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Improved Measures of Quality of Life, Lipid Profile and Lipoatrophy after Treatment Interruption in HIV-Infected Patients with Immune Preservation: results of ACTG 5170

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Abstract

Background: Antiretroviral treatment interruption (TI) occurs frequently in routine clinical practice. The consequences of TI on quality of life (QOL), body habitus and lipid parameters have not been studied.

Methods: We assessed QOL, symptoms, lipid measurements, and body circumference changes in patients who underwent prolonged TI (up to 96 weeks) in ACTG 5170, a multicenter, prospective study. Major entry criteria were pre-antiretroviral therapy (ART) and entry CD4 count >350 cells/mm^3, entry HIV RNA <55,000 copies/mL, and on ART for >6 months. QOL was assessed at baseline and subsequent timepoints (to week 96) by patient self-report (0-100 scale), by patient reported symptoms distress module, and by the multidimensional health status tool (MHS). Fasting total, HDL and LDL cholesterol, and triglycerides were measured at baseline and subsequent time points to week 24. Neck, arm, mid-thigh, waist and hip circumferences were measured through week 96. Paired t-tests, Wilcoxon signed rank tests, and the GEE approach were used in the data analysis.

Results: 167 subjects enrolled with median baseline and nadir CD4 count of 833 and 436 cells/mm, respectively, and median time on ART 4.5 years. One-hundred forty-nine subjects were receiving a thymidine analogue containing regimen (zidovudine or stavudine prior to TI). Self-reported QOL score on ART started high (mean 83.4 at baseline) and remained so following TI (83.0 at week 96, p = 0.49). Mean number of symptoms decreased from 8.2 at baseline to 7.0 at week 96, p = 0.016. The overall symptom summary score decreased from baseline to week 96, p = 0.01. The symptoms most frequently reported during TI were fatigue, feeling sad, nervousness, insomnia, myalgias and changes in body appearance. There were no significant changes from baseline in the MHS mental or physical domain scores. Following TI, lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) decreased at weeks 12 and 24. Lipid changes were similar in patients stopping an NNRTI vs a PI regimen, except for HDL which showed greater decreases in those interrupting an NNRTI. Body circumference measurements of arm, waist, hip, and mid-thigh increased following TI.

Conclusions: In a cohort of individuals with high QOL and preserved immune function, QOL did not change during a prolonged TI. Modest decreases in total cholesterol, LDL and HDL cholesterol, and triglycerides, and a modest increase in limb fat was observed.

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Combination antiretroviral therapy (ART) has led to prolonged survival and a decrease in AIDS related complications [1-3]. The optimal time to begin antiretroviral therapy remains an unanswered question. Previous treatment guidelines recommended ART in patients with preserved immune function [4, 5]. However, the inability of ART to eradicate HIV infection and the growing recognition of ART toxicities led to reassessment of these treatment guidelines. Subsequent recommendations have suggested deferring ART until the CD4 cell count is less than 350 cells/mm^3 [6, 7].

The appropriate management of patients who began ART with high CD4 cell counts (e.g. in accordance with previous treatment guidelines) has been the subject of study. We and others demonstrated that patients with high CD4 cells (and no prior AIDS defining illnesses) could stop therapy for a period of time, with relatively low morbidity [8, 9]. However, due to the smaller sample size of these studies, the ability to recognize rare but significant events was limited. Other studies in patients with more advanced disease found somewhat higher morbidity and mortality in those who stopped antiretroviral therapy [10, 11]. In SMART, the largest study, an increased risk for serious events was observed even among patients with CD4 preservation following treatment interruption (TI), albeit at a low frequency [11].

Combination ART may be associated with poor tolerability, adverse metabolic consequences (e.g., lactic acidosis, insulin resistance, hyperlipidemia), body habitus changes (lipoatrophy and lipohypertrophy) and in some cases may adversely affect quality of life due to chronic side effects [7]. We sought to determine the impact of stopping ART on quality of life and to determine the metabolic consequences and effect on body habitus of stopping ART.

Methods

AIDS Clinical Trials Group (ACTG) 5170 was a multicenter, observational, prospective, two-step study in asymptomatic HIV-infected patients who wished to discontinue ART. The primary objective of A5170 was to determine the rate of HIV progression in patients who underwent a prolonged TI. The objectives of this analyses were to determine secondary outcomes of TI including lipid changes, body habitus changes and quality of life. The criteria for enrollment in A5170 have been described previously [8]. Briefly, the study included patients with documented HIV-1 infection, CD4 count >350 cells/mm^3 immediately prior to first ART and at time of study entry, plasma HIV-1 RNA viral load (VL) <55,000 copies/mL at screening, currently receiving ART with ≥ 2 drugs for ≥ 6 months, Karnofsky score ≥ 70 and no history of CDC category B or C HIV-related illness. The study was approved by the institutional review boards at each site. All patients gave written consent prior to enrollment.

Study Design

Patients underwent treatment interruption upon entry (Step 1) and were followed for up to 96 weeks. Baseline assessments included physical examination, routine laboratory tests including fasting lipid and metabolic panels, body circumference measurements, symptom self-reports and instruments to assess QOL. Anthropometric measurements (body circumference- neck, arm, thigh, hip, waist) were made by trained study coordinators in a standardized fashion according to ACTG standard procedures at weeks 8, 24, 48, 72, and 96. Fasting lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) were obtained at weeks 12 and, 24.

QOL was assessed by three separate survey instruments (ACTG self-report, Symptoms Distress Module, and Multi-dimensional Health Status), which have previously been used in ACTG studies [12]: 1. The ACTG patient self-report form asked about level of functioning in the past four months and used a visual analogue scale (0-100) to describe current state of health,

with “death or worst possible health” at the low end and “perfect or best health” at the high end; 2. The Symptoms Distress Module was comprised of 20 patient symptoms, each on a scale from 0 to 4. The symptoms queried included both physical and psychological symptoms. Four responses were possible for each question: ‘0’ indicated the subject does not have the symptom; ‘1’ indicated the symptom was present but not considered bothersome, “2” indicated the symptom was present but minimally bothersome; ‘3’ indicated the symptom was present and was bothersome;‘4’ means the symptom was present and bothered the subject a lot. We devised three summary components to analyze these data: the number of symptoms reported, the number of bothersome symptoms reported (defined as answering a ‘3’ or ‘4’), and an overall symptom summary score (defined as the sum of all 20 symptom scores); and 3. the Multidimensional Health Status (MHS) assessment consisted of 20 questions which were drawn from a large pool of existing questions that make up the Medical Outcomes Study [13]. This instrument assessed physical functioning, role functioning, pain, social functioning, mental health, cognitive functioning and energy level.

Patient QOL assessments were done at baseline, and at weeks 24, 48, 72, and 96 in Step 1. We examined the change in QOL by looking at the difference in each week from Step 1 baseline. A higher score indicates an increase in QOL. For the MHS each question was categorized as representing either the ‘physical’ or ‘mental’ domain. The physical and mental domains were analyzed separately and a score was calculated for each domain. A total MHS score was also calculated.

Patients entered Step 2 if patient and/or provider desired to reinitiate ART, and were then followed for at least 24 weeks. The same laboratory parameters and QOL measurement instruments described above were utilized in step 2.

Statistical Analyses

Paired t-tests compared changes in quality of life score, number of symptoms, and lipids from baseline to each week of the scheduled evaluations. Because of extreme outliers and skewed data, Wilcoxon signed rank tests were used to compare changes in body measurements over time to baseline. In addition, generalized estimating equations (GEE) were used to test the linear trend of changes in quality of life scores and number of symptoms over time. To assess whether drop out has impact on the above analyses, we performed two sensitivity analyses. In the first analysis, we repeated the above analyses but, only included subjects who completed the 96 weeks of follow-up in Step 1; in the second analysis, we used a linear mixed-effect model to evaluate the liner trend of changes in quality of life scores and number of symptoms over time. In the linear model, subject-specific intercept and slope were modeled as random effects, and the time (in weeks) was modeled as a fixed effect. Results were similar to results obtained using the GEE approach.

The above analyses were repeated by the drug class that subjects were receiving at study entry (NNRTI-containing, PI-containing, and NRTI-only). All tests were two-sided and $P < 0.05$ was considered significant. No adjustments for multiple comparisons were made. Statistical analyses were performed with SAS9.1 (Cary, NC, USA).

Results

167 subjects enrolled; the mean age was 42 years and 83% were men. The median baseline and nadir CD4 counts were 833 cells/mm^3(IQR 668-989 cells/mm^3) and 436 cells/mm^3 (IQR 375-510 cells/mm^3), respectively. Eighty-two percent of participants had VL < 400 copies/mL at study entry. The median time on ART was 4.5 years and the median number of antiretroviral drugs was 3 (range, 3-9) (table 1). At baseline, sixty patients (36%) were receiving non-nucleoside reverse transcriptase inhibitor (NNRTI) based treatment, 62 (37%) patients were

receiving protease inhibitor based treatment and 39 patients (23%) were receiving combination nucleoside analogues without a protease inhibitor or NNRTI. Six patients (4%) received a combination of an NNRTI and protease inhibitor without nucleoside analogues. Among patients receiving a nucleoside analogue as part of their regimen, 149 received a thymidine analogue (zidovudine or stavudine) as part of their regimen (irresepective of whether they were taking an NNRTI or protease inhibitor). Of the 62 patients receiving a protease inhibitor based regimen, eight received a ritonavir boosted protease inhibitor.

The main results of A5170 have been reported previously [8]. Clinical progression was uncommon. By 96 weeks, 17 of 167 participants had confirmed CD4 ≤250 cells/mm^3; two patients had a CDC category B and C event, respectively, and there were five deaths (none related to AIDS progression). Forty-six patients restarted ART.

QOL following TI

In general, study participants reported a high QOL on the visual analogue scale at baseline, which did not significantly change during follow-up. Mean (median) QOL score was 83.4 (90) at baseline (n=150) and was 83.0 (85) at week 96 (n=105), on a scale of 0-100, p = 0.49. The overall test for trend using all time points did not indicate a significant change in self-reported QOL over time, GEE method p=0.237 (Figure 1). Post-hoc analyses by drug class at time of interruption showed non-significant changes in QOL for PI and NNRTI groups and decrease in QOL (baseline to week 96) for the NRTI group (−5.5 at Week 96, p=0.03). Results from sensitivity analyses were similar to those from analyses using all subjects.

We further analyzed changes in QOL according to CD4 cell counts. We restricted this analysis to those 105 subjects who completed 96 weeks of follow-up without ART resumption. Among the 62 subjects with high (> 85) week 96 QOL, 36 maintained a CD4 cell count >=400 cells/mm^3 while off of ART, compared to 26 who had a least one CD4 cell count 400 cells/mm^3, p = 0.63. Thus maintaining a high CD4 cell count was not predictive of higher QOL at 96 weeks.

We also compared QOL among subjects who stayed in step 1 (off ART) with those who entered step 2 (restarted ART). The median time to ART resumption was 48.7 weeks. Therefore, we compared QOL at week 48 in step 1 (among those remaining off ART) to QOL at step 2 entry (about to resume ART). Mean QOL was higher among those who remained off ART compared to those who resumed: 83 vs 72, p < 0.0001. This difference was not fully explained by differing QOL at baseline to step 1, e.g. these groups had similar QOL prior to ART cessation (84 vs 81, respectively, p=0.30).

Symptoms

The most frequently reported symptoms at baseline and which were reported by at least half of patients were fatigue (67%), feeling sad (58%), insomnia (56%), nervousness (55%), myalgias (55%), concerns about body fat deposits (55%), difficulty remembering things (54%), and bloating or abdominal discomfort (51%).. Following TI, the types of symptoms reported did not change appreciably (data not shown).

The mean number of patient reported symptoms at baseline was 8.2 (n = 152); among the 105 subjects with data at week 96, the mean decreased from baseline by −1.2, p= 0.016 (Table 2). The overall test for trend using all time points indicated a significant decrease in number of symptoms from baseline (GEE method p=0.043). The overall mean symptom summary score (sum of all 20 questions) also showed a significant decrease from baseline using data from all time points, GEE method p=0.02. The mean number of bothersome symptoms did not significantly change over the course of the study, GEE method p=0.29. Results from sensitivity analyses were similar to those from analyses using all subjects. In the subgroup analysis by

drug class at baseline (NRTI, PI, NNRTI) higher number of symptoms decreased from baseline to weeks 72 (−2.1, p = 0.02) and 96 (−1.8, p = 0.02), for those who had received a PI regimen at baseline, as compared to other drug classes (range −0.8 to −0.1, all p>0.1). The symptom summary score also decreased from baseline to weeks 24, 48 and 72, only in those who were receiving a PI based regimen at baseline (p = 0.01, p = 0.04 and p=0.05, respectively).

Mean physical and mental health scores were high at baseline, 85.7 and 78.6, respectively and remained high throughout the period of TI. Among patients who remained off ART, the MHS scores did not change significantly at any subsequent week during TI compared to baseline. Results from sensitivity analyses were similar to those from analyses using all subjects.

No significant change in subjective QOL score, overall number of symptoms, type of symptoms, or MHS was observed in Step 2 among the 46 subjects who reinitiated ART (data not shown).

Body measurements

Body circumference measures generally increased during TI for arm, waist, hip, and mid-thigh, for comparison of each subject's measurements versus baseline in patients who remained off ART (Table 3). Waist and hip circumference showed modest increases following TI at all time points; while arm circumference occurred from week 24 onward and mid-thigh circumference increased following TI after week 48. In contrast, measurements of neck circumference did not change appreciably during TI. Results from sensitivity analyses were similar to those from analyses using all subjects.

Lipid Parameters

We analyzed changes in lipid parameters through week 24, by excluding subjects (n=5) who either stopped or started lipid lowering agents during this part of the study. Decreases in fasting lipids occurred following TI (Table 4). At baseline, mean LDL cholesterol was 118 mg/dl. Following TI, total, LDL and HDL cholesterol as well as triglycerides decreased significantly at weeks 12 and 24 compared to baseline. No significant changes in fasting glucose levels were observed after TI. The frequency of grade 3 or 4 lipids or glucose was low at baseline (1%) and remained low throughout the study. The mean changes in LDL, total cholesterol and triglyceride levels were similar in those patients on NNRTIs or PIs (significant decrease in all parameters). HDL decreased overall, an effect which was somewhat more pronounced in those patients on NNRTIs at baseline compared to those on PIs at baseline (change from baseline to week 24: −3.43 vs −7.47 mg/dL, PI vs NNRTI, p < 0.05). Those patients on NRTIs alone did not show significant changes in lipid parameters from baseline, although the number in this category was low.

Since both HDL-cholesterol and total cholesterol (as well as LDL cholesterol) decreased with TI, we also compared the total cholesterol to HDL cholesterol ratio at baseline and each time point. At baseline the mean ratio was 4.8. There was no significant change in the ratio during Step 1. Results from sensitivity analyses were similar to those from analyses using all subjects.

Upon resumption of ART, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides increased significantly within the first eight weeks of resuming ART (data not shown).

Discussion

While most patients who start ART should continue treatment indefinitely, in practice there are some patients who will interrupt therapy for various reasons [14]. Such reasons may include

drug toxicity or intolerance, drug related metabolic or body habitus changes, pill fatigue, lack of financial resources and negative effects on QOL. TIs may be relatively brief (weeks to a few months) in cases of medication toxicity, short term adherence difficulties, intolerance or may be longer (months to a few years), for example, in cases of ongoing substance abuse, lack of financial resources, or in cases in which therapy was recommended to be initiated at higher CD4 cell counts than is currently recommended. Since in practice TIs are common [14, 15], it is important to know the affects of TI on quality of life, as well as on metabolic profile and body habitus. Such knowledge may help providers and patients who are faced with a scenario in which TI is being considered.

In our cohort of individuals with preserved immune function and no prior AIDS related conditions, ART interruption was generally safe [8]. Patient reported QOL scores remained high following TI and did not significantly change following TI. The overall symptoms summary score decreased following TI. In addition, the mean number of symptoms per patient decreased during TI. Importantly, there was no evidence that QOL worsened by any of the measured parameters e.g. visual analogue score, self reported symptoms (including bothersome symptoms), or the physical or mental aspects of the MHS. Although QOL was generally high, the fact that QOL among those who resumed ART was lower than those who continued a drug holiday suggests there is a subset of individuals who feel worse off therapy. Although QOL scores were generally high, most patients did report some symptoms both at baseline and following TI. At baseline more than half of patients reported fatigue, feeling sad, insomnia, concerns about lipohypertrophy, feeling anxious, myalgias, and trouble remembering things. Although these symptoms generally decreased following TI, a majority of patients continued to have symptoms following TI. Prior studies have documented that symptoms associated with HIV disease progression and/or therapy adversely affect health related QOL. [16-21]. Antiretroviral medications that result in increased symptoms and thus adversely affect QOL may result in decreased adherence [22], which may ultimately lead to virologic and clinical failure.

Although symptoms directly or indirectly related to HIV replication were generally low in our cohort others have reported higher rates. Thus, while our study only reported one documented case of definite acute retroviral rebound syndrome (0.6%) some TI studies have reported higher rates of symptoms typical of ARS [9]. The possibility of transient ARS symptoms needs to be considered in patients undergoing TI. Furthermore, as we and others have reported there is a small but finite risk of non-AIDS defining conditions developing during TI, such as herpes zoster, mucosal candidiasis and thrombocytopenia [8, 9, 11]. The possibility of such conditions following a TI should be considered.

Few other studies have evaluated QOL following ART interruption. Small studies of intermittent short treatment interruption (30 day TIs) have reported differing results. Some have shown mild QOL improvements [23], while others have not [14, 24]. Another small non-randomized, prospective study that compared a group that underwent TI to a group that did not undergo a TI found no improvement in physical or mental health scores after TI. [25] A study by Ruiz et al did demonstrate improvement in psychosocial aspects of QOL among patients who underwent a TI compared to those who continued therapy [26]. However, physical aspects of QOL did not differ among patients who continued therapy compared to those who interrupted therapy. A larger study, e.g. SMART, recently reported that QOL decreased in patients receiving intermittent therapy compared to those who received continuous therapy [27]. However, the SMART study population differed considerably from that of A5170. Patients who enrolled in SMART were more immunologically and clinically advanced and only three-fourths were receiving ART at time of enrollment.

Lipoatrophy and lipohypertrophy, which are associated with ART, are considered negative consequences of ART by patients and adversely affect patient QOL. One study indicated that some patients were sufficiently concerned about the development of lipodystrophy that they were willing to trade years of life if they did not develop the syndrome [28]. Approximately half of patients in our cohort were concerned about changes in body appearance including fat deposition and/or weight gain at the time of TI. However, we did not have a specific question to address patient concerns about lipoatrophy. Patients interrupting ART (a thymidine analogue containing regimen in the majority) had immediate increases in waist and hip circumference and delayed (small) statistically significant gains in limb fat. The slow increase in limb fat in patients interrupting therapy is consistent with other studies and suggests a residual effect of these medications. These results are consistent with prior data showing that among nucleoside analogues, thymidine analogues are most commonly associated with lipoatrophy [29]. Another recent study of prolonged TI reported some improvement in lipodystrophy in patients who underwent TI compared to those who continued ART, however, this study was limited by the fact that lipodystrophy was self reported [9].

Multiple ART regimens have been associated with adverse effects on lipid parameters, e.g., increase in total and LDL cholesterol and triglycerides [30, 31]. Some studies have also documented a small but significant increased risk of cardiac events in patients receiving ART [32-34]. Switching therapy to more “lipid friendly” regimens or interrupting therapy may have beneficial effects on lipid parameters. We observed small but significant improvements in several lipid parameters in patients who interrupted ART. Total and LDL cholesterol improved (decreased) as did triglycerides. Similar changes in the above lipid parameters were observed in patients interrupting NNRTI and PI based regimens. HDL cholesterol decreased as well an effect which was more pronounced in patients on an NNRTI at baseline. The decrease in HDL may negatively affect the overall cardiac risk profile; importantly, however, there was no significant change in the total to HDL cholesterol ratio. Our findings with regards to improvement of lipid mirror those of recent studies, which have also noted an improvement in lipid parameters following TI [9, 35, 36]. However, one large study also noted that the total cholesterol to HDL cholesterol ratio increased, an effect which could negatively affect the cardiac risk profile [37].

Our study has limitations. While it was prospective, we did not include a control group in whom therapy was continued. Thus, we could not directly compare QOL in patients who continued therapy compared to those who interrupted therapy. However, we do have baseline QOL assessments and were thus able to compare each patient's QOL at various study time points to the baseline assessments. Similarly, we could not compare lipid parameters and body measurement in patients who continued therapy to those who interrupted therapy, but we did compare subsequent lipid and body measurements following TI to baseline values. As in other studies of lipodystrophy, changes in body fat occur very slowly following discontinuation of offending antiretroviral agents and it is not clear if the body fat changes seen in our study are clinically significant. The majority of patients in our study interrupted a thymidine analogue containing regimen. Thus it is not clear if similar results would be obtained with antiretroviral regimens not containing thymidine analogues. Our study also included few patients who interrupted a boosted protease inhibitor reflecting the prevailing clinical practice at the time. Thus, our results can not necessarily be extrapolated to patients receiving this combination. Finally, since patients were free to restart ART at any time, there are decreasing numbers of patients contributing data over time. The sensitivity analysis which included only those subjects who were in Step 1 for 96 weeks gave similar results to that which included all subjects, and the marginal model using the GEE method produced similar results to those given by the subject-specific model (liner mixed-effect model).

In conclusion, in patients with preserved immune function who started ART (most including a thymidine analogue) at high CD4 cell counts and later discontinued therapy, quality of life remained high. There was no evidence of worsening quality of life in patients who underwent TI and there was some improvement in overall symptoms. In addition, lipids (total cholesterol, LDL cholesterol, and triglycerides) generally improved following TI. Following TI, arm and thigh circumference increased slowly, resulting in a mild improvement in limb fat. Despite the potential benefits of TI in our study, TI entails important risks, which must be carefully considered. Future TI studies should include evaluation of QOL, lipids and lipodystrophy in addition to clinical, virologic and immunological endpoints.

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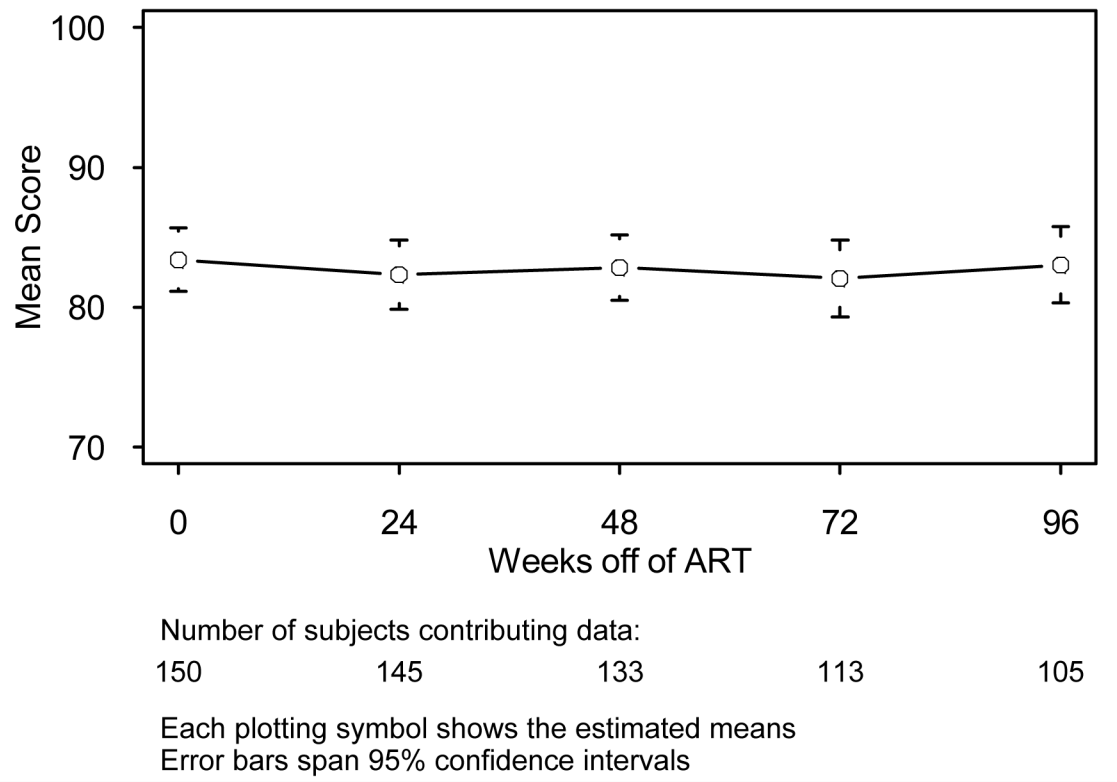

Figure 1.
Self-Reported Quality of life over time.

Table 1

Baseline antiretroviral characteristics.

Time on ART, median, (range)	**4.5 yrs. (0.5-15)**
Nucleoside analogues	n
Zidovudine	88
Stavudine	61
Didanosine	18
Abacavir	44
Lamivudine	136
Tenofovir	8
Zalcitabine	3
Non-Nucleoside Reverse Transcriptase Inhibitors	n
EFV	39
NVP	27
Protease inhibitors	n
Nelfinavir	31
Indinavir	24
Ritonavir	11
Saquinavir	6
Lopinavir-ritonavir	6
Amprenavir	3

Table 2

Symptoms Distress

	Week	*N*	*Mean*	*Median*	*Mean change from baseline*	*95% CI of change from baseline*	*T-test p -value*[*]
Number of Symptoms	0	152	8.2	7	-	-	-
	24	149	7.3	7	−0.8	(−1.7, 0.04)	0.061
	48	137	7.8	7	−0.6	(−1.4, 0.2)	0.167
	72	114	7.6	7	−0.9	(−1.8, 0.1)	0.081
	96	105	7.0	7	−1.2	(−2.2, −0.2)	0.016
Number of Bothersome Symptoms	0	152	2.0	1	-	-	-
	24	149	1.6	0	−0.4	(−0.9, 0.1)	0.151
	48	137	1.7	0	−0.4	(−0.9, 0.05)	0.079
	72	114	2.0	1	0.1	(−0.4, 0.7)	0.683
	96	105	1.8	1	−0.1	(−0.7, 0.5)	0.692
Symptom Summary Score	0	149	17.2	14	-	-	-
	24	144	14.9	12	−2.4	(−4.3, −0.6)	0.011
	48	133	15.7	14	−1.8	(−3.5, 0.01)	0.051
	72	113	15.8	13	−0.9	(−2.9, 1.1)	0.375
	96	105	14.6	13	−1.8	(−3.9, 0.2)	0.082

[*] P value for comparison of mean value at corresponding week to baseline value

Table 3

Body Circumference Measurements

	Week	*N*	*Mean*	*Median*	*Median change from baseline*	*IQR (25% -75%)*	*Wilcoxon p-value**
Neck (cm)	0	162	39.0	39.3	-	-	-
	8	160	39.2	39.4	0.0	(−0.7, 0.7)	0.637
	24	147	38.7	39.4	0.0	(−0.8, 1.0)	0.607
	48	135	39.1	39.6	0.3	(−0.7, 1.3)	0.027
	72	111	39.4	39.2	0.0	(−0.7, 1.2)	0.162
	96	105	39.5	39.3	0.1	(−0.9, 1.0)	0.531
Arm (cm)	0	162	31.9	32.0	-	-	-
	8	160	32.0	32.0	0.0	(−0.6, 0.7)	0.237
	24	147	32.2	32.4	0.3	(−0.6, 1.5)	0.031
	48	135	32.6	32.4	0.5	(−0.8, 1.6)	0.015
	72	111	32.9	32.6	0.1	(−0.7, 1.8)	0.053
	96	105	33.0	32.4	0.5	(−0.9, 1.8)	0.012
Thigh (cm)	0	162	50.7	50.8	-	-	-
	8	160	50.9	50.6	0.0	(−1.3, 0.8)	0.702
	24	147	50.4	50.9	0.0	(−1.7, 2.0)	0.949
	48	135	51.0	51.2	0.4	(−1.3, 2.0)	0.131
	72	111	53.0	52.6	1.0	(−0.9, 3.2)	0.0004
	96	105	52.1	51.5	0.7	(−1.1, 2.8)	0.01
Waist (cm)	0	162	90.4	90.0	-	-	-
	8	160	91.7	89.5	0.6	(−0.5, 2.2)	0.0007
	24	147	90.6	89.8	0.8	(−1.1, 3.4)	0.014
	48	135	90.9	91.0	0.9	(−1.9, 3.8)	0.008
	72	111	93.6	93.1	2.3	(−0.2, 5.6)	<.0001
	96	105	92.4	93.9	1.8	(−2.0, 6.1)	0.001
Hip (cm)	0	162	96.6	96.0	-	-	-
	8	160	97.8	96.5	0.4	(−0.7, 2.0)	0.007
	24	147	95.8	96.8	0.6	(−1.1, 2.5)	0.011
	48	135	96.9	97.0	0.8	(−1.5, 3.1)	0.021

	Week	*N*	*Mean*	*Median*	*Median change from baseline*	*IQR (25% -75%)*	*Wilcoxon p-value*[*]
	72	111	98.8	97.9	0.8	(−1.6, 3.5)	0.022
	96	105	97.8	98.2	1.2	(−1.3, 0.8)	0.002

[*] P value for comparison of median value at corresponding week to baseline value

Table 4

Fasting lipids values

	Week	*N*	*Mean*	*Median*	*Mean change from baseline*	*95% CI of change from baseline*	*T-test p-value**
Total Cholesterol (mg/dL)	0	152	195.0	192.0	-	-	-
	12	150	174.4	170.5	−23.4	(−29.6, −17.2)	<.0001
	24	144	175.4	173.0	−19.8	(−27.8, −11.7)	<.0001
LDL Cholesterol (mg/dL)	0	152	117.9	114.0	-	-	-
	12	150	109.1	108.0	−9.5	(−15.1, −3.9)	0.001
	24	144	110.2	111.0	−9.8	(−16.7, −2.9)	0.006
HDL Cholesterol (mg/dL)	0	152	43.5	42.0	-	-	-
	12	150	39.4	36.5	−4.743	(−6.1, −3.4)	<.0001
	24	144	39.8	36.0	−4.144	(−6.6, −1.7)	0.001
Triglycerides (mg/dL)	0	152	200.2	149.0	-	-	-
	12	150	136.7	122.0	−59.5	(−81.0, −38.0)	<.0001
	24	144	156.8	121.5	−41.1	(−61.4, −20.7)	0.0001

* P value for comparison of mean value at corresponding week to baseline value