Health related quality of life outcomes in HIV-infected patients starting different combination regimens in a randomised multinational trial: the INITIO-QoL Substudy

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The health-related quality of life (HRQoL) outcomes in HIV-infected, treatment-naive patients starting different HAART regimens in a 3-year, randomised, multinational trial were compared. HRQoL was measured in a subgroup of patients enrolled in the INITIO study (153/911), using a modified version of the MOS-HIV questionnaire. The regimens compared in the INITIO trial were composed by two NRTIs (didanosine+stavudine) plus either a NNRTI (efavirenz) or a PI (nelfinavir), or both (efavirenz+nelfinavir). Primary HRQoL outcomes were Physical and Mental Health Summary scores (PHS and MHS, respectively). During follow up, an increase of PHS score was observed in all treatment arms. The MHS score remained substantially unchanged with the 4-drug combination and showed with both NNRTI- and PI-based 3-drug regimens a marked trend toward improvement, which became statistically significant when a multiple imputation method was used to adjust for missing data. Overall, starting all the combination regimens compared in the INITIO study was associated to a maintained or slightly improved HRQOL status, consistently with the positive immunological and virological changes observed in the main study. The observed differences in the MHS indicate a possible HRQoL benefit associated to the use of 3-drug, 2-class regimens and no additional benefit for the use of 4-drug, 3-class regimens, confirming that 3-drug, 2-class regimens which include 2NRTIs plus either a NNRTI or a PI should be preferred as initial treatment of HIV infection.

Key words: HIV-infection, health-related quality of life, untreated patients, antiretroviral therapy

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INTRODUCTION

Guidelines recommendations for treatment in HIV infection are generally based on the information obtained in clinical trials. Traditionally, this has been mostly represented by immunological and virological response and by a safety profile defined through the adverse events occurring during the study.

Such measures, however, only provide an incomplete assessment of the complex effects of treatment, and lack a patient-centered perspective. Health Related Quality of life (HRQoL) has been recently recognised by guidelines as a main therapeutic objective and is therefore increasingly used in the comparison of anti-HIV drugs and as an additional or independent measure of drug evaluation[1].

We here report the results of a specific QoL substudy nested in the large, multinational INITIO trial, which compared different treatment strategies for starting and continuing HIV treatment in naive patients. The INITIO-QoL substudy aimed to detect differences in patient's HRQoL between the three study treatment groups. Its final purpose was to provide, by patient's reported outcome (pro), potentially relevant additional information, alongside clinical data, for making decisions on medical treatment.

METHODS

Study treatments and patients

INITIO was a randomised, multinational, open-label study conducted at outpatient clinic sites in Australia, Brazil, Canada, New Zealand and 17 European countries[2]. The trial compared three different treatment strategies based on the use of non-nucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitors (PI) for starting and continuing HIV treatment in naive patients. Participants (n=911) were randomised in a 1:1:1 ratio to a 3-drug, NNRTI-based regimen [didanosine+stavudine+efavirenz (ddI/d4T/EFV)], a 3-drug, PI-based regimen [didanosine+stavudine+nelfinavir (ddI/d4T/NFV)], or a 4-drug, NNRTI- and PI-based regimen [didanosine+stavudine+efavirenz+nelfinavir (ddI/d4T/EFV/NFV)].

Investigators could substitute one drug with another from the same class for intolerance and so continue the allocated drug classes. This was not regarded as a regimen change. The selection of regimens after second therapeutic failure in the three-drug arms or first failure in the four-drug arm was at the discretion of the investigators.

The countries participating in the INITIO-QoL substudy were Australia, Brazil, Canada, Italy, New Zealand and UK. Patients enrolled in the main study in these countries were offered participation in this substudy and evaluated over 3 years for HRQoL. Each site obtained ethics committee approval and participants provided written informed consent.

Data Collection

Baseline demographic data included gender, age, route of transmission and duration of HIV disease. Clinical information included HIV disease status (CDC disease stage), HIV RNA viral load (VL) and CD4+ cell count. Trial visits for CD4 count, viral load, clinical symptoms, treatment status and adverse events were performed at baseline, at weeks 4, 8, 12, and every 12 weeks thereafter, with a final assessment at three years of follow-up. HRQoL assessments followed the same time points. Data collection for the substudy was coordinated by the National Italian Coordinating Center (Istituto Superiore di Sanità), where the analysis of the substudy was also performed.

HRQoL Measurement

Quality of life was assessed using the medical Outcomes Study (MOS)-HIV questionnaire, which represents a brief, comprehensive and HIV-targeted measure of health-related QoL [3,4]. The questionnaire is structured in 33 questions grouped into nine scales from which two synthetic indexes can be obtained, concerning the physical and the mental component: Physical Health Summary (PHS) and Mental Health Summary (MHS) , respectively.

Each scale examines a specific aspect of QoL: physical functioning (PF), bodily-pain (BP), vitality (VT), role functioning (RF), general health perceptions (GH), cognitive functioning (CF), health distress (HD), mental health (MH) and social functioning (SF).

The MOS-HIV questionnaire was validated in all the countries involved in the INITIO-QoL substudy as a measure of functional status and well-being in people with HIV disease, with extensive testing for reliability and validity[5-6]. The psychometric performance of the scales was retested on the substudy population performing the following evaluations: 1) internal consistency reliability, using Cronbach's alpha (value required: ≥0.70), 2) convergent validity, measured through the linear correlation between each item and its respective scale (correlation coefficient value requested: ≥0.40); 3) discriminant validity [correlation of questions with their respective scales should be higher than correlations with the other scales ($\Delta \geq 2SE$)]; and, 4) inter-scales correlation (value requested: correlation range of 0.40-0.80).

Statistical Analysis

The main trial sample size was calculated on the basis of trial endpoints, represented by virological and immunological efficacy. Additional enrollment in the HRQol substudy was free and no predetermined sample size was calculated for this substudy, which represents a secondary analysis of an exploratory nature. The aim of this sub-study was to compare the effects of the three different strategies on health related quality of life through the whole follow up period.

HRQoL analyses were performed according to both an "intention-to-treat" (ITT) and an "on treatment" (OT) approach. The OT analysis was based on QoL data observed on first allocated regimen.

Baseline characteristics (demographic, clinical and HRQoL) were compared between treatment groups with the F-Fisher test for continuous variables and with Pearson's χ^2 test for categorical variables.

Patients with incomplete data were not excluded from the analysis, which was carried out based on all the available patient information.

To evaluate the nature of the missing data occurred in the substudy, mean changes of both PHS and MHS scores were assessed in patients with/without complete data. For this analysis, patients who had final information available at the end of the study were considered to have complete data also if one or more observations were missing between

baseline and end of the study. A general linear mixed model was used to evaluate the differences between treatments in terms of changes from baseline in PHS and MHS indexes over follow-up. Change from baseline in both PHS and MHS scores was considered as an outcome in this model, with treatment regimens and time of follow-up considered as independent variables.

Missing data were handled with a multiple imputation (MI) method, and the analyses were repeated after the imputation had been done.

Statistical calculations were performed using SAS statistical package, version 8.2 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

1. Baseline characteristics

Overall, 153 patients participated to the QoL substudy, from Italy (35%), Australia (28%), UK (27%), Canada (7%) and Brazil (3%) (figure 1). There were no significant differences at baseline between treatment groups with respect to demographic and clinical variables (Table 1). The baseline characteristics of these patients were similar to those of the 911 patients randomized to the main INITIO study. The percentages of patients which agreed to join the substudy were, for each of three treatment groups, 16% (EFV), 17% (NFV) and 17% (EFV/NFV).

Baseline QoL values for all the scales and for synthetic indexes (PHS and MHS) were similar for the three treatment groups (Table 1). The tests on psychometric assumptions showed a good reliability (Cronbach's alpha ≥ 0.80 for all scales) and satisfied assumptions for construct validity (data non shown).

2. Physical and mental health summary indexes

During follow-up, an increase of PHS score (mean change from baseline) was observed in all treatment arms, while MHS increased only in both the three-drug regimen groups. Mean changes from baseline in PHS and MHS at one, two and three years are reported in figure 2.

The nature of missing data was assessed analysing the plots of PHS and MHS mean changes from baseline in patients with and without complete data, respectively. The observed results showed that the missing data operated differently in the two groups (data not shown). We therefore concluded that missing data in this study could be considered as MAR, allowing use of the general linear mixed application and of a multiple imputation strategy.

The results of the general linear mixed model showed no statistically significant differences over time in PHS scores among the treatment arms. The results for the MHS scores showed a trend toward a better response with both the 3-drug regimens, compared to the 4-drug regimen: differences in MHS score were 2.6 (95% CI: -0.4 - 5.6) between EFV and EFV/NFV (p=0.09); and 2.6 (95% CI -0.3 - 5.6) between NFV and EFV/NFV (p=0.08).

The above trend for MHS scores achieved statistical significance with the MI imputation method: differences with the EFV/NFV arm for EFV and NFV arms were, respectively 3.8 (95% CI 0.6 - 6.7, p=0.02) and 3.3 (95% CI 0.1 - 6.4, p=0.04).

The results of OT analyses regarding changes from baseline in MHS and PHS scores were similar to those provided by the ITT analysis (data not shown).

DISCUSSION

This exploratory substudy on quality of life in HIV-infected, antiretroviral naive starting different HAART regimens showed that the three-drug regimens studied produced, during three years of follow up, a general and sustained improvement of HRQoL, as assessed by mental and physical health summary scores. The four-drug regimen was associated to positive changes in the physical component of QoL, but not in the mental component of QoL.

When the extent of changes was compared among the three treatment groups, the results showed that changes in the mental health dimension were similar between the two three-drug regimens, and confirmed that both of them were superior to the four-drug regimen. No advantage for the mental component was therefore evident from starting with a four–drug regimen including both a PI and a NNRTI, because MHS scores remained in this

group similar to baseline values or decreased below such values at some points of follow-up.

In terms of changes of physical health dimension, no statistically differences were found among of three therapeutic strategies.

Our results are consistent with those by A. Casado, X. Badia et al, who also showed equivalence in HRQoL between different triple combinations in a clinical trial[7], where, however, patients with AIDS-defining diseases were not included and the follow-up period was only 1 year.

In the interpretation of our results, it is important to define the clinical relevance of the differences observed in MHS and PHS. The 2.6 point advantage in MHS observed for the three-drug combinations is clearly lower than the average differences observed between patients with and without AIDS, which amounted to 6.7 points in PHS and 4.5 points in MHS[8] that are considered clinically significant. However, in the INITIO study, the vast majority of patients were asymptomatic, and all the treatments studied had the same clinical and immunological efficacy. It is therefore likely that the QoL differences that we observed were mostly due to side effects of drugs and adherence with complex therapeutic regimens. The differences observed, even if statistically significant, may therefore either have no clinical relevance, suggesting similar QoL profile for all regimens, or indicate actual subtle differences attributable to different treatment profiles and captured by the HRQoL instrument.

In the patients belonging to the substudy, a traditional analysis of toxicity (grade>=3) did not reveal any differences among the three treatment that could explain the observed differences in QoL. However, grade 1 and 2 adverse events, also expected to affect the HRQoL, were not collected in this trial.

Our result therefore can be considered as preliminary evidence of QoL differences to be confirmed.

The causes for the lower performance of the four-drug regimen in terms of mental health can only be hypothesized. The lower quality of life observed for the mental component with the 4-drug regimen might be in some way related to psychological effects related to the more complex therapeutic scheme, the larger number of pills required and/or the

difficulties related to maintaining adherence with the regimen. No studies have investigated this issue, and further research on this argument would be useful. What is missing in the field is a list of patient-reported symptoms which better define all the heterogeneous components that affect QoL in patients receiving treatment in the HAART era[9-13].

It is important to note that, consistently with the clinical, immunological and virological results of the main study, this HRQoL evaluation did not show any benefit for starting antiretroviral treatment with a four-drug combination compared to starting with three-drug regimens, confirming that 3-drug, 2-class regimens which include 2NRTIs plus either a NNRTI or a PI should be preferred as initial treatment of HIV infection.

Furthermore, the HRQoL increases from baseline observed with these regimens can be considered as particularly positive, indicating that no major negative effect on quality of life is evident in patients starting combination antiretroviral regimens.

A possible limitation of the study is represented by patients with missing information; we addressed this phenomenon using imputation methods to treat missing data. However, it has to be considered that this is a common problem in clinical trials, and few studies have obtained QoL information over a follow up of similar length. Future studies which include QoL evaluations or other patient-reported outcomes should address this problem trying to maintain a complete data collection over the entire follow up period.

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Overall co-ordination of the trial was carried out by the MRC CTU (London) with databases held and maintained at National Centre in HIV Epidemiology and Clinical Research, University of NSW, Sydney, Australia; INSERM SC10, Paris, France; Co-ordinating Centre for Clinical Studies (KKS), Philipps University, Marburg, Germany; Laboratory of Virology and Department of Clinical Research and Evaluation, Istituto Superiore di Sanità, Rome Italy and MRC Clinical Trials Unit, London UK.

Figure 1

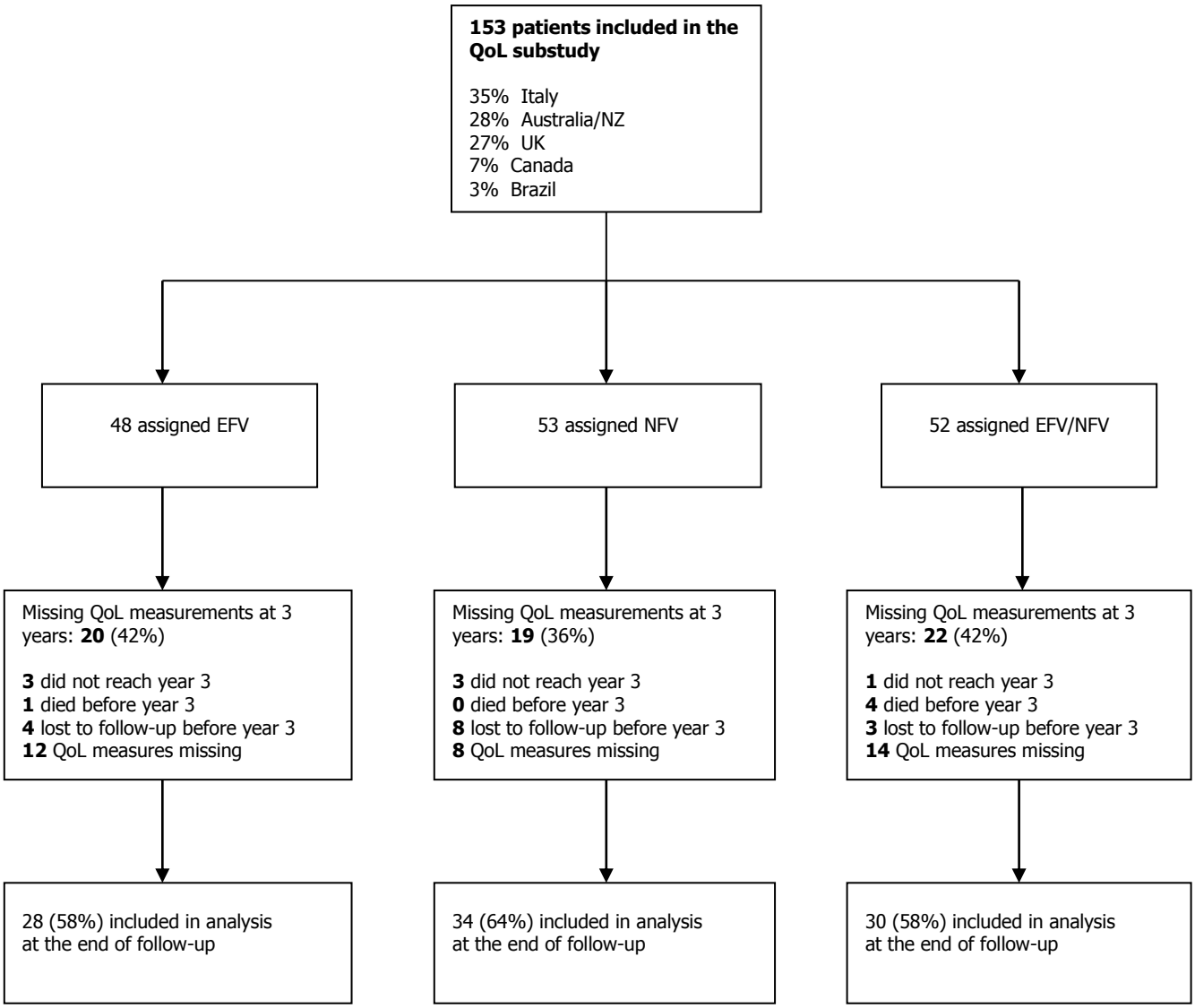
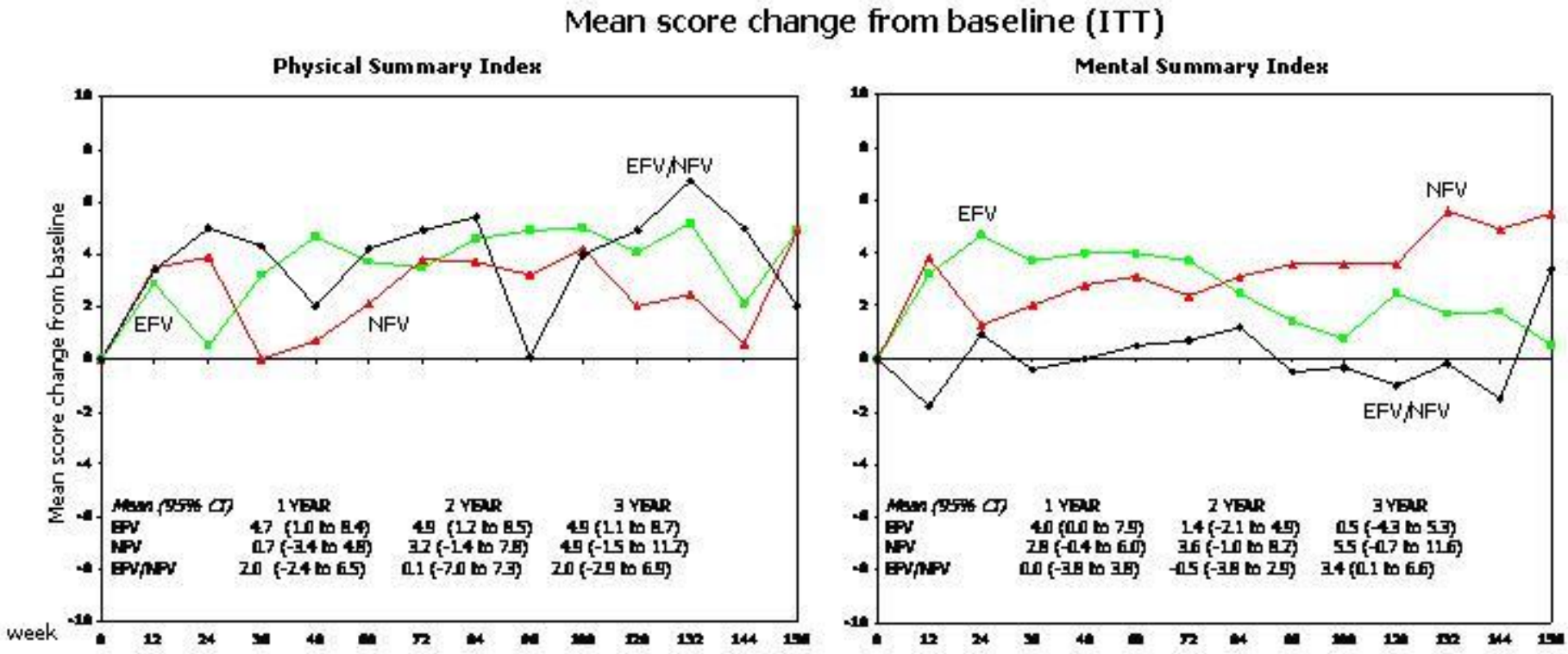

153 patients included in the QoL substudy
35% Italy
28% Australia/NZ
27% UK
7% Canada
3% Brazil
48 assigned EFV
53 assigned NFV
52 assigned EFV/NFV
Missing QoL measurements at 3 years: 20 (42%)
3 did not reach year 3
1 died before year 3
4 lost to follow-up before year 3
12 QoL measures missing
Missing QoL measurements at 3 years: 19 (36%)
3 did not reach year 3
0 died before year 3
8 lost to follow-up before year 3
8 QoL measures missing
Missing QoL measurements at 3 years: 22 (42%)
1 did not reach year 3
4 died before year 3
3 lost to follow-up before year 3
14 QoL measures missing
28 (58%) included in analysis at the end of follow-up
34 (64%) included in analysis at the end of follow-up
30 (58%) included in analysis at the end of follow-up

Table 1. Baseline characteristics

	EFV	NFV	EFV/NFV	ALL	p value
N°, randomized	48	53	52	153	
Gender: -Female: *n* ***(%)*** -Male: *n (%)*	 11 **(22.9)** 37 **(77.1)**	 10 **(18.9)** 43 **(81.1)**	 12 **(23.1)** 40 **(76.9)**	 33**(21.6)** 120 **(78.4)**	0.84 *
Age (*years):* **-**All, mean±*SD (n ,range)* mediana	 **39.7**±11.1 (48, 20-63) **40**	 **37.3**±8.7 (53, 22-56) **35**	 **38.4**±9.9 (52, 21-62) **37**	 **38.5**±9.8 (153, 20-63) **36**	0.98 **
Predominant risk factor: *n* ***(%)*** **-**Homo / bisexual: -I.V.drug use: -Heterosexual: -Other/unknown:	 25 **(52.1)** 2 **(4.2)** 19 **(39.6)** 2 **(4.2)**	 23 **(43.3)** 9 **(17.0)** 20 **(37.8)** 1 **(1.9)**	 24 **(46.1)** 6 **(11.5)** 21 **(40.4)** 1 **(1.9)**	 72 **(47.1)** 17 **(11.1)** 60 **(39.2)** 4 **(2.6)**	0.23 *
CD4+/mm³ mean *±SD (n, range)* median	 **164**±168 (48, 0-851) **106**	 **210**±153 (53, 10-630) **193**	 **204**±201 (52, 4-1056) **168**	 **193**±175 (153, 0-1056) **168**	1.00 **
HIV-RNA cp/ml (log10) mean ±SD (n, range) median	 **5.2**±0.6(48, 3.4-6.1) **5.3**	 **5.0**±0.6 (53, 3.7-5.9) **5.1**	 **5.1**±0.7 (52, 3.4-6.3) **5.2**	 **5.1**±0.6 (153, 3.4-6.3) **5.2**	1.07 **
Stage at randomization: *n* ***(%)*** -CDC A -CDC B -CDC C	 24 **50.0)** 10 **(20.8)** 14 **(29.2)**	 34 **(64.2)** 9 **(17.0)** 10 **(18.9)**	 21 **(40.4)** 18 **(34.6)** 13 **(25.0)**	 79 **(51.6)** 37 **(24.2)** 37 **(24.2)**	0.10 *
General health mean ±SD (n, range)	**42**±27 (46, 0-95)	**38**±28 (51, 0-100)	**42**±26 (50, 0-100)	**41**±27 (147, 0-100)	0.65**
Bodily pain mean ±SD (n, range)	**80**±25 (47, 22-100)	**76**±24(53, 11-100)	**74**±29 (52, 11-100)	**76**±26 (152, 11-100)	0.50**
Physical functioning mean ±SD (n, range)	**79**±24 (48, 17-100)	**70**±30 (50, 0-100)	**79**±26 (52, 17-100)	**76**±27 (150, 0-100)	0.14**
Physical role limitations mean ±SD (n, range)	**78**±37 (47, 0-100)	**67**±45 (51, 0-100)	**70**±43 (51, 0-100)	**71**±42 (149, 0-100)	0.41**
Social functioning mean ±SD (n, range)	**72**±31 (48, 0-100)	**75**±31 (52, 0-100)	**73**±32 (52. 0-100)	**73**±31 (152, 0-100)	0.88**
Mental health mean ±SD (n, range)	**65**±20 (48, 24-100)	**63**±23 (52, 0-100)	**61**±20 (52, 8-96)	**63**±21 (152, 0-100)	0.68**
Vitality mean ±SD (n, range)	**56**±24 (47, 5-100)	**55**±22 (53, 15-100)	**58**±26 (51, 0-100)	**56**±24 (151, 0-100)	0.85**
Health distress mean ±SD (n, range)	**67**±26 (47, 5-100)	**71**±26 (53, 0-100)	**71**±28 (51, 0-100)	**70**±27 (151, 0-100)	0.64**
Cognitive functioning mean ±SD (n, range)	**82**±20 (47, 10-100)	**78**±23 (53, 15-100)	**80**±23 (51, 10-100)	**80**±22 (151, 10-100)	0.69**
Quality of life mean ±SD (n, range)	**60**±26 (46, 0-100)	**56**±28 (52, 0-100)	**59**±24 (51, 0-100)	**58**±26 (149, 0-100)	0.67**
Health transition mean ±SD (n, range)	**62**±27 (46, 0-100)	**59**±21 (53, 0-100)	**59**±21 (52, 0-100)	**60**±23 (151, 0-100)	0.81**
Physical health summary scores mean ±SD (n, range)	**50**±11 (44, 25-63)	**46**±13 (47, 19-67)	**48**±12 (48, 22-64)	**48**±12 (139, 19-67)	0.45**
Mental health summary scores mean ±SD (n, range)	**49**±10 (44, 30-83)	**48**±10 (47, 19-65)	**50**±9 (48, 33-76)	**49**±10 (139, 19-83)	0.75**

*** χ^2 test; **F-Fisher test**

Figure 2



Week	0	12	24	36	48	60	72	84	96	108	120	132	144	156
EFV (n)	44	34	27	29	24	24	25	26	25	23	18	19	19	18
NFV (n)	47	38	37	33	33	31	26	25	29	25	25	20	21	22
EFV/NFV (n)	48	36	38	36	31	32	26	25	24	23	20	16	17	22