td>&lt;4 TAM versus ≥4 TAM</td>
<td>36% versus 15%</td>
<td>0.066</td>
</tr>
</tbody>
</table>

In the small dataset, we have not subdivided patients according to the type of TAMs.

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### Discussion

This study suggests that a simplified regimen of trizivir and tenofovir is able to achieve virological suppression at 1 year, in a majority of patients who have failed previous antiretroviral therapies. We observed that accumulation of more than 2 TAMs, decreased the number of individuals achieving undetectability at 1 year. Therefore, we also conclude from our small dataset that the number of TAMs can be used to guide future strategies in which this regimen is considered. Trizivir and tenofovir should be considered in those individuals who have failed previous antiretrovirals and who have zero or one TAM only. We were unable to conclude the additional significance of K65R or M184V mutation. Despite the extensive experience of these 122 individuals to lamivudine and/or zidovudine, previous use of these nucleoside analogues did not appear to affect the response to our simplified regimen (it is also unclear here whether the M184V mutation may restore zidovudine sensitivity).

We noted significant benefits on cholesterol levels that were maintained from 6 months to 1 year, regardless of outcome. In a large prospective randomized study comparing the safety and efficacy of tenofovir with stavudine (both in combination with lamivudine and efavirenz), a more favourable change in cholesterol was found in the tenofovir group at week 144, and these patients also had less lipodystrophy. Switching from stavudine to tenofovir is also associated with reversal of dyslipidaemia.
Simplified salvage therapy

has also been extensively studied in this setting and in a number of comparative studies, median decreases in cholesterol were greater in those patients who received trizivir.\textsuperscript{28–30} It is therefore not necessarily surprising that a trizivir and tenofovir combination was successful at reducing cholesterol although this is an important benefit of this regimen.

Lack of adherence to HAART is a significant reason for treatment failure. Trizivir and tenofovir has a lower pill burden in terms of both number of tablets and frequency of administration (and food restrictions)\textsuperscript{16} and we also found that those individuals with increased adherence, as measured by a higher MCV,\textsuperscript{23,24} were significantly more likely to have virological suppression at any of the time points measured.

In conclusion, the combination of trizivir and tenofovir was well tolerated and associated with a decreased cholesterol. Virological suppression could be achieved in those individuals with a previous history of exposure to components of this regimen and adherence to this protease inhibitor sparing regimen was associated with achieving undetectability. The measurement of TAMs can be used to guide treatment strategies in patients requiring salvage therapy.

References


