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Nieuwkerk, P.T.

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Chapter 4

Long-term quality of life outcomes in three antiretroviral treatment strategies for HIV-1 infection.

Nieuwkerk PT, Gisolf EH, Reijers MH, Lange JM, Danner SA, Sprangers MA. NATIVE Study Group, Prometheus Study Group, ADAM Study Group.

Abstract

Objective: To compare changes in quality of life (QoL) over 96 weeks in patients enrolled in either a triple-therapy protocol, a treatment-intensification protocol, or an induction-maintenance therapy protocol, and to compare QoL between patients who continued and discontinued their antiretroviral regimen.

Patients: Naive patients enrolled in a triple-therapy protocol (zidovudine/lamivudine or stavudine/didanosine or stavudine/lamivudine supplemented with protease inhibitor therapy of choice) \( (n = 35) \), a protocol of treatment-intensification (ritonavir/saquinavir or ritonavir/saquinavir/stavudine) \( (n = 74) \) in which therapy was intensified with nucleoside analogue(s) in case of insufficient viral suppression, and a protocol of induction- (saquinavir/nelfinavir/lamivudine/ stavudine) maintenance (saquinavir/nelfinavir or stavudine/nelfinavir) therapy \( (n = 50) \).

Main outcome measure: Changes from baseline in QoL assessed by the Medical Outcomes Study HIV Health Survey at weeks 0, 12, 24, 36, 48, 72 and 96.

Results: Patients in the triple-therapy and treatment-intensification protocols showed more favourable changes in physical function, social function, mental health, energy/fatigue, health distress and overall QoL compared to patients in the induction-maintenance protocol, with patients in the first two protocols showing improvements in QoL and those in the induction-maintenance protocol showing declining- or unchanged QoL. Patients who discontinued study medication due to insufficient efficacy, toxicities or at their own request showed less favourable changes in QoL compared with patients who continued their regimen. The highest proportion of discontinuations was within the induction-maintenance protocol.

Conclusion: Antiretroviral treatment strategies that are effective and tolerable have the potential to improve patients' QoL over 96 weeks.
Introduction

The advent of antiretroviral therapy comprising a protease inhibitor (PI) and two nucleoside reverse transcriptase inhibitors (NRTI) has resulted in a major decline in HIV-1 related morbidity and mortality and became the standard of care in the treatment of HIV-1 infection in the western world [1, 2]. However, such triple-therapies are far from convenient to patients. Short- and long-term toxicities frequently occur and lead to discontinuation of therapy in a considerable number of patients [3]. Moreover, the daily burden of triple-therapy may be large, requiring strict adherence to a substantial number of pills, rigid time schedules, and for some drugs, dietary prescriptions. The ultimate goal of antiretroviral therapy is to improve the length and the quality of the patient’s life. However, both adverse effects and the need for strict adherence may diminish patients’ quality of life (QoL). The drawbacks of triple-therapy prompted the search for more patient-friendly treatment strategies. One option is induction-maintenance therapy, namely starting with a potent regimen to induce suppression of HIV-1 replication and subsequently switch to a less intense regimen once virologic suppression has been achieved [4]. An alternative strategy is treatment intensification, namely starting with a potent but relatively simple regimen and intensifying treatment in cases of inadequate viral suppression [5]. To date, limited information is available on the impact of highly active antiretroviral therapy (HAART) on patients’ QoL. Although the present perspective is that HAART should be taken for life, published studies have reported on a follow up period ranging from 24 weeks to 48 weeks only [6-10]. We anticipated that QoL might be temporarily diminished in patients who discontinue their antiretroviral regimen.

The objective of this study was to compare the impact on QoL over a period of 96 weeks between patients enrolled in a strategy of triple therapy compared to a strategy of treatment intensification and a strategy of induction-maintenance therapy. In addition, we compared QoL in patients who discontinued their initial or assigned regimen compared to those who did not.

Methods

Patients

Patients were HIV-1 infected and participated in three antiretroviral clinical trials. The NATIVE study enrolled antiretroviral naïve patients with less than 500 x 10^6 CD4 cells/l or at least 10 000 HIV-1 RNA copies/ml or HIV-1-related symptoms, between December 1996 and May 1998. Patients were assigned to either zidovudine [300 mg twice daily (bid)] plus lamivudine (150 mg bid); or stavudine (40 mg bid) plus didanosine (400 mg
once daily); or stavudine (40 mg bid) plus lamivudine (150 mg bid). All patients received additional treatment of choice comprising one or two PIs.

The PROMETHEUS study enrolled PI- and stavudine-naive patients who were randomly assigned to either ritonavir (400 mg bid) plus saquinavir-hard-gel capsules (HCG) (400 mg bid); or ritonavir (400 mg bid) plus saquinavir-HCG (400 mg bid) plus stavudine (40 mg bid), between January 1997 and January 1998 [5]. In patients with a serum HIV-RNA above 400 copies/ml at week 12 and week 18, therapy was intensified with NRTIs. After the original 48-week follow-up, the clinical protocol was extended to a follow-up of 96 weeks. The QoL study was extended to 96 weeks in seven of the 14 participating centres. For the present report, we included totally antiretroviral naive patients enrolled in these seven centres.

The ADAM-study enrolled antiretroviral-naive patients with at least $200 \times 10^6$ CD4 cells/l and 1000 HIV-1 RNA copies/ml, between March 1997 and April 1998 [4, 11]. All patients received induction therapy comprising stavudine (40 mg bid), lamivudine (150 mg bid), nelfinavir [750 mg three times a day (tid)] and saquinavir-HCG (600 mg tid) or saquinavir-soft-gelatin capsules (SGC) (800 mg tid). During follow-up, patients were switched to SQV-SGC (1200 bid) and nelfinavir (1250 mg bid). At week 26 or week 50, patients with plasma HIV-1 RNA below the lower limit of quantification of an ultrasensitive assay were randomly assigned to prolonged induction versus maintenance therapy (stavudine/nelfinavir or saquinavir/nelfinavir). Randomisation at week 26 was prematurely discontinued due to inferior viral suppression of viral replication in the maintenance arms [4].

Each study was approved by the Institutional Review Boards of participating centres. All patients signed written informed consent.

**Quality of life measurement**

QoL was assessed by the Medical Outcomes Study Health Survey for HIV (MOS-HIV), a widely used questionnaire of health-related QoL in HIV/AIDS with established reliability and validity [12, 13]. The MOS-HIV comprises ten subscales: physical-, role-, social-, and cognitive function, mental health, energy/fatigue, health distress, health perceptions, pain, and overall quality of life. Subscale scores may range between 0 to 100. A physical health and a mental health summary score can be calculated on the basis of these subscale scores. Higher scores indicating better QoL. The QoL questionnaire was administered at the start of treatment and after 12, 24, 36, 48, 72 and 96 weeks.

**Statistical analyses**

Patient characteristics at baseline were compared between the three treatment strategies by $X^2$ tests for categorical variables and by one-way analysis of variance or Kruskal-Wallis tests for continuous variables, if appropriate.
Changes in QoL were calculated by subtracting baseline QoL-scores from week 12, 24, 36, 48, 72 and week 96 scores, respectively. Missing values were handled using the last-observation-carried-forward approach. Repeated measures analysis of variance was performed to compare changes in QoL between the three treatment strategies. Because of differences in inclusion criteria between the three trials we controlled for baseline HIV-1 RNA $\log_{10}$ copies/ml, baseline CD4 cells $\times 10^6$/L, CDC clinical stage, age, gender and baseline QoL score. If a statistically significant effect of treatment strategy was found, post-hoc tests were performed to establish between-group differences.

The percentages of patients who discontinued their initial- or assigned regimen was compared between the three studies by $X^2$ test. A second repeated measures analysis of variance was performed using discontinuation of study-medication (yes/no) as between-subject factor.

Analyses was by intention to treat. $P$ values < 0.05 were considered to indicate statistical significance. Data analyses was performed using the SPSS software package for Windows (SPSS, Systat, Chicago, Illinois, USA).

Results

Response and baseline characteristics

Of the 45 patients enrolled in the NATIVE study, 35 (78%) participated in the QoL study. In the seven centres that extended the QoL-protocol of the PROMETHEUS study up to week 96, a total of 91 antiretroviral naive patients had been enrolled. Of these, 74 (81%) participated in the QoL study. A total of 65 patients were enrolled in the ADAM-study of which 50 (77%) participated in the QoL study.

Participants in the QoL study were comparable to non-participants regarding age, gender, baseline CDC clinical stage, baseline HIV RNA and baseline CD4 cell count (data not shown). Characteristics at baseline of participants in the QoL study from the three clinical trials are shown in Table 1.

Response rates for the MOS-HIV were 91% at week 12, 92% at week 24, 82% at week 36, 91% at week 48, and 70% at weeks 72 and 96.

Patient disposition

Thirteen patients (37%) from the NATIVE study were assigned to zidovudine/lamivudine, nine were assigned to stavudine/lamivudine (26%) and 13 (37%) were assigned to stavudine/didanosine. Additional therapy of choice of the initial regimen comprised indinavir (800 mg tid) in 16 (46%) patients, ritonavir (600 mg bid) in 7 (20%) patients, ritonavir (400 mg bid) combined with saquinavir-HCG(400 mg bid) in 7 (20%) patients and saquinavir-HCG (1200 mg tid) in 5 (14%) patients.
### Table 1: Characteristics at baseline and discontinuation of study medication over 96 weeks

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NATIVE study (n=35)</th>
<th>PROMETHEUS study (n=74)</th>
<th>ADAM Study (n=50)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>37.9 (8.0)</td>
<td>37.8 (9.2)</td>
<td>39.8 (8.0)</td>
<td>0.41&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male (%)</td>
<td>27 (77%)</td>
<td>65 (88%)</td>
<td>48 (96.0%)</td>
<td>0.03&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CDC clinical stage (%) at baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.004&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>A</td>
<td>22 (63%)</td>
<td>36 (48%)</td>
<td>38 (76.0%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>9 (26%)</td>
<td>19 (26%)</td>
<td>11 (22.0%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>4 (11%)</td>
<td>19 (26%)</td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Baseline median (IQR) CD4 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>230 (90-400)</td>
<td>260 (68-415)</td>
<td>380 (318-508)</td>
<td>&lt;0.00&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baseline median (IQR) HIV RNA log&lt;sub&gt;10&lt;/sub&gt; copies/ml</td>
<td>4.5 (3.7-5.2)</td>
<td>4.6 (4.1-5.1)</td>
<td>4.5 (4.2-5.1)</td>
<td>0.89&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Discontinuation of study medication
- Therapy failure/ detectable plasma HIV-1 RNA: 1 4 24
- Toxicities: 9 16 8
- Patient request: 5 8 9

SD, standard deviation; CDC, Centers for Disease Control; IQR, interquartile range. <sup>a</sup> One-way analysis of variance; <sup>b</sup> X<sup>2</sup> test; <sup>c</sup> Kruskal-Wallis test.

Thirty-six patients (49%) from the PROMETHEUS study had been assigned to ritonavir/saquinavir and 38 (51%) to ritonavir/saquinavir/stavudine. In 13 patients (18%), treatment was intensified with NRTIs according to protocol.

Eighteen patients enrolled in the ADAM study were randomised at week 26 only, of whom 12 (24%) were assigned to maintenance therapy and nine (18%) were assigned to prolonged induction therapy. Three other patients who had been assigned to prolonged induction therapy at week 26 were subsequently randomised at week 50, of whom two (4%) were assigned maintenance therapy and one (2%) was assigned prolonged induction therapy. Ten patients were randomised at week 50 only, of whom five (10%) were assigned to maintenance therapy and five others (10%) were assigned prolonged induction therapy. Sixteen patients (32%) never were randomly assigned treatment.

The numbers of patients enrolled in the three studies that had discontinued study medication at week 96 are shown in Table 1.

**Comparison of changes in QoL between the three treatment strategies**

There were no statistically significant differences in QoL at baseline between the three treatment strategies (data not shown). There were statistically significant differences in changes in QoL over 96 weeks between the three treatment strategies regarding physical function (P=0.042), social function (P=0.021), mental health (P=0.007), energy/fatigue (P=0.015), health distress (P=0.006) and overall quality of life (P=0.012) (Figure 1). In addition, there were statistically significant differences between the three trials regarding the physical health (P=0.026) and mental health (P=0.46) summary scores.
Figure 1: Changes from baseline in QoL-scores

Circles = triple combination therapy protocol (NATIVE-study), diamonds = treatment-intensification protocol (PROMETHEUS-study), triangles = induction-maintenance protocol (ADAM-study). Solid line at zero indicates no change in QoL-score from the start of treatment. Values > 0 indicate improvement in QoL, values < 0 indicate decline in QoL.

Post-hoc tests revealed no difference in changes in QoL between the NATIVE study and the PROMETHEUS study. Both patients from the NATIVE and PROMETHEUS study showed more favourable changes in QoL as compared to patients from the ADAM study regarding physical function, social function, mental health, energy/fatigue, health distress, and overall quality of life. A tendency toward the same pattern was observed for health perceptions (P=0.075) and pain (P=0.066). QoL improved in patients enrolled in both the NATIVE and the PROMETHEUS study, whereas it remained unchanged or declined among patients enrolled in the ADAM study.
Treatment discontinuation and effect on patients' QoL

The percentage of patients who discontinued their initial or assigned regimen differed between the three treatment strategies, with the highest proportion of discontinuations among participants in the ADAM study. Changes in QoL over 96 weeks significantly differed between patients who continued and discontinued their regimen regarding health perceptions ($P=0.013$), mental health ($P=0.023$), health distress ($P=0.001$), pain ($P=0.037$), energy/fatigue ($P=0.037$), social function ($P=0.041$), overall quality of life ($P=0.002$), and physical function ($P=0.078$). On average over 96 weeks, patients who continued their initial or assigned regimen showed improvement in their QoL, whereas average QoL scores over 96 weeks remained unchanged in patients who had discontinued their initial- or assigned regimen. We found no difference in impact on QoL among patients who discontinued for reasons of insufficient efficacy, toxicities, or patient request (data not shown).

Discussion

The impact on QoL was compared between patients enrolled in a protocol of triple-combination therapy and two treatment strategies designed to be more patient-friendly; a treatment-intensification- and an induction-maintenance protocol. Patients in the triple therapy--as well as patients in the treatment-intensification protocol showed significantly more improvements in their QoL during a 96-week follow-up period as compared with patients in the induction-maintenance therapy protocol, in whom QoL remained unchanged or declined.

The difference in the impact on QoL between the three strategies appeared to be related, in part, by the difference in the proportion of patients discontinuing their assigned or initial regimen between the three strategies. The highest proportion of discontinuations was observed within the induction-maintenance protocol. Patients who discontinued their assigned regimen showed less favourable changes in their QoL compared with patients who continued their regimen. In this, the present study supports the assumption that antiretroviral regimens that are effective and tolerable contribute to the patients' QoL.

Tolerability of antiretroviral regimens is a prime concern in the treatment of HIV-1 infection. The percentage of patients that discontinued their initial regimen due to toxicities, as an indication of tolerability, for the three trials combined was 21%. This is comparable with that previously reported among antiretroviral-naïve patients [3]. Details on toxicities in the three trials have been reported previously [4, 5, 14].
QoL outcomes reflect both the impact of treatment and disease progression. In a previous report on the 48 week QoL outcomes in the treatment-intensification protocol, a significant improvement was found in QoL relative to the start of treatment in symptomatic patients whereas QoL remained unchanged or declined among asymptomatic patients [8]. The triple-therapy and the treatment-intensification studies enrolled patients who generally had a more advanced HIV-1 disease stage compared to patients enrolled in the induction-maintenance study. In patients enrolled in the triple-therapy protocol and those enrolled in the treatment-intensification protocol, the possible negative effects of antiretroviral therapy were, on average, outweighed by the health benefits of therapy. This is encouraging given the perspective that HAART should probably be taken for life.

The majority of patients enrolled in the induction-maintenance protocol had an asymptomatic HIV-1 infection and had a relatively high median CD4 cell count, i.e., 380 x 10^5 cells/L. Among this group of patients, the burden of therapy was, on average, not outweighed by its benefits. This study therefore suggests that HAART should not be started too early and reinforces the new international guidelines that recommend starting HAART only when the CD4+ lymphocyte count drops below 350 x 10^6 cells/L [15].

We did not find a significantly better QoL in the treatment intensification protocol compared to the triple therapy protocol although the treatment intensification protocol was designed to be a more patient friendly option. It is likely that relatively small differences in the number of pills to be taken or the number of times each day that pills need to be taken do not result in a measurable improvement in QoL. Additionally, a small group of patients in the triple therapy protocol were treated with RTV/SQV combined with two NRTIs. This regimen is very similar to that of the treatment intensification protocol, especially in patients in whom therapy was intensifed with NRTIs. Another explanation is that we performed a between-study comparison. Although we controlled for differences in relevant baseline characteristics in all between-study comparisons, additional differences between patient populations may have existed that were not controlled for in our statistical analyses. Additionally, medication-intrinsic characteristics may have affected QoL outcomes within protocols.

We found less favourable changes in QoL in patients who discontinued their regimen as compared to patients who did not. Nevertheless, the timing of our measurements was not specifically tailored to assess this effect. QoL measurements were performed at predefined weeks from the start of treatment and discontinuations might have occurred between those measurements. Moreover, it is likely that the timing of the impact on QoL may have differed between various reasons for discontinuation. For instance, one might expect that toxicities will initially reduce QoL and that discontinuation of that specific regimen will subsequently lead to improvement in QoL. Conversely, we previously found that QoL declined in patients whose viral loads were not sufficiently suppressed. Consequently, one could anticipate
that QoL might decline following discontinuation due to insufficient efficacy [16]. We did not find a different impact on QoL after various reasons for discontinuation. However, this was probably due to the small number of patients discontinuing their treatments for various reasons.

Of note, the QoL profiles of patients from the ADAM study showed a negative slope between week 24 and week 36, indicating decline in QoL on the subscales related to well-being, namely mental health, energy/fatigue, health distress and overall QoL (Figure 1). This might have been caused by discontinuations due to insufficient viral suppression that occurred after week 24. In addition, the first clinical results of the ADAM study that led to preliminary discontinuation of the randomisation at week 26 might have caused disappointment among participants because the option of randomisation to a regimen containing less pills was postponed. It is important to note that plasma HIV-1 RNA measurements in the ADAM study were performed using ultra sensitive assays, whereas assays with a lower quantification limit of 400 copies/ml were used in the PROMETHEUS and NATIVE studies. This suggests that most likely, it was the patients' awareness of insufficient viral suppression that negatively affected their well being because actual viral suppression did not necessarily differ between protocols.

In conclusion, QoL significantly improved during 96 weeks among patients in a triple combination therapy- and a treatment- intensification protocol, whereas QoL remained unchanged or declined among patients in a induction-maintenance protocol. Patients who discontinued their study medication showed less favourable changes in QoL compared to patients who continued their regimen. Our results suggest that antiretroviral treatment strategies that are tolerable and effective have the potential to improve patients' QoL during a 96 week follow-up period.

**Acknowledgements**

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References


