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Temporary antiretroviral treatment during primary HIV-1 infection has a positive impact on health-related quality of life: data from the Primo-SHM cohort study

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Abstract

Objectives
The aim of the study was to compare health-related quality of life (HRQL) over 96 weeks in patients receiving no treatment or 24 or 60 weeks of combination antiretroviral therapy (cART) during primary HIV-1 infection (PHI).

Methods
A multicentre prospective cohort study of PHI patients, with an embedded randomized trial, was carried out. HRQL was assessed with the Medical Outcomes Study Health Survey for HIV (MOS-HIV) and a symptom checklist administered at weeks 0, 8, 24, 36, 48, 60, 72, 84 and 96. Mixed linear models were used for the analysis of differences in HRQL among the three groups.

Results
A total of 112 patients were included in the study: 28 received no treatment, 45 received 24 weeks of cART and 39 received 60 weeks of cART. Over 96 weeks of follow-up, the groups receiving 24 and 60 weeks of cART had better cognitive functioning than the no-treatment group ($P = 0.005$). Patients receiving 60 weeks of cART had less pain ($P = 0.004$), better role functioning ($P = 0.001$), better physical functioning ($P = 0.020$) and a better physical health summary score ($P = 0.006$) than the groups receiving no treatment or 24 weeks of cART. Mental health was better in patients receiving 24 weeks of cART than in patients in the no-treatment group or the group receiving 60 weeks of cART ($P = 0.020$). At week 8, patients in the groups receiving 24 and 60 weeks of cART reported more nausea ($P = 0.002$), diarrhoea ($P < 0.001$), abdominal pain ($P = 0.023$), stomach pain ($P = 0.049$) and dizziness ($P = 0.011$) than those in the no-treatment group. These differences had disappeared by week 24.

Conclusions
Temporary cART during PHI had a significant positive impact on patients’ HRQL as compared with no treatment, despite the initial, short-term occurrence of more physical symptoms, probably related to drug toxicity.
Introduction
The impact of temporary combination antiretroviral therapy (cART) during primary HIV-1 infection (PHI) on viral setpoint and HIV disease progression has recently been studied in three randomized clinical trials (RCT) and showed that early cART provided a clinical benefit [1-3]. In the Primo-SHM trial, an open-label RCT comparing no treatment with 24- or 60-weeks of cART during PHI, we demonstrated that temporary early cART lowered the viral setpoint and deferred the need for reinitiation of cART during chronic HIV-1 infection [1]. Both the SPARTAC trial, which compared no therapy with 12 or 48 weeks of cART in PHI, and the SETPOINT study, which compared no therapy with 36 weeks of cART, reported that a period of 48 and 36 weeks of cART, respectively, modestly delayed disease progression [2, 3]. However, during the acute stage of HIV-1 disease patients are often physically and emotionally distressed, and the initiation of cART may have a negative impact on their health-related quality of life (HRQL) as a result of pill burden, the need for strict adherence to cART and potential drug-related adverse events and toxicity [4, 5]. Conversely, early cART may also have a positive effect on patients’ HRQL, by delaying disease progression, lowering the plasma viral load and because patients may feel they are actively “doing something” about the PHI [6]. In chronic HIV infection the potential negative effects of cART on patients’ HRQL are generally offset by positive effects [7-10]. The aim of the current Primo-SHM substudy was to compare the impact on HRQL of 24- or 60-weeks of cART during PHI versus no treatment, over a study period of 96 weeks.

Methods
Patients
Patients were selected between May 2003 and April 2010 from the Primo-SHM cohort, a multi-center prospective cohort study in the Netherlands, with an embedded RCT, that investigates the natural course of HIV-1 infection, and the effects of 24- and 60-weeks of early cART in PHI-patients [1, 11]. For the present substudy, we included both patients from the cohort and the RCT. Main inclusion criteria were age ≥ 18 years and laboratory evidence of PHI, defined as having a negative or indeterminate Western Blot in combination with detectable plasma HIV-1 RNA, or, in case of a positive Western Blot, a proven negative HIV screening test result within the previous 180 days. Early cART consisted of a triple-class regimen of zidovudine/lamivudine (300/150 mg BID), efavirenz (600 mg QD), and lopinavir/ritonavir capsules (533/133 mg BID). Lopinavir/ritonavir was discontinued when the pVL dropped below 50 copies/ml. After January 2008, zidovudine/lamivudine was replaced by tenofovir/emtricitabine (245/200 mg QD), and lopinavir/ritonavir tablets (600/150 mg BID) replaced the capsules. Patients needed to have sufficient fluency in Dutch or English to complete a self-administered HRQL-questionnaire. Recruitment of participants and study design have been described previously [1, 11]. The study was approved by the Medical Ethics Committee of each participating site and written informed consent was obtained from all participants.

Quality of life measurement
Patients received a self-report questionnaire measuring HRQL when attending the outpatient clinic for the study visits at weeks 0, 8, 24, 36, 48, 60, 72, 84 and 96. The questionnaire consisted
Quality of life during primary HIV infection

of two parts: the Medical Outcomes Study Health Survey for HIV (MOS-HIV) and a symptom checklist. The MOS-HIV is a widely used questionnaire comprising 10 subscales [12]. Physical health (PHS-) and mental health summary (MHS-) scores can be calculated on the basis of these subscale scores [13]. Higher scores indicate a better HRQL.

The symptom checklist consisted of 14 items referring to symptoms related to PHI or to side-effects of cART, i.e.: difficulty with sleeping, lack of appetite, nausea, vomiting, diarrhoea, abdominal or stomach pain, fever, flu-like symptoms such as myalgia or chills, tingling of hands or feet, numb feeling in fingers or toes, dizziness, itchiness and skin changes. These items were derived from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 and an HIV/AIDS-specific questionnaire [9]. The questions related to the experience of symptoms during the past week. Symptoms were scored on a four-point scale with the response categories `not at all’, `a little’, `quite a bit’, and `very much’. The 4-point scale scores were linearly transformed to a scale of 0 to 100, with higher scores indicating more symptoms.

Statistical analyses
We included patients who completed a HRQL-questionnaire at baseline and at least one questionnaire during follow-up. Baseline characteristics were compared using Chi-squared tests for categorical variables and general linear models or Kruskal-Wallis tests for continuous variables. Linear mixed effect models for repeated measurements were used to test for differences in MOS-HIV and symptoms scores during follow-up between the three groups, with baseline values included as covariate. Model results were summarized by the estimated mean values during follow-up for the three groups, adjusted for baseline measurements. To investigate potential short-term toxicity of cART, we also compared the symptom scores among the three groups at week 8 using general linear models, with the baseline measurement included as covariate.

To increase the sample size, we also included untreated patients who were not randomized in the trial but were enrolled in the Primo-SHM cohort. To assess a potential difference between randomized and non-randomized untreated patients, we compared their baseline characteristics using Chi-squared tests or Kruskal-Wallis tests, if appropriate, and their HRQL at baseline and at each follow-up visit using student t-tests. Additionally, we repeated the mixed linear models including only those patients who were enrolled in the RCT. Analyses were according to intent-to-treat, regardless of treatment changes or discontinuation. Two-sided P-values <0.05 were considered statistically significant. Data were analyzed using SPSS version 16.0 (IBM Corporation, USA).

Results

Patient characteristics
Of 168 participants enrolled in the Primo-SHM RCT, 100 (60%) were included in the present study: 16 in the no treatment, 45 in the 24-weeks of early cART and 39 in the 60-weeks of early cART group. For 25 of the 168 participants (15%), no baseline HRQL-questionnaire was available, and they were therefore excluded from further analyses. The reasons for excluding the other 43 participants (26%) were that the patient had insufficient language skills or did not want to complete the HRQL questionnaires, or that the specific study site did not participate in this
substudy. Twelve of the 16 eligible non-randomized untreated patients in the Primo-SHM cohort completed HRQL-questionnaires and were included in the present analysis. A total of 631 questionnaires were completed, with a median of 5 (IQR: 4-8) per patient. Most patients (85%) were men who have sex with men (MSM), 71% had a negative or indeterminate Western blot (Fiebig stage I-IV) and 80% were symptomatic during PHI. Patient characteristics are summarized in Table 1.

**Quality of life**

At baseline, patients receiving no treatment had significantly lower mental health scores \( (P = 0.02) \), lower energy/fatigue scores \( (P = 0.03) \) and lower MHS-scores \( (P = 0.04) \) than patients receiving 60-weeks of cART. Model results were adjusted for these baseline differences.

We found a significant difference between the three groups in five of the ten MOS-HIV subscales and in the PHS-score over the follow-up period of 96 weeks. Patients receiving 24- and 60-weeks of early cART showed better cognitive functioning than patients receiving no treatment \( (P = 0.005, \text{Figure 1A}) \). Participants receiving 60-weeks of early cART experienced less pain \( (P = 0.004) \), and showed better role \( (P = 0.001) \) and physical functioning \( (P = 0.02) \) and had a better PHS-score \( (P = 0.006) \) than patients receiving no treatment or 24-weeks of early cART (Figure 1B-E). Patients receiving 24-weeks of early cART showed a better mental health than patients receiving no treatment or 60-weeks of early cART \( (P = 0.02, \text{Figure 1F}) \). Social functioning, health distress, overall quality of life, energy/fatigue and the MHS-score improved significantly from baseline to 96 weeks of follow-up irrespective of the treatment group (data not shown).

Four symptoms differed significantly between the three groups over the follow-up period of 96 weeks. Patients receiving 24-weeks of early cART more often reported tingling in the hands or

### Table 1. Patient characteristics of the 112 PHI-patients at study entry

|                      | No treatment (N=28) | 24-weeks of early cART (N=45) | 60-weeks of early cART (N=39) | P-value* \\
|----------------------|---------------------|-------------------------------|-------------------------------|---------
| Male                 | 27 (96)             | 40 (89)                       | 36 (92)                       | 0.5     \\
| Age (years), mean (SD)| 44 (10)             | 41 (9)                        | 39 (9)                        | 0.1     \\
| Born in the Netherlands | 22 (79)            | 39 (87)                       | 34 (87)                       | 0.6     \\
| MSM                  | 26 (93)             | 37 (82)                       | 32 (82)                       | 0.4     \\
| Stage of PHI:        |                     |                               |                               |         \\
| - Fiebig I-IV        | 19 (68)             | 34 (76)                       | 27 (69)                       | 0.7     \\
| - Fiebig V-VI        | 9 (32)              | 11 (24)                       | 12 (31)                       |         \\
| Acute retroviral syndrome | 22 (79)       | 34 (76)                       | 34 (87)                       | 0.4     \\
| Plasma HIV-1 RNA (log₁₀ copies/ml), median (IQR) | 5.2 (4.6-5.8) | 5.0 (4.6-5.7) | 5.1 (4.4-5.7) | 0.6     \\
| CD4 count (cells/mm³), median (IQR) | 500 (333-670) | 550 (420-735) | 430 (310-650) | 0.2     \\
| Early cART nucleoside backbone |             |                               |                               |         \\
| - zidovudine/lamivudine | n.a.              | 26 (58)                       | 24 (62)                       | 0.7     \\
| - tenofovir/emtricitabine | n.a.              | 19 (42)                       | 16 (41)                       | 0.9     \\

* Data are n (%) unless indicated otherwise. cART, combination antiretroviral therapy; IQR, interquartile range; MSM, men who have sex with men; PHI, primary HIV-1 infection; SD, standard deviation.
* P-value based on \( \chi^2 \) tests for proportions and general linear models or Kruskal-Wallis tests for continuous variables.
Figure 1. A: Cognitive functioning, B: Pain, C: Role functioning, D: Physical functioning, E: Physical Health Summary score, F: Mental health.

---•---: no treatment
---*---: 24-weeks of early cART
---Δ---: 60-weeks of early cART

feet ($P = 0.02$) and a numb feeling in fingers or toes ($P = 0.01$) than patients receiving 60-weeks of early cART or no treatment. Patients receiving no treatment reported more itchiness ($P = 0.001$) and skin changes ($P = 0.04$) than patients receiving 24- or 60-weeks of early cART. At week 8, patients receiving 24- or 60-weeks of early cART reported more nausea ($P = 0.002$), diarrhoea ($P < 0.001$), abdominal pain ($P = 0.02$), stomach pain ($P = 0.049$) and dizziness ($P = 0.01$) than patients receiving no treatment (Figure 2). These differences had disappeared at week 24.
No differences in patient characteristics and HRQL at baseline and during follow-up were seen between the randomized (n=16) and non-randomized (n=12) untreated patients, except that the randomized patients were more often born in the Netherlands (15/16 (94%) versus 7/12 (58%), \(P = 0.02\)). When we repeated the mixed linear models including only the RCT patients, the significant differences in HRQL between the three groups disappeared for cognitive functioning and mental health, even though the trend remained similar. The differences in pain, physical functioning, role functioning and the PHS-score remained significant. For these scales, patients receiving 60-weeks of early cART had significantly better HRQL than patients receiving 24-weeks of early cART. The differences seen in reported symptoms remained the same.

Discussion

The present study was set up as a substudy of the Primo-SHM RCT, which demonstrated a clinical benefit of 24- and 60-weeks of cART initiated during PHI [1]. This substudy provides the first data on the effects on HRQL of temporary treatment during PHI. Early cART did not have a negative impact on patients’ HRQL over a study period of 96 weeks as compared with no treatment. Overall, patients receiving 60-weeks of cART showed a better HRQL than patients in whom treatment was deferred. Although the patients on early cART initially suffered more from physical symptoms, which were probably related to drug toxicity, this seemed to have minor effects on their HRQL perception. This is in agreement with a previous study in which chronic HIV positive persons on cART made distinctions between symptoms caused by HIV itself or by drug toxicity when evaluating HRQL. Disease-related symptoms, but not side effects, were related to perceptions of general health. [14]. Regardless of cART intervention, social functioning, health distress, overall quality of life, energy/fatigue and the MHS-score improved significantly during

![Figure 2](image-url)

**Figure 2.** Five symptoms were significantly different between the three groups at week 8.

- •: no treatment
- ••••: 24-weeks of early cART
- △△△: 60-weeks of early cART
the 96 weeks of follow-up in all groups. This might be explained by initial psychological distress as a consequence of being diagnosed with PHI and its acceptance over time. In addition, the symptoms occurring during PHI will also diminish without early treatment over time.

In the Primo-SHM trial, receiving 60-weeks of early cART offered no additional benefit over 24-weeks of early cART with respect to lowering the viral setpoint and the total time off therapy [1]. An unexpected finding of the present study was that patients receiving 60-weeks of early cART had a better HRQL on some of the physical MOS-HIV subscales than patients receiving 24-weeks of early cART. Because this is the first study to report the impact of early cART during PHI on HRQL, we cannot relate this finding to previous studies. This result can either be a real finding or may be the consequence of selection bias, because not all participants enrolled in the RCT completed HRQL-questionnaires. Clearly, this finding should be corroborated in future studies.

The limitation of this substudy is that we included non-randomized untreated PHI-patients to increase the sample size of the no treatment group. However, no differences were observed in HRQL between randomized and non-randomized untreated patients. Additionally, we found a similar trend in results when analyzing only the randomized patients.

In conclusion, in addition to the clinical benefit of temporary cART initiated during PHI, this substudy demonstrates that temporary early cART had a significant positive impact on patients’ HRQL over a study period of 96 weeks, despite the initial, short-term occurrence of physical symptoms, which were most likely related to drug toxicity. These findings provide important additional support for early intervention in patients with PHI and should be taken into account when considering early cART in patients with PHI.

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Contributors
MLG, JMP and PTN drafted the manuscript. MLG, RS and JMP established the cohort and together with MGA, MK and CJK were responsible for patient enrolment and trial conduct at each study site. GK performed the data entry and PTN conducted the statistical analysis. All authors provided valuable input into protocol development and interpretation of data, and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.
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