

Low-grade Symptoms Worsen Quality of Life (QoL) for HIV- infected Individuals in Antiretroviral Therapy (ART) Clinical Trials

**Mannheimer S*¹, Matts J², Child C³,
Chesney M⁴, Telzak E⁵, Wu A⁶ and
Friedland G⁷**

for the Terry Beirn Community Programs
for Clinical Research on AIDS (CPCRA)

¹Harlem Hospital Center/Columbia University College of Physicians & Surgeons, New York, NY; ²CPCRA Statistical and Data Management Center, University of Minnesota, Minneapolis, MN; ³University of California at San Francisco, San Francisco, CA; ⁴National Center for Complementary & Alternative Medicine (NCCAM), National Institutes of Health, Bethesda, MD; ⁵Bronx-Lebanon Hospital Center/Albert Einstein College of Medicine, New York, NY; ⁶Johns Hopkins University, Baltimore, MD; ⁷Yale School of Medicine, Yale New Haven Hospital, New Haven, CT.

Abstract

Background: While the most severe symptoms (grade 4) are associated with higher mortality and poorer QoL in persons with HIV, little is known about the frequency of less severe symptoms or their impact on QoL in HIV.

Methods: Participants (pts) who completed at least 12 mos. of follow-up in 1 of 2 prospective, randomized antiretroviral therapy (ART) clinical trials for ART-naïve (CPCRA 058) or -experienced pts (CPCRA 057) were included in this cross-protocol analysis to assess if symptoms lower QoL. Self-reported *symptoms* were assessed by a standardized NIH/DAIDS scale of adverse events (AEs) (grade 0=none through grade 4=most severe) at baseline, 1, 4, 8 and 12 mos. *QoL* was measured at the same times using the SF-12. QoL physical (PCS) and mental (MCS) component summary scores were calculated using standard methods. Data were analyzed using ANOVA.

Results: 512 pts included: 20% women, 52% African Americans, 16% Latinos, 15% injection drug users; 28% with AIDS; mean age 39 yrs; mean baseline CD4 234 cells/mm³, mean baseline HIV RNA 4.94 log₁₀ copies/ml; 91% were ART-naïve. Symptoms were common: 70% of pts at 12 mos reported at least 1 symptom; <5% had severe (grade 3 or 4) symptoms. Mean QoL summary scores by symptom status (- or +) at baseline and at 12 mos. were:

Symptom (- or +) at baseline/12 months

QoL	-/-	+/-	-/+	+/+	p-value
PCS	54.7	50.9	49.4	45.3	<0.001
MCS	48.7	46.2	44.0	43.6	<0.001

Having symptoms (mostly mild or moderate) was strongly associated with lower QoL scores. Similar findings were seen at 1, 4, and 8 mos (p<0.001). Pts who developed symptoms at 12 mos after having none at baseline (-/+) had a decrease in QoL (mean ΔPCS -3.2 from baseline to 12 mos), while all other pts had improved QoL (mean ΔPCS +2.4 to +7.2), p<0.001. An inverse relationship was seen between the number of symptoms and QoL: mean PCS scores were 52.3, 48.8, 48.7, 43.9, and 39.5 for pts reporting 0, 1, 2, 3, or >3 symptoms at 12 mos (p<0.001); similar findings were seen for MCS (mean score 47.1 if 0 symptoms vs. 39.8 if >3, p<0.001).

Conclusion: The presence of symptoms was associated with poorer quality of life. Most symptoms were mild or moderate (grade 1 or 2). These findings highlight the importance of even mild symptoms experienced by pts receiving ART.

Background

- **Quality of life (QoL)** is an important outcome in the treatment of persons with HIV
- The most severe symptoms (grade 4) are known to be associated with poorer quality of life and higher mortality
- Little is known about the frequency of less severe symptoms or their impact on QoL in persons with HIV

Methods 1

- **Design:** Cross-protocol analysis of participants in the two CPCRA HIV clinical trials
- **Purpose:** to assess the frequency and severity of symptoms and the effect of symptoms on QoL in persons with HIV
- **Setting:** Participants enrolled and followed at 15 CPCRA sites
 - **CPCRA is an NIH-sponsored national clinical trials group that conducts community-based HIV/AIDS research targeting underserved populations**

Methods 2

- **Patients:** This analysis included participants who completed at least 12 months of follow-up in 1 of 2 prospective, randomized CPCRA antiretroviral therapy (ART) clinical trials:
 - **CPCRA 057 (PIP study)** compared salvage ART for ART-experienced individuals failing their first PI regimen
 - or**
 - **CPCRA 058 (FIRST study)** compared first ART regimens for ART-naïve individuals
 - In both studies, participants were randomized at baseline to begin new ART regimens

Data Collection

- Participant demographics and HIV transmission risk category were collected at baseline
- Additional data collected for the two CPCRA trials at baseline, and at 1, 4, 8, and 12 months after randomization included:
 - CD4+ lymphocyte cell count
 - HIV RNA level (RT-PCR, ultrasensitive Roche Amplicor HIV assays, Alameda, CA)
 - History of AIDS-defining illnesses
 - Symptom severity
 - QoL

Symptom severity

- Self-reported *symptoms* and their severity were assessed by a standardized NIH/DAIDS scale of adverse events (AEs) at baseline, 1, 4, 8 and 12 months.
- This scale assesses 13 symptoms (see **Figure 1** – CPCRA Symptom Severity Form 316)
- Severity was graded from 0-4:
 - Grade 0 = none**
 - Grade 1 = mild**
 - Grade 2 = moderate**
 - Grade 3 = severe**
 - Grade 4 = most severe, life-threatening**

Quality of Life (QoL)

- *Quality of Life (QoL)* was measured at baseline, 1, 4, 8 and 12 months using the SF-12 instrument (© 1995, John E. Ware, Jr.)
- **SF-12** (see Figure 2):
 - A short form of the MOS SF-36
 - Consists of 12 items
 - QoL scoring by SF-12 significantly correlates with SF-36
 - Reduces redundancy and data requirements of longer instruments
 - Allows discrimination between physical and mental health functioning

QoL Scoring

- Participants' responses to the 12-item SF-12 were grouped into Physical Component and Mental Component Summary Scores
- Physical (PCS) and Mental (MCS) component summary scores are standardized scores calculated to have means of 50 and standard deviations of 10 in the general US population
 - **Summary scores were calculated using standard methods for all participants who responded to every QoL question (Ware *et al.*, 1998)**
 - **Differences of 3 to 5 points are considered clinically meaningful**

Table 1. Baseline Participant Characteristics

Characteristic	N=512
Age, mean years	39
Gender, % female	20
Race/ethnicity, %	
African American	52
Latino	16
White	29
Other	3
Injection drug use history, %	15
Proportion with AIDS-defining illness, %	28
CD4+ lymphocyte count, mean cells/mm ³	234
HIV RNA level, mean log ₁₀ copies/mL	4.94

Symptoms Reported among ART Trial Participants

Symptoms were common:

70% of participants at 12 months reported at least one symptom (any grade)

- **41%** had **Gastrointestinal** symptoms (nausea, vomiting, diarrhea, oral discomfort, constipation)
- **38%** **Neurological** (neuropathy, cerebellar, mood)
- **36%** **Constitutional** (fever, headache, fatigue)
- **19%** **Allergic** (rash, allergic)

Severe symptoms were rare:

- **2%** reported **grade 3** symptoms at 12 mos.
- **No grade 4 symptoms** were reported at 12 months
- **<1%** of participants reported **grade 4 symptoms at any time**

% of Participants Reporting Symptoms at 12-months

<u>Number of Symptoms</u>	% of Participants
0	30%
1	25%
2	20%
3	11%
>3	13%

Summary:

30% reported no symptoms

70% reported 1 or more symptom

44% reported 2 or more symptoms

24% reported 3 or more symptoms

Impact of Symptoms on QoL

Mean QoL summary scores by absence (-) or presence (+) of any symptom at baseline and at 12 months:

Symptom (- or + at baseline/12 mos.)

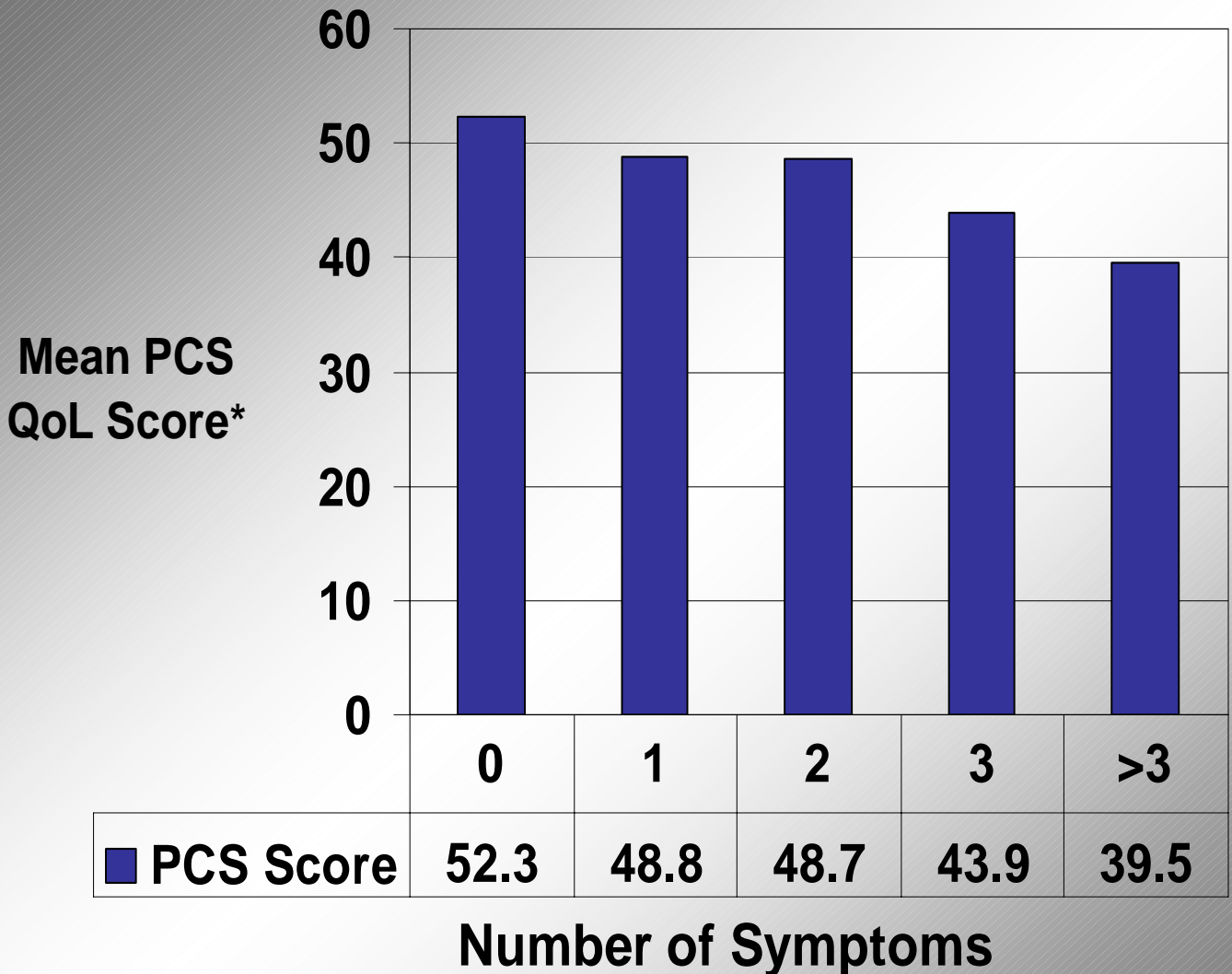
<u>QoL</u>	<u>-/-</u>	<u>+/-</u>	<u>-/+</u>	<u>+/+</u>	<u>p-value*</u>
PCS	54.7	50.9	49.4	45.3	<0.001
MCS	48.7	46.2	44.0	43.6	<0.001

*for comparison by ANOVA of QoL among the 4 symptom groups for each QoL component summary score

Summary: Patients with no symptoms at baseline and 12 months (-/-) had the highest QoL scores, followed by those whose baseline symptoms resolved (+/-).

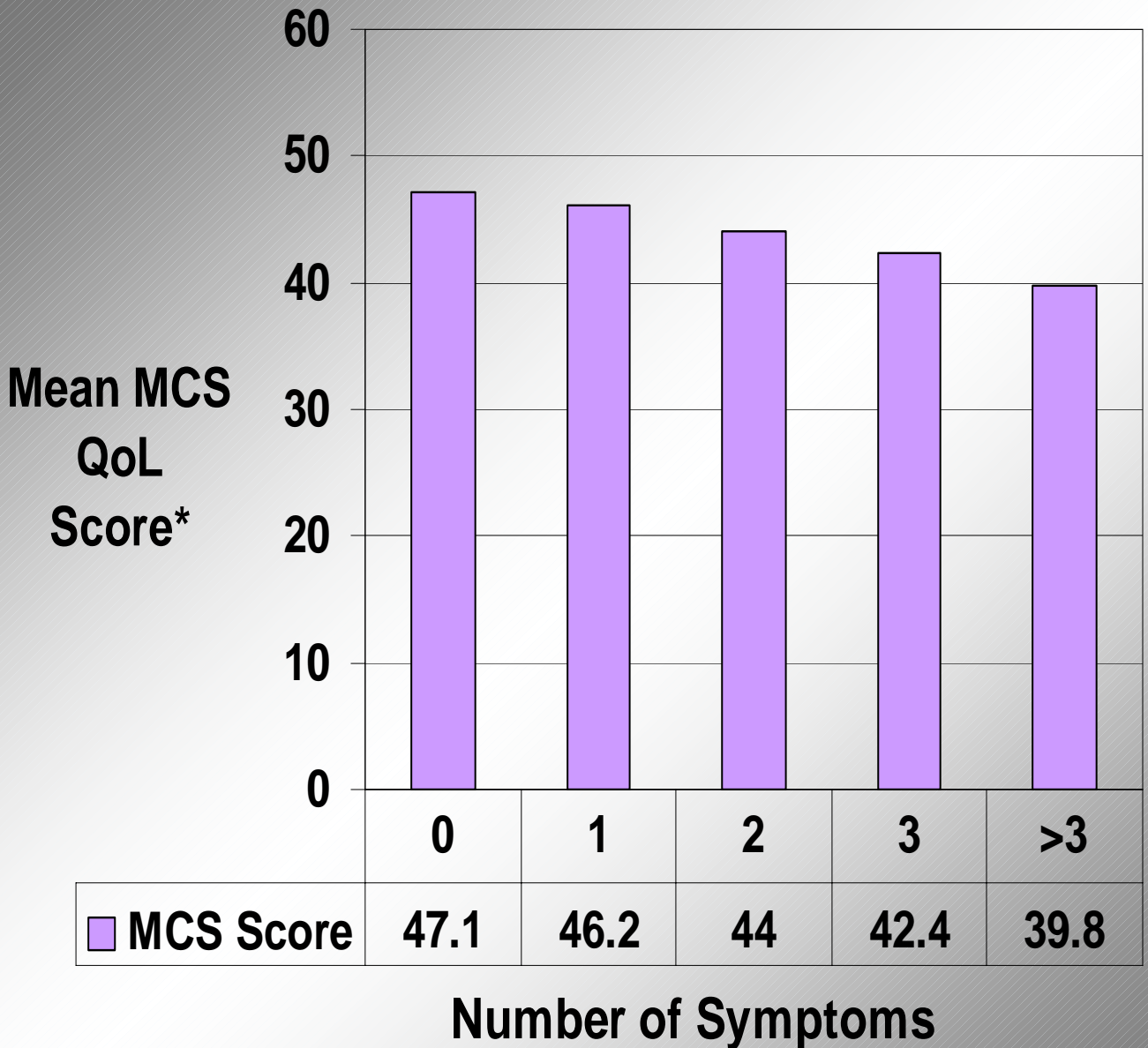
Participants with symptoms at both time-points had the poorest QoL (+/+).

Impact of Number of Symptoms on Physical Component Summary (PCS) QoL Score at 12 months



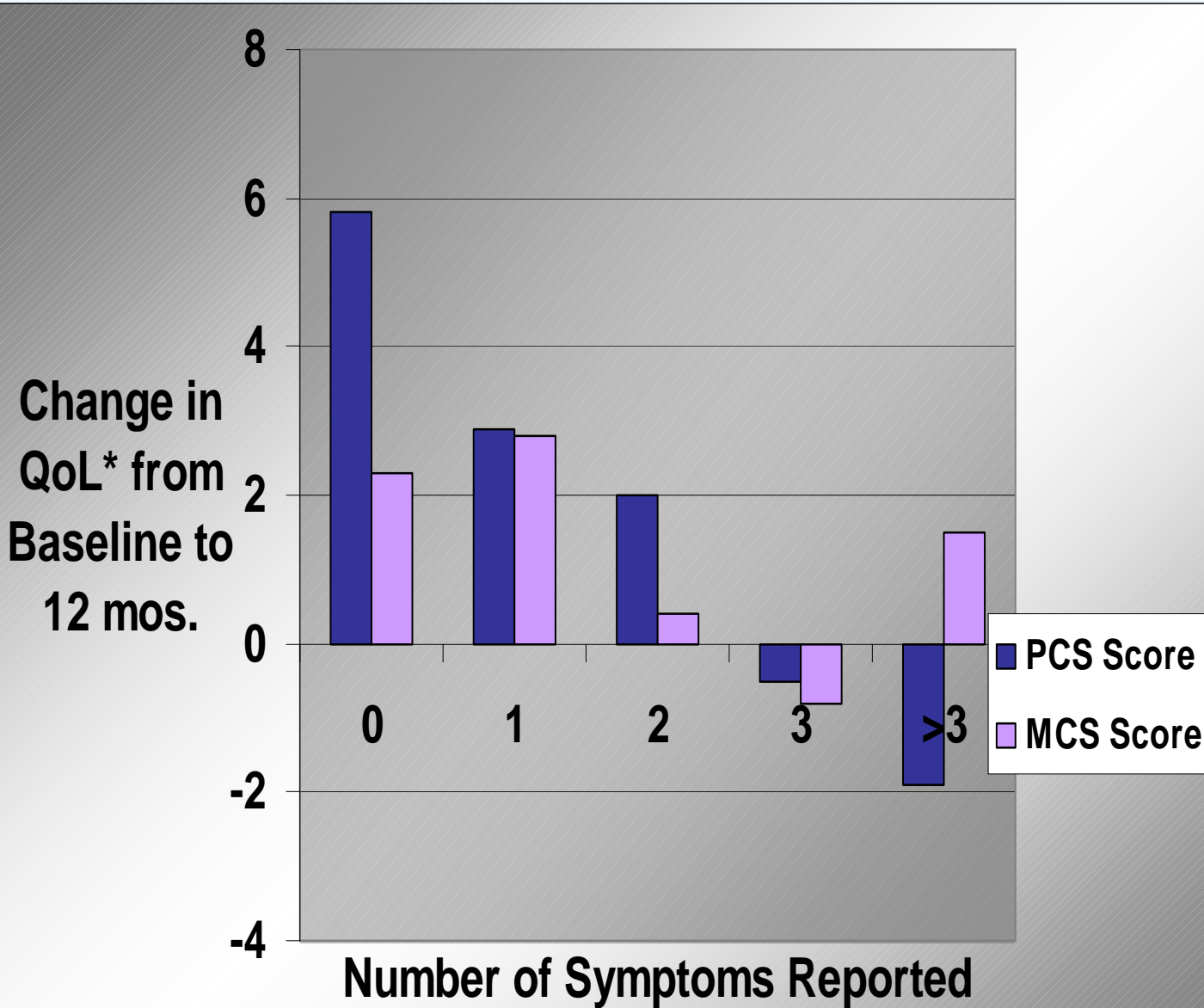
**p < 0.001 for comparison of PCS QoL Scores by ANOVA (p < 0.001 for comparisons at months 1, 4, and 8 as well)*

Impact of Number of Symptoms on Mental Component Summary (MCS) QoL Score at 12 Months



** $p < 0.001$ for comparison of MCS QoL Scores by ANOVA
($p < 0.001$ for comparisons at months 1, 4, and 8 as well)*

Change from Baseline QoL by Number of Symptoms Reported at 12 Months



**(p < 0.001 for comparison by ANOVA of Physical Component Summary (PCS) QoL scores among the 4 symptom groups)*

Conclusions

- Among ART clinical trials patients, symptoms were common and the great majority were mild or moderate (grade 1 or 2)
- The presence of symptoms was associated with poorer quality of life
- There was a dose-response relationship between the number of symptoms and poorer QoL
- While HIV clinicians and trial investigators focus on severe adverse events, mild symptoms have an impact on quality of life and should receive more attention