

# Fatigue, Physical Fitness and Quality of life in Patients with Hepatitis C Virus Infection During the Combination Therapy

Project No. : NHRI-EX103-10121PC

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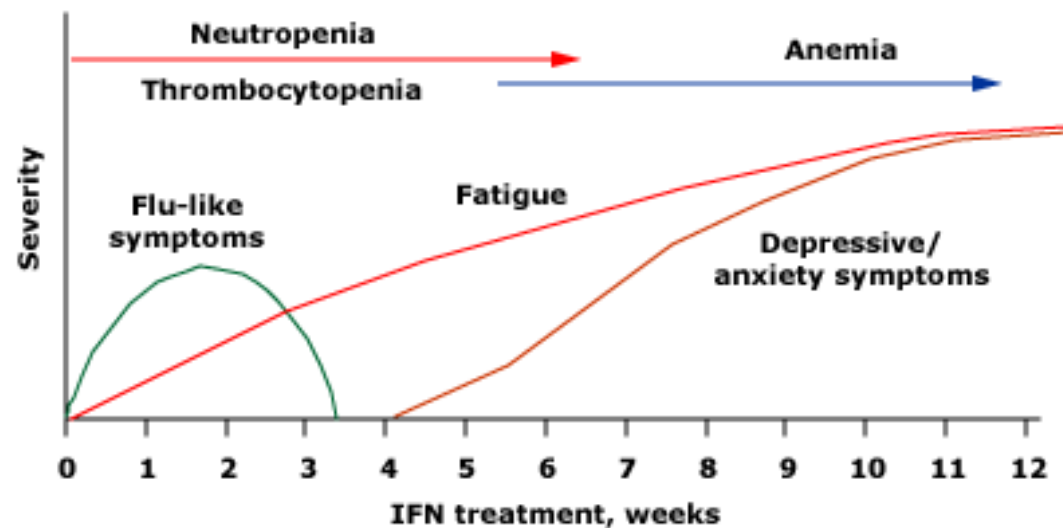
Affiliation/Institution : National Taiwan University



# Introduction

- **An increasing incidence of HCC mainly attributed to HCV infection has been observed in Taiwan over the last 20 years** (Lai, 2006; Lu et al., 2006 )
- **Current mainstay of treatment** (Yu, & Chuang, 2009; Zic, 2005)
  - Pegylated interferon  $\alpha$  (Peg-IFN  $\alpha$ ) plus ribavirin (RBV):
  - 12-16 (Genotype 2, 3 RVR +), 24 (Genotype 2, 3), 48, 72(Genotype 1,4, 5,6) (Note: Rapid Virological Response, RVR)
- **Multiple symptoms along with the therapy** (Horsmans, Y., 2006; Lotrich, F.E., et al., 2007; Raison, C.L., et al., 2005)
  - Severe fatigue, insomnia, flu-like symptoms, muscle aches, depression or even suicidal ideation
  - 10-14% stop treatment due to side effects (Fried et al, 2002, Jun et al, 2012, Yu et al, 2005)

## The time course of side effects associated with interferon

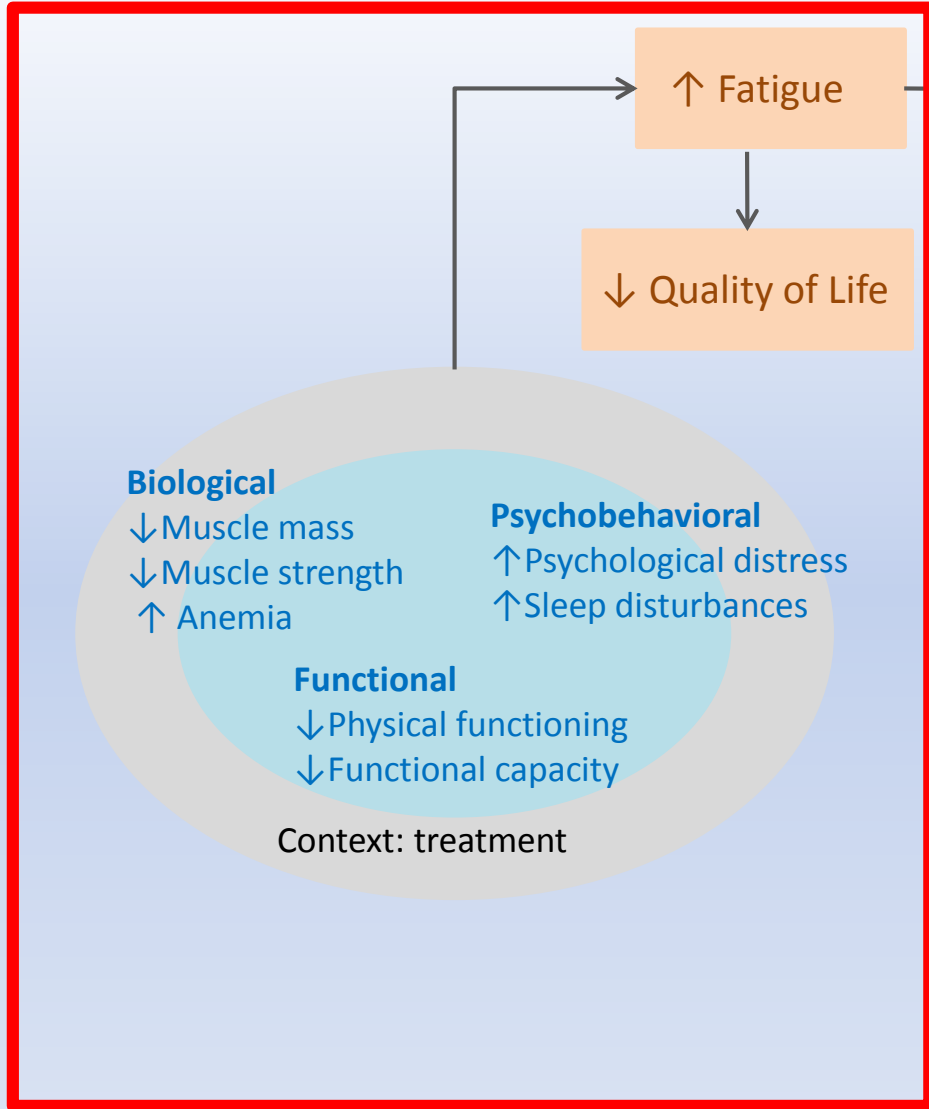


Courtesy of Nezam H Afdhal, MD and T Barry Kelleher, MD, MRCPI.

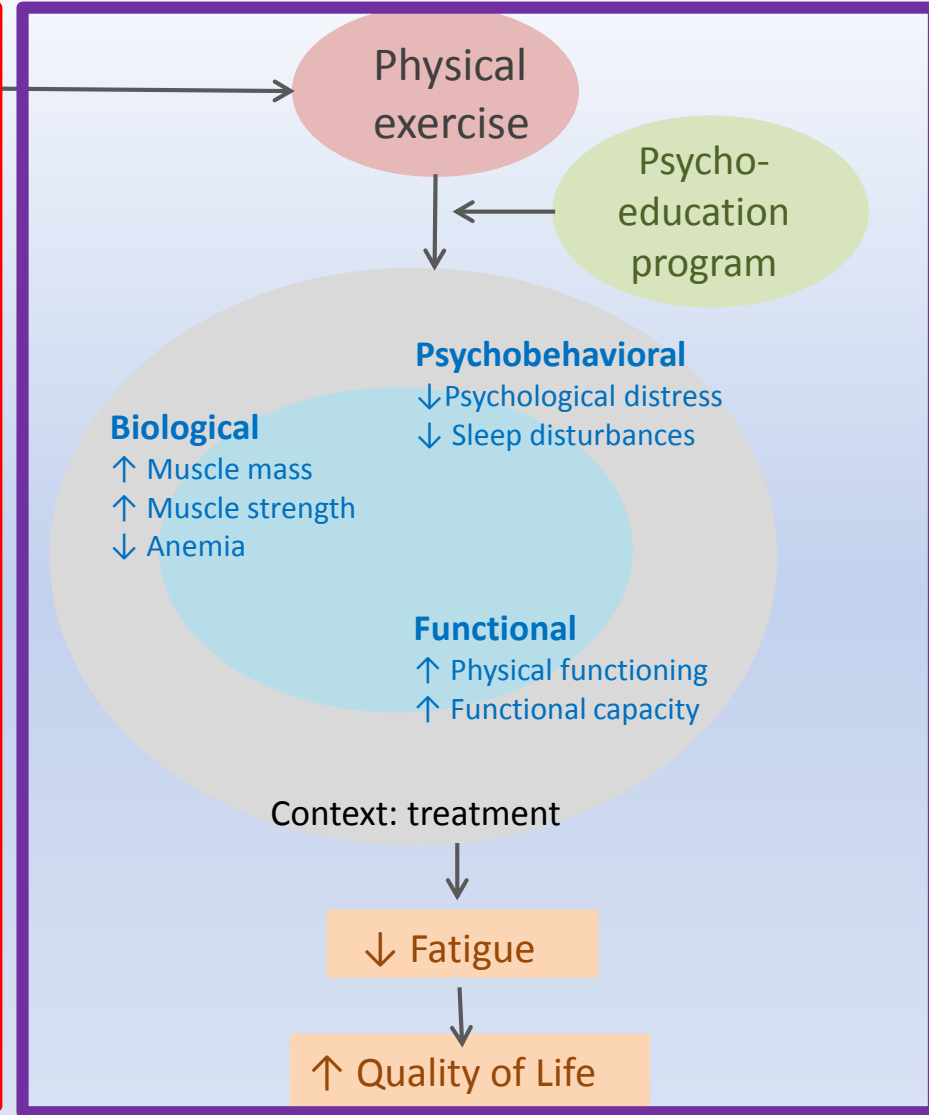
# **Introduction**

- **Physical and psychological distresses deteriorate patients' quality of life** (Chang, S.C., et al., 2008; Kang, S.C., et al., 2005)
- **Physical activity has been supported to ameliorate both physical and psychological distress, but not in this population**

## The First Phase: 1-2 years (2012-2013)



## The Second Phase: 3-4 years (2014-2015)<sup>5</sup>



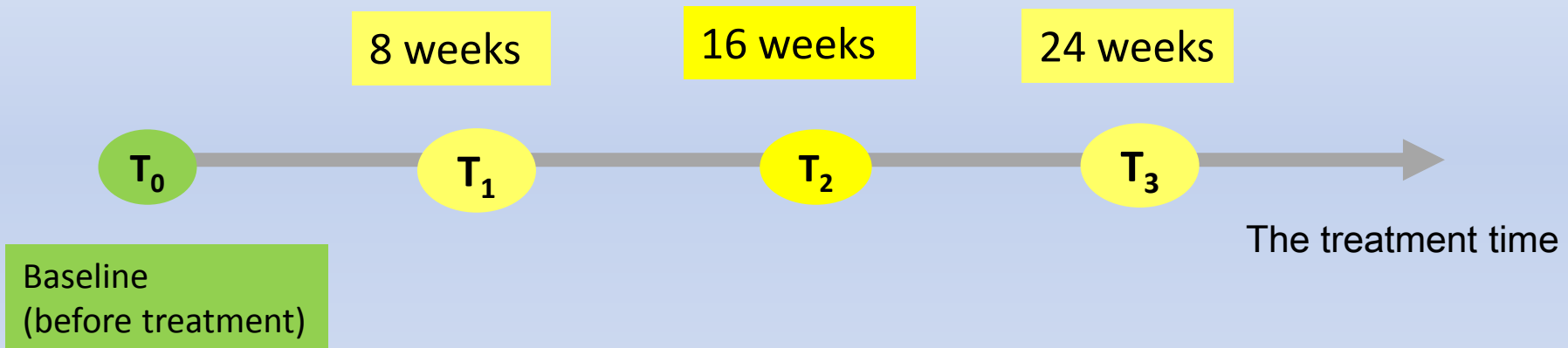
*Figure 1: A Revised Biobehavioral Model for the Study*

# Purposes

- (1) Examine the changes of physical fitness component (e.g., muscular strength and cardiopulmonary fitness), fatigue, and quality of life
- (2) Explore the significant factors related to QOL over the 24 weeks of combined treatment

# Methods

- A prospective correlational and longitudinal design (four time points)



- Patients were recruited from a medical center at outpatient settings in Northern Taiwan

# Inclusion and Exclusion criteria

## Inclusion criteria

- Adult ( $\geq 20$  years old) with chronic hepatitis C
- Receive Peg-IFN  $\alpha$  plus RBV combined therapy at least 24 weeks
- Able to communicate verbally

## Exclusion criteria

- Patients with recent unstable angina, myocardial infarction, severe arterial hypertension at rest, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
- Karnofsky functional status  $< 60$
- Malnutrition (BMI  $< 18$  kg/m<sup>2</sup>)

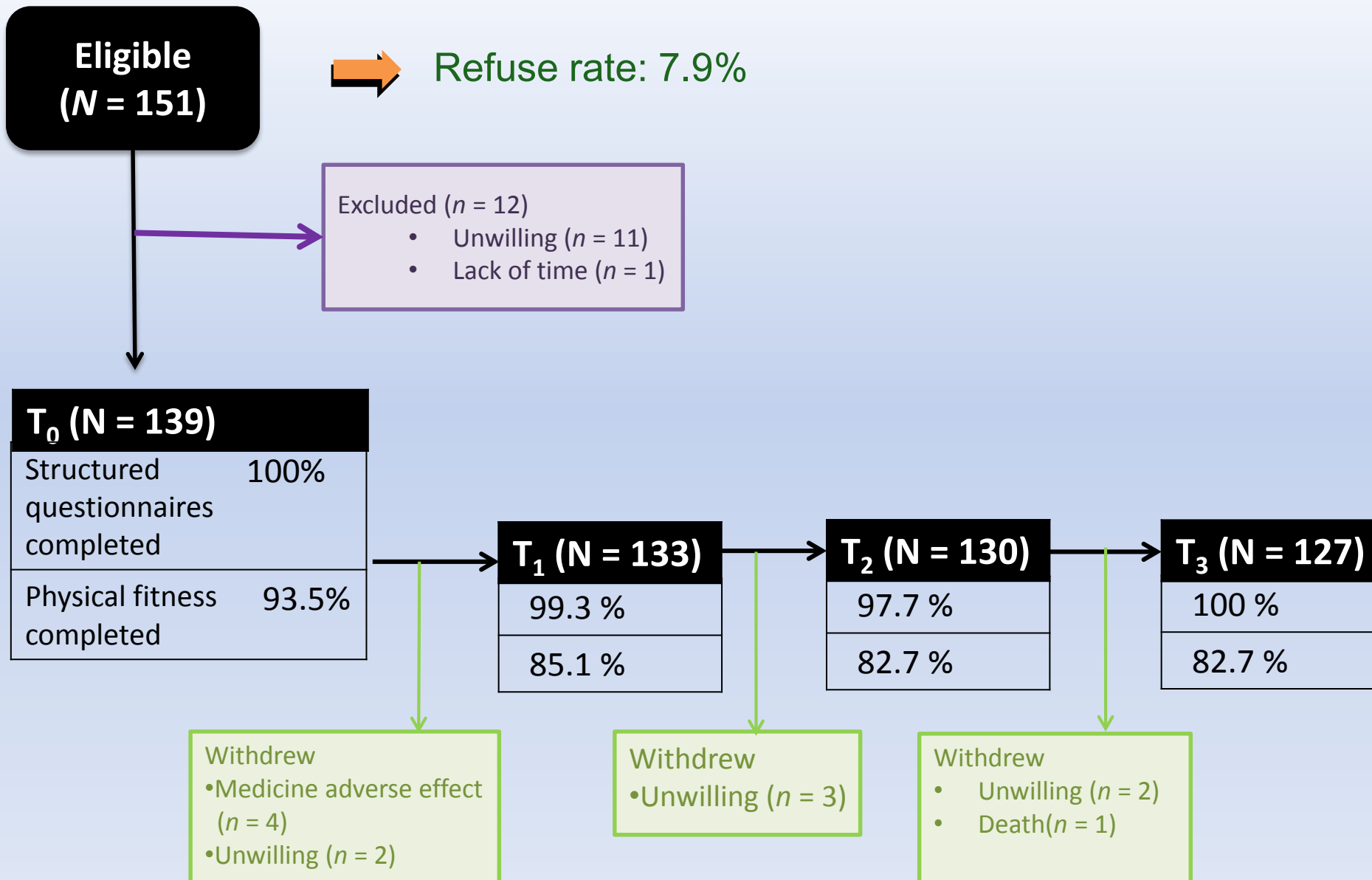


# Variables and Measures

Variables	Measures
	<b><u>Questionnaire</u></b>
Demographic and clinical disease*	Background Information Form
Functional status	Karnofsky Performance Status (KPS)
Fatigue	Fatigue Symptom Inventory (FSI)
Anxiety and depression	Hospital Anxiety and Depression Scale (HADS)
Sleep disturbance	Medical Outcomes Study (MOS)-Sleep Scale
Quality of life	The 36-item Short-Form Health Survey (SF-36)
	<b><u>Physical fitness Measurement</u></b>
Cardiopulmonary fitness	Field test (6-minute walk test)
Strength of the upper extremity muscles	Grip strength measured by digital hand dynamometer
Strength of the lower extremity muscles	Knee extension and hip flexion measured by a power track 2 commander hand-held dynamometer

\* Only measured at baseline (before treatment,  $T_0$ )

# Flow chart



# Result

## (Demographic and Clinical Disease Characteristic )

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- **Average age:** 47.3years
- **Male :** Female = 2.1 :1
- **Functional Status by Karnofsky Performance Status**
  - 100%: 7 (5 %)
  - 90%: 132 (95%)
- **Genotype**
  - **Type 1 (49.7%)**, Type 2 (32.4%), Type 6 (7.9%), Type 1+2 (5.8%), other (4.2%)
- **Comorbidity**
  - n = 86 (61.9%)
  - HIV (36.7%), hypertension (20.9%)

## Change of Laboratory Data During 24 Weeks

Variable (unit)	T <sub>0</sub> <sup>a</sup> (N = 139)		T <sub>1</sub> (N = 133)		T <sub>2</sub> (N = 130)		T <sub>3</sub> (N = 127)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hb (g/dl)	14.50	1.78	12.02	1.96	11.319	1.70	11.91	4.87
WBC (/μL)	5611.29	1444.01	3660.45	1319.42	3254.53	1071.64	3230.55	1105.67
PLT (K/μL)	203.91	53.59	158.37	52.57	171.12	153.82	157.35	55.83
AST (U/L)	64.76	56.04	34.14	29.06	33.23	23.15	31.88	24.27
ALT (U/L)	104.29	116.06	32.28	31.90	29.70	27.61	28.50	24.69

*Note:* <sup>a</sup>Four time points, baseline (before treatment, T<sub>0</sub>), and at 8 weeks (T<sub>1</sub>), 16 weeks (T<sub>2</sub>), and 24 weeks (T<sub>3</sub>) during treatment.

# Change of Symptom Distress During Treatment

Rank	T <sub>0</sub> (N = 139)			T <sub>1</sub> (N = 133)			T <sub>2</sub> (N = 130)			T <sub>3</sub> (N = 127)		
	Symptom	M	SD	Symptom	M	SD	Symptom	M	SD	Symptom	M	SD
1	Fatigue	1.19	1.04	Fatigue	1.95	1.12	Fatigue	1.78	1.09	Fatigue	1.46	1.05
2	Insomnia	0.97	1.19	Dry mouth	1.29	1.13	Dry mouth	1.40	1.13	Alopecia	1.40	1.38
3	Memory decline	0.65	0.84	Insomnia	1.28	1.25	Insomnia	1.32	1.21	Insomnia	1.30	1.20
4	Dry mouth	0.60	0.80	Appetite decline	1.18	1.16	Skin itch	1.08	1.14	Skin itch	1.06	1.14
5	Inattention	0.58	0.85	Short of breath	1.00	1.10	Appetite decline	1.05	1.18	Dry mouth	1.04	1.05

Note: Symptom distress was measured by the SDS ranging from 0 (no distress at all) to 4 (as much distress as possible);

# Change of Fatigue Characteristics, Psychological Distress, and Sleep Disturbance During 24 Weeks

Variable	T <sub>0</sub> <sup>a</sup> (N = 139)		T <sub>1</sub> (N = 133)		T <sub>2</sub> (N = 130)		T <sub>3</sub> (N = 127)		beta	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
<b>FSI</b>	30.14	24.45	<b>44.20</b>	27.70	40.29	24.89	37.65	27.33		
Fatigue intensity <sup>b</sup>	11.20	8.40	<b>15.50</b>	8.50	14.56	8.26	13.61	8.49	.753	<b>.002</b>
Worst fatigue	4.55	3.01	<b>5.91</b>	2.78	5.44	2.68	4.96	2.89	.116	.196
Average fatigue	3.06	2.23	<b>4.20</b>	2.26	3.95	2.183	3.69	2.24	.177	<b>.006</b>
Fatigue Duration	5.63	4.30	<b>7.70</b>	4.70	6.83	3.98	6.43	4.52	.236	.053
Number of days fatigued <sup>c</sup>	2.83	2.36	<b>3.64</b>	2.23	3.38	2.11	3.24	2.31	.116	.069
Much of the days fatigued <sup>d</sup>	2.79	2.34	<b>4.07</b>	2.85	3.45	2.24	3.19	2.44	.115	.103
Fatigue interference with functioning	13.30	14.10	<b>21.00</b>	16.9	18.9	14.73	17.61	16.00	1.197	<b>.007</b>
<b>HADS</b>										
Anxiety	4.50	4.54	5.08	5.00	<b>5.65</b>	4.97	5.22	4.64	.264	<b>.030</b>
Depression	3.60	3.47	4.66	4.04	<b>4.91</b>	4.16	4.79	4.06	.399	<b>.001</b>
<b>MOS</b>										
Sleep disturbance	27.33	25.04	34.54	28.48	36.07	25.79	<b>36.46</b>	24.33	3.031	<b>.000</b>
Sleep problems index II	24.92	17.40	31.75	20.60	<b>31.86</b>	18.58	31.08	16.65	1.994	<b>.000</b>

## Change of Quality of Life During 24 Weeks

Variable	<u>T<sub>0</sub><sup>a</sup> (N = 139)</u>		<u>T<sub>1</sub> (N = 133)</u>		<u>T<sub>2</sub> (N = 130)</u>		<u>T<sub>3</sub> (N = 127)</u>		Beta	p value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
<b>SF-36</b>										
<b>Physical component summary</b>	52.89	7.04	<b>49.22</b>	7.42	49.65	7.26	50.42	7.23	-.811	<b>.000</b>
<b>Mental component summary</b>	47.82	10.74	44.52	10.97	<b>43.66</b>	10.73	43.77	10.19	-1.357	<b>.000</b>
<b>Physical functioning</b>	54.25	4.96	<b>50.16</b>	7.12	50.82	6.12	51.35	5.81	-.968	<b>.000</b>
<b>Role physical</b>	49.69	9.66	44.17	10.39	<b>44.05</b>	10.61	44.57	9.67	-1.714	<b>.000</b>
<b>Bodily pain</b>	55.26	9.05	<b>51.77</b>	10.32	52.03	9.84	52.51	9.70	-.969	<b>.001</b>
<b>General health</b>	45.73	11.95	45.12	11.19	<b>44.16</b>	10.65	44.88	10.74	-.387	.160
<b>Vitality</b>	52.59	10.72	<b>46.90</b>	10.85	47.14	10.53	48.41	10.72	-1.451	<b>.000</b>
<b>Social functioning</b>	48.97	9.79	<b>45.99</b>	9.81	46.08	9.73	46.26	9.16	-.929	<b>.002</b>
<b>Role emotional</b>	48.43	9.59	45.01	10.86	43.80	11.41	<b>43.56</b>	10.34	-1.963	<b>.000</b>
<b>Mental health</b>	48.18	10.38	45.68	11.06	<b>45.15</b>	10.91	45.38	10.45	-.953	<b>.001</b>

# Change of Physical Fitness During 24 Weeks

Variable	T <sub>0</sub>		T <sub>1</sub>		T <sub>2</sub>		T <sub>3</sub>		β	p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Body weight	65.24	11.64	64.08	11.62	62.97	11.40	62.71	11.59		
<b>BMI</b>	23.61	3.31	23.20	3.31	22.87	3.24	22.76	3.22	-.292	.000
<b>Muscular strength</b>										
Hand grip	32.02	12.19	30.31	12.52	29.43	11.44	28.29	10.65	-1.216	.000
Hip flexion	20.34	5.12	20.27	5.45	20.38	5.22	20.02	4.74	-.082	.513
Knee extension	18.07	4.85	17.93	4.27	17.78	3.80	17.66	3.20	-.138	.297
<b>Muscular endurance</b>										
30s chair stand test	18.91	7.65	18.02	7.19	18.24	7.43	18.44	7.20	-.139	.411
<b>Cardiopulmonary</b>										
6MWT <sup>b</sup>	486.78	99.03	472.59	109.45	467.64	100.93	460.56	102.61	-.8491	.001
<b>Subjective strain</b>	3.02	2.31	3.03	1.52	2.90	1.58	2.83	1.26	-.067	.339
<b>KPS<sup>d</sup></b>	90.5	2.2	89.4	2.69	89.22	2.69	89.59	2.37	-.305	.000

Note: <sup>a</sup>KPS: karnofsky Performance Scale; <sup>b</sup>Generalized estimating equations were used to examine the change of measured variable.



## *Associated Factors Related to Change of Physical Related Quality of Life in the Generalized Estimating Equations Analysis*

Variable	Coefficient	Std. Err.	Wald chi-square	p-value
Age	-.009	.047	.041	.840
Marry (1=Married; 0= the others)	-.727	1.077	.456	.499
Education	.009	.123	.006	.940
Feeling tired	<b>-.033</b>	.013	6.482	<b>.011</b>
HIV (0=NO; 1=YES)	-1.779	1.059	2.822	.093
KPS	<b>.581</b>	.143	16.486	<b>.000</b>
Average Fatigue	<b>-.796</b>	.232	11.740	<b>.001</b>
Symptom distress	<b>-.170</b>	.042	16.684	<b>.000</b>
Sleep disturbance	.001	.014	.012	.914
Anxiety	<b>.207</b>	.100	4.262	<b>.039</b>
Depression	-.116	.124	.869	.351
Hand of muscle strength	.003	.045	.006	.938
Hip of muscle strength	.034	.081	.175	.675
Knee of muscle strength	.091	.125	.527	.468
30-sec chair stand test	-.002	.066	.001	.978
6-minute walking test	<b>.013</b>	.004	8.406	<b>.004</b>
Subjective strain	.003	.275	.000	.991
Time	<b>.557</b>	.272	4.186	<b>.041</b>
Intercept	-3.520	13.520	.068	.795

## *Associated Factors Related to Change of Mental Related Quality of Life in the Generalized Estimating Equations Analysis*

Variable	Coefficient	Std. Err.	Wald chi-square	p-value
Age	.002	.049	.002	.964
Marry (1=Married; 0= the others)	-.018	1.086	.000	.987
Education	-.086	.112	.595	.440
Feeling tired	-.002	.011	.020	.888
HIV (0=NO; 1=YES)	-.268	1.241	.047	.829
KPS	-.296	.205	2.078	.149
Average Fatigue	-.350	.217	2.589	.108
Symptom distress	<b>-.146</b>	.045	10.528	<b>.001</b>
Sleep disturbance	-.004	.018	.043	.836
Anxiety	<b>-.934</b>	.116	64.446	<b>.000</b>
Depression	<b>-.743</b>	.138	28.919	<b>.000</b>
Hand of muscle strength	-.027	.057	.227	.634
Hip of muscle strength	.016	.116	.019	.891
Knee of muscle strength	.021	.146	.021	.886
30-sec chair stand test	.073	.074	.978	.323
6-minute walking test	-.001	.005	.025	.873
Subjective strain	-.566	.293	3.734	.053
Time	-.504	.340	2.196	.138
Intercept	85.709	18.948	20.461	.000

# Discussion

- There is no study focused on changes of fatigue and physical fitness in this population.
- Fatigue was the most distressed symptoms before and during treatment and it was mild intensity at baseline and became moderate level during treatment. The peak of worst fatigue was at T1 (post 8 weeks of treatment).
- The level of anxiety and depression, and sleep disturbance statistically significant increased from T0 to T3 and significant decreased in mental related quality of life.

# Discussion

- All the measures of physical fitness decreased during treatment, but only hand grip and 6-minutes walking distance (6-MWD) were significantly decrease.
- Only the 6-MWD was positively related to change of physical related QOL.

# Discussion

- There are some concerns for exercise enhancement in this population during treatment (Gapinski & Zucker, 2005; Harrington, 2000; Martin Escudero, 2002; Zucker, 2010)
- Progressive home walking is an easy-to-do and safe activity for this population (Zucker, 2010); exercise enhancement on walking distance are suggested to improving their quality of life during combined therapy.

# Conclusion

- (1) Fatigue was the most distressed symptoms before and during treatment and it was mild intensity at baseline and became moderate level during treatment.
- (2) Decreasing the 6-MWD was the factor associated with decreasing the level of physical related QOL.
- (3) During the treatment, exercise enhancement on walking distance are suggested to improving their quality of life during combined therapy.

# Acknowledgement

- Grant support from NHRI
- All patients participated in this study
- Research Assistants



**Thank you for  
attention !**

