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

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Abstract

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 a very high plasma viraemia.

Design
National observational HIV cohort in the Netherlands.

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

Results
675 patients were included: 125 (19%) initiated quadruple and 550 (81%) triple therapy. Median pVL was 5.9 (IQR 5.8-6.1) log_{10} c/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 (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 vs. 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-naïve patients with very high viraemia and did not result in a faster pVL decline, 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 decline, a reduced probability of achieving virologic 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 cART. Several randomized and nonrandomized 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 regard to virologic response [5-15]. In most studies quadruple therapy consisted of a regimen in which the fourth drug was an older generation unboosted 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 c/ml). We assessed whether quadruple or triple-class therapy provides a more rapid pVL decline and an improved virologic 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 ≥18 years, treatment-naïve, a pVL of more than 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 (Pis/r) were considered a single drug.

The primary endpoint was the time to viral suppression, defined as the time to the first of two consecutive pVL measurements below 50 c/ml, and the proportion of patients with a pVL below 50 c/ml after the first year of treatment. Secondary endpoints were the tolerability of the regimens and the number of patients experiencing virological failure (pVL >1000 c/ml) after initial viral suppression (pVL <50 c/ml).

Demographic characteristics, clinical and laboratory data were compared between the two groups using Kruskal-Wallis, chi-square or Fisher’s exact tests where appropriate. Time to viral suppression was compared between quadruple and triple therapy using Kaplan-Meier plots and multivariate Cox regression analysis. Patients who discontinued cART for more than two weeks or 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 analyzed using SAS version 9.2.
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} c/ml in both groups (P=0.95). The median CD4 count was significantly lower in the patients initiating quadruple therapy (P=0.009). All patients, except one, initiated cART with at least two NRTIs. Patients on quadruple therapy received in addition to these NRTIs a regimen containing a third NRTI plus an NNRTI (18%), a third NRTI plus a PI/r (25%), an NNRTI plus a PI/r (50%), or an integrase inhibitor plus a NNRTI or PI/r (5%). Of the patients on 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 patients (5%) on quadruple and 10 patients (6%) on triple therapy harboured one or more transmitted drug resistance mutations in 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.

Table 1. Patient characteristics at start of therapy

<table>
<thead>
<tr>
<th></th>
<th>Quadruple therapy (N=125)</th>
<th>Triple therapy (N=550)</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></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>0.50</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (5)</td>
<td>27 (5)</td>
<td></td>
</tr>
<tr>
<td>Co-infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>7 (6)</td>
<td>29 (5)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hepatitis C virus</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 count (cells/mm^3)</td>
<td>80 (40-191)^b</td>
<td>125 (41-230)^bb</td>
<td>0.009</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log_{10} c/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^c</td>
<td>2 (5)</td>
<td>10 (6)</td>
<td>1.0</td>
</tr>
<tr>
<td>cART regimen including</td>
<td></td>
<td></td>
<td></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>&lt;0.001</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 are no. of patients (%) or medians (inter quartile ranges).
* P-value based on the Kruskal-Wallis test for continuous variables and χ^2 or Fisher’s exact tests for proportions.
^b 3 patients and ^bb 16 patients with missing data.
^c HIV genotyping was available for 43 patients on quadruple and 178 patients on triple therapy.
The median time spent on the first treatment regimen was 105 (IQR 28-240) days for patients on quadruple therapy and 415 (156-978) days for patients on triple therapy ($P<0.001$). Twenty-two patients (18%) on quadruple therapy switched to an alternative regimen within a year because of drug-related adverse events, as compared to 63 patients (12%) on triple therapy ($P=0.06$). Seventy-nine patients (63%) on quadruple therapy simplified the regimen to triple therapy during the first year. Seven patients (6%) on quadruple and 51 (9%) on triple therapy interrupted treatment for more than two 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 (4.0-9.4) months in the patients on triple therapy (log rank, $P=0.42$; Figure 1A). The KM-estimates of the proportion of patients that had achieved a viral suppression <50 c/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 triple therapy for whom follow-up pVL measurements were available experienced virological failure (pVL>1000 c/ml) after initial viral suppression ($P=0.05$), after a median time of 12 (IQR 8-23) months. In the adjusted Cox regression analysis, quadruple therapy was not associated with time to viral suppression (HR 1.07 (95%CI 0.86-1.33), $P=0.53$). As expected, a regimen containing an integrase inhibitor was associated with a more rapid time to viral suppression (HR 1.90 (95%CI 1.13-3.18), $P=0.02$).

**Triple- versus dual-class therapy**

A total of 72/673 patients (11%) initiated triple-class therapy and 601/673 patients (89%) started dual-class therapy. Thirteen patients (18%) on triple-class therapy and 72 (12%) on dual-class therapy switched to an alternative regimen because of drug-related adverse events ($P=0.14$). The median time to viral suppression after initiation of triple- versus dual-class therapy was 5.7 (IQR 4.7-7.6) and 6.0 (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 (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-naïve patients with a pVL above 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 the literature, our work is supported by several studies in which no differences were seen in viral suppression between treatment-naïve 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
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Figure 1. Kaplan-Meier curves of the probability of achieving a viral suppression. Kaplan-Meier curves of the probability to achieve a viral suppression below 50 c/ml for patients on quadruple and standard of care triple therapy (1A), and patients on triple- and dual-class therapy (1B).

fourth drug or third drug-class [5-9, 11, 14, 15], did not include treatment-naïve 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 c/ml) lower than in ours.

Two nonrandomized studies showed a faster decline to pVL <50 c/ml after triple-class quintuple therapy [9] as compared to standard triple therapy, with an improved reduction of low-level viraemia (pVL 5-50 c/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 to 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, which 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 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). In spite of 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 centers, 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 nonadherence to therapy, which is an important determinant of virologic 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 nonadherence.

In conclusion, this study provides no evidence to support the use of quadruple/triple-class therapy in treatment-naïve 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.

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No advantage of quadruple therapy

Contributors

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.
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