Short communication

No advantage of quadruple- or triple-class antiretroviral therapy as initial treatment in patients with very high viraemia

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Background: We assessed whether quadruple or triple-class therapy for the initial treatment of HIV-1 infection provides a virological benefit over standard triple therapy in patients with very high plasma viraemia. The assessment was made based on a national observational HIV cohort in the Netherlands.

Methods: Inclusion criteria were age ≥18 years, treatment-naive, plasma viral load (pVL) ≥500,000 copies/ml and initiation of quadruple or triple therapy between 2001 and 2011. Time to viral suppression, defined as pVL < 50 copies/ml, was compared between the two groups using Kaplan–Meier plots and multivariate Cox regression analysis.

Results: A total of 675 patients were included: 125 (19%) initiated quadruple and 550 (81%) triple therapy. Median pVL was 5.9 (IQR 5.8–6.1) log10 copies/ml in both groups (P=0.49). 22 (18%) patients on quadruple and 63 (12%) on triple therapy interrupted the treatment regimen because of drug-related toxicity (P=0.06). Median time to viral suppression was 5.8 (IQR 4.6–7.9) and 6.0 (4.0–9.4) months in the patients on quadruple and triple therapy, respectively (log–rank, P=0.42). In the adjusted Cox analysis, quadruple therapy was not associated with time to viral suppression (HR 1.07 [95% CI 0.86, 1.33], P=0.53). Similar results were seen when comparing triple- versus dual-class therapy (n=72 versus n=601, respectively).

Conclusions: Initial quadruple- or triple-class therapy was equally effective as standard triple therapy in the suppression of HIV-1 in treatment-naive patients with very high viraemia and did not result in faster pVL decreases, but did expose patients to additional toxicity.

Introduction

A higher baseline plasma HIV-1 RNA is an independent predictor of virological treatment failure [1,2]. Plasma viral load (pVL) levels above 100,000 copies/ml are associated with a slower pVL decrease, a reduced probability of achieving virological suppression and an increased risk of mortality [1,3,4]. Dual- or triple-class quadruple therapy has been suggested to increase the antiretroviral activity of combination antiretroviral therapy (cART). Several randomized and non-randomized studies have compared the potency of quadruple therapy with that of standard-of-care triple therapy in treatment-naive patients and found inconsistent results with regards to virological response [5–15]. In most studies, quadruple therapy consisted of a regimen in which the fourth drug was an older generation unboosted protease inhibitor (PI), questioning its relevance to current clinical practice. Furthermore, the effectiveness of quadruple/triple-class therapy has not yet been answered in the subgroup of patients with very high viraemia (≥500,000 copies/ml). We assessed whether quadruple- or triple-class therapy provides a more rapid pVL decrease and an improved virological response compared with standard dual-class triple therapy in treatment-naive patients with very high viraemia.
Methods

Data used in this study were selected from the Dutch observational HIV cohort (ATHENA) [16]. Inclusion criteria were: age \( \geq 18 \) years, treatment-naive, a pVL of >500,000 copies/ml at start of therapy and initiation of quadruple or triple therapy between January 2001 and June 2011. Patients with primary HIV infection were excluded. The decision to initiate quadruple or triple therapy was at the discretion of the treating physician.

Quadruple and triple therapy was defined as cART with four and three effective drugs, respectively, including at least two different drug classes. Triple- and dual-class therapy was defined as cART containing three and two effective drug classes. Ritonavir-boosted PIs (PI/r) were considered a single drug.

The primary end point was the time to viral suppression, defined as the time to the first of two consecutive pVL measurements \(< 50 \) copies/ml, and the proportion of patients with a pVL \(< 50 \) copies/ml after the first year of treatment. Secondary end points were the tolerability of the regimens and the number of patients experiencing virological failure (pVL>1,000 copies/ml) after initial viral suppression (pVL<50 copies/ml).

Table 1. Patient characteristics at start of therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quadruple therapy</th>
<th>Triple therapy</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>110 (88)</td>
<td>454 (83)</td>
<td>0.14</td>
</tr>
<tr>
<td>Age, years</td>
<td>40 (35–46)</td>
<td>41 (35–48)</td>
<td>0.39</td>
</tr>
<tr>
<td>Native Dutch residents</td>
<td>78 (62)</td>
<td>322 (59)</td>
<td>0.43</td>
</tr>
<tr>
<td>HIV transmission route</td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Homosexual</td>
<td>77 (62)</td>
<td>307 (56)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>39 (31)</td>
<td>208 (38)</td>
<td></td>
</tr>
<tr>
<td>Injecting drug use or blood-blood</td>
<td>3 (2)</td>
<td>8 (1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (5)</td>
<td>27 (5)</td>
<td></td>
</tr>
<tr>
<td>Coinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>7 (6)</td>
<td>29 (5)</td>
<td>0.88</td>
</tr>
<tr>
<td>HCV</td>
<td>3 (2)</td>
<td>22 (4)</td>
<td>0.39</td>
</tr>
<tr>
<td>History of CDC-C event</td>
<td>65 (52)</td>
<td>234 (43)</td>
<td>0.05</td>
</tr>
<tr>
<td>CD4(^+) T-cell count, cells/mm(^3)</td>
<td>80 (40–191)(^a)</td>
<td>125 (41–230)(^b)</td>
<td>0.009</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA, log(_{10}) copies/ml</td>
<td>5.9 (5.8–6.1)</td>
<td>5.9 (5.8–6.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Drug resistance mutations</td>
<td>2 (5)(^c)</td>
<td>10 (6)(^d)</td>
<td>1.0</td>
</tr>
<tr>
<td>cART regimen including</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NNRTI</td>
<td>23 (18)</td>
<td>328 (60)</td>
<td></td>
</tr>
<tr>
<td>Boosted PI</td>
<td>31 (25)</td>
<td>214 (39)</td>
<td></td>
</tr>
<tr>
<td>NNRTI plus boosted PI</td>
<td>63 (50)</td>
<td>1 (0)</td>
<td></td>
</tr>
<tr>
<td>Integrase inhibitor</td>
<td>8 (6)</td>
<td>7 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as \( n \) (%) or median (IQR). *P-value based on the Kruskal–Wallis test for continuous variables and \( \chi^2 \) or Fisher's exact tests for proportions. *Three patients and 16 patients with missing data. HIV genotyping was available for 43 patients on quadruple and 178 patients on triple therapy. cART, combination antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Results

Quadruple versus triple therapy

The study population consisted of 675 patients of whom 125 (19%) initiated quadruple therapy and 550 (81%) triple therapy. Patient characteristics prior to treatment are summarized in Table 1. The median pVL was 5.9 (IQR 5.8–6.1) log\(_{10}\) copies/ml in both groups (\( P = 0.95 \)). The median CD4\(^+\) T-cell count was significantly lower in the patients initiating quadruple therapy (\( P = 0.009 \)). All patients, except one, initiated cART with at least two nucleoside reverse transcriptase inhibitors (NRTIs). Patients on quadruple therapy received, in addition to these NRTIs, a regimen containing a third NRTI plus a non-nucleoside reverse transcriptase inhibitors (NNRTI; 18%), a third NRTI plus a PI/r (25%), an NNRTI plus a PI/r (50%), or an integrase inhibitor plus an NNRTI or PI/r (6%). Of the patients on quadruple and triple therapy using Kaplan–Meier plots and multivariate Cox regression analysis. Patients who discontinued cART for >2 weeks or who were lost to follow-up were censored in the survival analyses. All variables listed in Table 1 were considered potential confounders and entered into the Cox model. Analyses were repeated for triple- versus dual-class therapy. Data were analysed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).
triple therapy, 60% initiated a regimen of NRTIs with an NNRTI, 39% NRTIs with a PI/r and 1% NRTIs with an integrase inhibitor. One patient on triple therapy initiated with one NRTI, an NNRTI and a PI/r (Table 1). HIV genotyping was available for 221 (33%) of the patients. Two (5%) patients on quadruple and 10 (6%) patients on triple therapy harboured one or more transmitted drug resistance mutations in the reverse transcriptase or protease (P=1.0) [17]. As a result, two patients on triple therapy were retrospectively treated with an ineffective triple regimen and were therefore excluded from further analyses. Participants were followed for a median of 50 (IQR 27–82) months.

The median time spent on the first treatment regimen was 105 (IQR 28–240) days for patients on quadruple therapy and 415 (IQR 156–978) days for patients on triple therapy (P<0.001). Twenty-two (18%) patients on quadruple therapy switched to an alternative regimen within a year because of drug-related adverse events, as compared with 63 (12%) patients on triple therapy (P=0.06). Seventy-nine (63%) patients on quadruple therapy simplified the regimen to triple therapy during the first year. Seven (6%) patients on quadruple and 51 (9%) on triple therapy interrupted treatment for ≥2 weeks or were lost to follow-up in the first year of treatment before reaching viral suppression and were censored in the survival analyses.

The median time to viral suppression after initiation of therapy was 5.8 (IQR 4.6–7.9) months in the patients on quadruple therapy and 6.0 (IQR 4.0–9.4) months in the patients on triple therapy (log-rank, P=0.42; Figure 1A). The Kaplan–Meier estimates of the proportion of patients who had achieved a viral suppression <50 copies/ml after the first year of treatment were 104/118 (88%) for patients on quadruple and 418/497 (84%) for triple therapy. 10/97 (10%) and 20/397 (5%) patients on quadruple and 51 (9%) on triple therapy interrupted treatment for >2 weeks or were lost to follow-up in the first year of treatment before reaching viral suppression and were censored in the survival analyses.

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The median time to viral suppression was 5.7 (IQR 4.7–7.6) and 6.0 (IQR 4.0–9.3) months, respectively (P=0.32; Figure 1B). 62/69 (90%) and 460/546 (84%) patients initiating triple or dual-class therapy achieved viral suppression within the first year. In the adjusted Cox analysis, triple-class therapy was not associated with time to viral suppression (HR 1.10 [95% CI 0.84, 1.44], P=0.48), but the use of an integrase inhibitor was (HR 1.87 [95% CI 1.11, 3.15], P=0.02).

**Discussion**

The present study demonstrates that quadruple/triple-class therapy was equally effective as standard-of-care triple therapy in treatment-naive patients with a pVL >500,000 copies/ml, although it did expose patients to more drug-related adverse events. These results provide no evidence of benefit of adding an additional fourth drug or third drug class to standard triple therapy.

Reviewing available literature, our work is supported by several studies in which no differences were seen in viral suppression between treatment-naive patients on quadruple/triple-class versus dual-class triple therapy [10–15]. Three randomized studies, however, demonstrated a virological benefit after initiation of triple-class therapy [5–7]. The difficulty in interpreting and comparing these findings is that some of these studies compared triple therapy with a dual-class quadruple regimen [10,12–14], included an older generation unboosted PI as the fourth drug or a third drug class [5–9,11,14,15], did not include treatment-naive patients [6,7] or contained only a small number of patients on quadruple therapy [8–10,13,14]. In all studies, the median baseline pVL was also significantly (at least ≥0.4 log10 copies/ml) lower than in ours.

Two non-randomized studies showed a faster decrease to pVL <50 copies/ml after triple-class quintuple therapy [9] as compared with standard triple therapy, with an improved reduction of low-level viraemia (pVL 5–50 copies/ml) after 144 weeks [8]. From our study, we cannot exclude that quadruple/triple-class therapy resulted in reduced low-level viral replication and a stronger long-term suppression of pVL when compared with dual-class triple therapy. Moreover, in the above two studies patients received prolonged triple-class therapy, whereas in our study more than half of patients on quadruple therapy switched to an alternative, often simplified regimen within the first year.

The current study has limitations that are inherent to observational cohort studies evaluating the effectiveness of cART. First, the preference of physicians to prescribe quadruple or triple therapy was not random and was possibly influenced by prognostic factors and therefore susceptible to bias [18]. The patients on quadruple therapy had a significantly lower
CD4⁺ T-cell count prior to treatment. We additionally adjusted for this difference by doing a propensity score weighted Cox regression analysis with weights [19] and found similar results (data not shown). Despite this, unmeasured, residual confounding might have biased our results. Second, follow-up visits including pVL measurements were scheduled arbitrarily and may differ between the physicians and HIV treatment centres, possibly resulting in a less accurate estimate of the time to viral suppression for patients who did not come for regular check-ups. However, we adjusted for this in an additional survival model using Weibull distribution and found similar results (data not shown). Third, HIV genotyping before the initiation of therapy was not available for more than half of the patients. Finally, our results are not adjusted for non-adherence to therapy, which is an important determinant of virological response [1] and may have compromised the effectiveness of the treatment regimen. This might explain the higher rate of virological failure in the patients on quadruple therapy since they were exposed to a higher pill burden and more drug toxicity, and may therefore have been at an increased risk of non-adherence.

In conclusion, this study provides no evidence to support the use of quadruple/triple-class therapy in treatment-naive patients with very high viraemia. Quadruple/triple-class therapy did not improve the antiretroviral activity of cART, yet did expose patients to additional drug toxicity.
Acknowledgements

The authors wish to thank Ard van Sighem for assisting with the data retrieval and Peter Reiss for critically reviewing the manuscript. The ATHENA national observational cohort has been made possible through the collaborative efforts of the physicians listed in Additional file 1.

MLG, JMP and FdW conceived the study. RH, LG and FWNMW conducted the statistical analysis. MLG and JMP provided valuable input into interpretation of data. MLG drafted the manuscript and JMP critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Disclosure statement

These results have not been presented before at a conference or meeting. The authors declare no competing interests.

Additional files

Additional file 1: A list of the ATHENA national observational cohort members can be found at http://www.intmedpress.com/uploads/documents/AVT-12-SC-2574_Grijsen_Add_file1.pdf

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Accepted 13 May 2012; published online 22 August 2012

Antiviral Therapy 17.8 1613