A randomized study comparing a three- and four-drug HAART regimen in first-line therapy (QUAD study)

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Background: Evidence from randomized controlled trials supports the use of triple therapy. Research is required on the effectiveness of quadruple therapy in comparison to this and the relative effectiveness of specific highly active antiretroviral therapy (HAART) combinations.

Methods: Antiretroviral-naive individuals (n = 53) with an HIV-1 viral load >100,000 copies/mL were randomized to receive three-drug HAART with zidovudine/lamivudine (Combivir) and efavirenz or quadruple therapy with zidovudine/lamivudine/abacavir (Trizivir) and efavirenz (quad regimen). Patients continued on HAART for 48 weeks with regular clinical and immunological assessment. Standard and ultrasensitive (<5 copies/mL) viral load testing was carried out.

Results: A DAVG (difference in averages) analysis of the fall in viral load and increase in CD4 count showed no significant differences between regimens. Triple therapy resulted in a 24.17 log change (95% CI, 24.48 to 23.85) and quadruple therapy in a 24.36 log change (95% CI, 24.68 to 24.03) in viral load. For CD4 counts, the triple therapy arm increased by 164 cells/mm3 (95% CI 112–217) and the quadruple arm by 185 (95% CI, 133–237). In an intent-to-treat analysis, 77% of patients in the triple therapy group reached an undetectable viral load (<50 copies/mL) compared with 84.2% of the quadruple therapy group. For ultrasensitive viral load testing, 23% and 18% of each group, respectively, reached undetectable viral loads. The hazard ratio for attaining a viral load of <5 copies/mL was 0.59 (95% CI, 0.26–1.33) for quadruple versus triple therapy. Three individuals in the triple therapy arm and nine in the quadruple therapy arm discontinued treatment.

Conclusions: No differences in any analyses were observed between a standard of care regimen (zidovudine/lamivudine and efavirenz) and the quad regimen (zidovudine/lamivudine/abacavir and efavirenz).

Keywords: HIV, HAART, combination, randomized, quadruple therapy

Introduction

Within 6 years of the events that heralded the onset of the HIV-1 epidemic,12 zidovudine was introduced as a potential treatment.13-14 The subsequent elucidation of the crystal structures of the HIV protease1 and reverse transcriptase4 led to an escalation of the number of antiretroviral agents available and the development of the two major potent classes of antiretrovirals used today.3,10 Currently, there are over 20 agents licensed for treatment and large studies have demonstrated their ability to reduce morbidity and mortality, mainly by preventing opportunistic infections that were common before the advent of combination antiretrovirals in 1996.11-15

Many combinations of drugs are possible although owing to resistance profiles, toxicities and interactions between drugs, the actual number of therapeutic options may be limited, particularly in previously treated individuals.16,17 This underscores the importance of initiating therapy for HIV-1 infection with the best possible regimen.18 Such decisions regarding initiation are guided by the patient’s HIV-1 RNA level, CD4 cell count, their clinical condition and available data regarding appropriate HAART.19

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Large randomized and cohort studies have demonstrated that in asymptomatic patients, non-nucleoside reverse-transcriptase inhibitors are at least as effective as protease inhibitors as part of initial triple-drug therapy, even in patients with large viral loads.\textsuperscript{20-25} A frequently used combination has been zidovudine/lamivudine and efavirenz (ZDV/3TC/EFV), which is highly effective in clinical trials at suppressing viral replication so that the viral load falls below the detection limit of an assay with a sensitivity of 50 copies/mL.\textsuperscript{20,26} It remains an open question as to whether addition of another nucleoside analogue to the standard regimen would produce a more rapid reduction in initial viral load and more complete suppression of viral replication producing a higher proportion of patients with a negative plasma viral load using an assay with a sensitivity of less than 5 copies/mL. Such changes might be a significant factor in maintaining durable suppression of HIV replication.

We therefore conducted an open-label randomized study to compare the triple highly active antiretroviral therapy (HAART) regimen of zidovudine/lamivudine (Combivir) and efavirenz with the quadruple regimen of zidovudine/lamivudine/abacavir (Trizivir) and efavirenz, in antiretroviral-naive individuals with a high HIV-1 plasma viral load.

Materials and methods

Between March and October 2001, 53 antiretroviral-naive individuals with a plasma viral load $>$100 000 copies/mL were randomized on a 1:1 basis to receive either the triple drug combination [zidovudine/lamivudine (Combivir) and efavirenz] or quadruple drug combination [zidovudine/lamivudine/abacavir (Trizivir) and efavirenz]. Patients were continued on their randomized regimen for the study duration of 48 weeks after which time they received continued therapy. All patients were from the Chelsea and Westminster Hospital, London, provided voluntary, written informed consent and the study received appropriate ethical approval in accordance with the declaration of Helsinki.

CD4 subset analysis was carried out at weeks 4, 8, 12, 16, 24, 36 and 48 using whole blood stained with murine anti-human monoclonal antibodies to CD4 (TetraOne; Beckman Coulter, High Wycombe, UK) and were evaluated on an Epics XL-MCL (Beckman Coulter) flow cytometer. Viral loads in patient plasmas were measured on day 0, 3, 7, 10 and 14 and weeks 4, 8, 12, 16, 24, 36 and 48 using the Quantiplex HIV RNA 3.0 assay with a lower limit of detection of 50 copies/mL.20,26 It remains an open question as to whether addition of another nucleoside analogue to the standard regimen would produce a more rapid reduction in initial viral load. Between March and October 2001, 53 antiretroviral-naive individuals with a plasma viral load $>$100 000 copies/mL were randomized on a 1:1 basis to receive either the triple drug combination [zidovudine/lamivudine (Combivir) and efavirenz] or quadruple drug combination [zidovudine/lamivudine/abacavir (Trizivir) and efavirenz].

Results

Fifty-three patients were randomized to receive either triple ($n = 26$) or quadruple ($n = 27$) HAART. There were no significant differences in baseline characteristics between the two groups. The median viral load in the triple therapy group was 323 593 copies/mL and in the quadruple therapy group, it was 309 030 copies/mL. The median CD4 count was 155 cells/mm$^3$ (triple therapy, range 61–266) versus 82 cells/mm$^3$ (quadruple therapy, 26–170; $P = 0.21$, Mann–Whitney $U$-test).

For all patients, the log changes in viral load during the 48 week study showed no significant differences between the triple

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1.png}
\caption{(a) DAVG (difference in averages) change in viral load during the 48 week study period for three- versus four-drug HAART. (b) Percentage decrease from baseline in viral load during the 48 week study period for three- versus four-drug HAART.}
\end{figure}
or quadruple therapy groups for time weighted averages (Figure 1a) or percentage decrease from baseline (Figure 1b), at any time point. Similarly, there were no significant differences between the two groups for increases in CD4 count using time weighted averages (Figure 2a) or percentage increase from baseline (Figure 2b).

For each study arm, data were analysed for those individuals on-treatment, as an ITT analysis with the last observation carried forward if data were unavailable at the time of analysis, and as an ITT analysis where any patient whose data were unavailable was assumed to have failed at the time of analysis. Using these criteria, comparisons were made of the proportion of individuals in each group who reached an undetectable viral load. Figure 3 shows that similar proportions of individuals in each group reached conventionally undetectable viral loads at each time point in the study. Using ultrasensitive viral load testing, no patients reached undetectable viral load in the quadruple therapy arm by 12 weeks whereas four individuals in the triple therapy arm reached undetectable viral load by this time (Figure 4a and b). Once again these changes were not significant as shown in Table 1 in which the hazard ratio for attaining a viral load of <5 copies/mL was 0.59 (95% CI, 0.26–1.33, Log rank $P = 0.2$) for quadruple versus triple therapy.

Three individuals discontinued treatment in the triple therapy arm and nine patients in the quadruple therapy arm (Table 2). Efavirenz-related mood changes and hepatotoxicity were the most common indications for coming off trial. One patient developed a hypersensitivity reaction to abacavir (an expected proportion).

Discussion

Triple therapy combinations, widely referred to as HAART, lead to a sustained suppression of HIV at levels below the detection limit of commercial viral load assays (<50 copies/mL) in the vast majority of treatment adherent and tolerant individuals. However, a range of different research methodologies have demonstrated that there remains ongoing viral replication in individuals with current viral suppression below commercial assay limits on HAART therapy. Attempts to more completely suppress HIV infection have led to the investigation of combinations of four (or more) antiretrovirals as initial therapy.

A previous large AIDS Clinical Trials Group 384 study compared four-drug regimens containing efavirenz and nelfinavir in combination with either didanosine and stavudine or zidovudine and lamivudine with therapy involving two consecutive threedrug regimens, the first of which contained either efavirenz or
nelfinavir. In 980 subjects followed for a median of 2.3 years, there were no significant differences in the duration of successful HIV-1 treatments between a single four-drug regimen and two consecutive three-drug regimens. Interestingly, the same trials group has found that the combination of zidovudine/lamivudine and efavirenz is superior to regimens containing didanosine, stavudine and nelfinavir, as initial therapy in HIV-1 infection. This small randomized study supports these earlier larger trials and demonstrates that over a 48 week study period, this specific triple therapy HAART regimen (ZDV/3TC/EFV) is as effective as a quadruple therapy regimen (ZDV/3TC/ABC/EFV) at suppressing HIV replication and facilitating reconstitution of the immune system. There were no significant differences in viral suppression or CD4 count restoration at any time point and the time to <5 copies/mL HIV-1 RNA was similar in both groups. Subgroup analyses of each arm also failed to show significant differences suggesting the potency of the ZDV/3TC/EFV combination. In addition, more individuals in the quadruple therapy group developed complications resulting in cessation of one or more antiretrovirals.

Systematic reviews have previously demonstrated that the escalation of combinations of antiretroviral drugs up to triple therapy is an effective strategy. Several studies have demonstrated the relative effectiveness of monotherapy versus placebo and double therapy versus monotherapy, although future work and trials in progress have often been designed to clarify which triple combination is most effective. There are no randomized data to suggest that the addition of further drugs to a standard triple therapy regimen improves rates of undetectable viral load in HIV-1-infected individuals. A non-randomized comparison of 30 controls who had not experienced virological failure during 3 years of standard therapy with 10 patients treated with a five-drug regimen showed longer-term suppression of plasma HIV-1 viral load in patients receiving the five-drug combination. However, a three-drug, three-class regimen used in an induction maintenance study could have some advantages. This study does not suggest that a quadruple therapy regimen containing an extra nucleoside analogue confers any benefit over a 48 week study period. Furthermore, as the number of drugs increases, quality of life and safety assume relatively greater importance and in this and other studies the rate of study discontinuation is higher in the arm where additional drugs are administered, whatever treatment is chosen for maximal suppression of viral replication.

In summary, in persons with high baseline viral load, use of three nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) does not lead to improved virological or immunological efficacy relative to a standard of care two NRTIs plus one NNRTI regimen. For individual patients, the exact balance of risks and benefits—namely, the chance for long-term viral suppression, the risk of certain side effects, the possibility of induction of drug resistance, and the ability to adhere to a particular regimen—is best addressed by open discussions between care providers and their patients.

**Table 1. Relative hazard showing likelihood of achieving undetectable HIV-1 RNA load (<5 copies/mL) since entry into the trial**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients achieving viral load, n (%)</th>
<th>Time (days) to &lt;5 copies/mL [median (IQR)]</th>
<th>Log rank</th>
<th>Relative hazard (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>&gt;5 copies/mL</td>
<td>&lt;5 copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple therapy</td>
<td>11 (42.3)</td>
<td>15 (57.7)</td>
<td>336 (203–371)</td>
<td>(\chi^2 = 1.671, P = 0.196)</td>
</tr>
<tr>
<td>Quadruple therapy</td>
<td>16 (59.3)</td>
<td>11 (40.7)</td>
<td>349 (259–393)</td>
<td>0.59 (0.26–1.33)</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>26</td>
<td></td>
<td></td>
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C. Orkin et al.

Table 2. Reasons for discontinuing trial

<table>
<thead>
<tr>
<th></th>
<th>Triple therapy (n = 3)</th>
<th>Quadruple therapy (n = 9)</th>
</tr>
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<tbody>
<tr>
<td>Toxicity</td>
<td>Abnormal LFTs</td>
<td>ABC hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>ZDV-induced anaemia</td>
<td>EFV-induced mood change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2 patients)</td>
</tr>
<tr>
<td></td>
<td>bowel obstruction</td>
<td>abnormal LETs</td>
</tr>
<tr>
<td></td>
<td>(unrelated to HAART)</td>
<td>ZDV-induced anaemia</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>patients did not wish to</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>attend clinic</td>
</tr>
<tr>
<td>Emigrated</td>
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ABC, abacavir; EFV, efavirenz; ZDV, zidovudine; LFTs, liver function tests.

References

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