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Predictors of health-related quality of life among military HIV-infected individuals

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Abstract

Objectives To determine long-term predictors of health-related quality of life (HRQOL) and evaluate the treatment effect of highly active antiretroviral therapy (HAART) on HRQOL in the US Military HIV Natural History Study (NHS) cohort.

Methods Participants were a nested cohort of the NHS who responded to the Rand Short Form 36 questionnaire administered from 2006 to 2010. Physical component summary scores (PCS) and mental component summary scores (MCS) were computed using standard algorithms. HAART-status was categorized as non-protease inhibitor-based (NPI-HAART), protease inhibitor-based (PI-HAART), HAART-naïve, or off-HAART. Mixed linear random effects models were used to estimate changes in PCS and MCS over time for treatment and covariates (including CD4 count, HIV viral load, medical and mental comorbidities).

Results Eight hundred and twelve participants met the inclusion criteria. There was no difference in PCS or MCS between those on PI-HAART compared to NPI-HAART. Significant predictors of PCS were CD4 count < 200 cells/mm^3 ($\beta = -2.90$), CD4 count 200–499 cells/mm^3 ($\beta = -0.80$), and mental comorbidity ($\beta = -3.23$). Others were medical comorbidity, AIDS-defining illness, being on NPI-HAART, HAART-naïve, age, and rank. Those with medical comorbidities experienced yearly improvement in PCS. Predictors of MCS were CD4 count < 200 cells/mm^3 ($\beta = -2.53$), mental comorbidity ($\beta = -4.58$), and being African American ($\beta = 2.59$).

Conclusion HRQOL was significantly affected by low CD4 count, medical and mental comorbidities. Addressing these modifiable factors would be expected to improve the physical and mental HRQOL of the cohort. Our study did not find any treatment benefit of NPI-HAART over PI-HAART on HRQOL in the long term.

Keywords HIV · Health-related quality of life · Highly active antiretroviral therapy · Physical component summary scores · Mental component summary scores

Introduction

Health-related quality of life (HRQOL) is a patient-centered outcome measure used to assess an individual's well-being in chronic diseases. HRQOL is particularly useful in chronic illnesses such as HIV/AIDS where therapeutic goals are not aimed at a cure but in halting disease progression, alleviating symptoms, improving functional capabilities, and mitigating adverse psychosocial consequences that may be associated with the disease [1]. With improving therapeutic success in HIV/AIDS recorded over the last few decades, HRQOL will continue to play a pivotal role in monitoring patients' perception of disease outcome. In an earlier study, we determined the factors associated with HRQOL measures

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at baseline for our cohort including CD4 count less than 200, military rank, medical and mental comorbidities, AIDS diagnosis, being married, and being African American [2]. In this study, we further investigate the long-term predictors of HRQOL in our cohort and examine changes in HRQOL among participants on different classes of highly active antiretroviral therapy (HAART) and those not on HAART. This will enable us to evaluate the HRQOL trajectory of these groups and compare regimens to better understand factors that might predict HRQOL in HIV-infected individuals [3].

Longitudinal studies looking into the long-term predictors of HRQOL are few, and most are limited to 1 year of follow-up or less [4]. Predictors of HRQOL include treatment with combination antiretroviral therapy (cART), lower CD4 count, time since HIV diagnosis, medical and mental comorbidities, medication side effects, AIDS defining illness, and increasing age, family/social support, and active coping strategies [4–13]. The impact of these factors depends on the population studied and possibly the duration of follow-up, given the dynamic nature of HRQOL measures even in the same individual. This work is predicated on the need to better understand factors affecting HRQOL over a longer period of follow-up and changes in HRQOL in a cohort with free movement of participants among the HAART groups necessitated by disease indicators and clinical factors. Finally, the unique military population of our cohort may provide further insights into the longitudinal relationship between HAART and HRQOL. Some of these unique features include equal access to healthcare including medications, racial diversity, and very low prevalence of injection drug use [2, 14, 15].

Methods

Study participants and cohort

The participants are a nested cohort of the larger U.S. Military HIV Natural History Study (NHS) cohort, which has been described elsewhere [14–17]. Briefly, the NHS is a dynamic cohort of military personnel and their dependents who are followed at five military medical treatment facilities. Participants included were those who completed the RAND Short Form 36 (SF-36) at baseline in 2006 and yearly through September 2010. All participants provided informed consent, and approval for this research was obtained from the institutional review board centrally and at each participating site.

Health-related quality of life scores

The norm-based physical component summary scores (PCS) and mental component summary scores (MCS) were computed from the eight health domains in the SF-36 questionnaire in line with the recommended scoring algorithm for the RAND 36-item health survey 1.0. [18, 19]. PCS and MCS, measured yearly from 2006 to 2010, were the outcome variables in our analyses. Higher PCS or MCS scores represent better health; summary score level differences of 2 to 3 were considered clinically and socially relevant [20].

HAART (treatment) variable

HAART was defined as a combination of at least three antiretroviral agents in line with previous investigations for this cohort [14]. In line with our baseline study [2], HAART treatment was categorized into four groups: protease inhibitor-based HAART (PI-HAART) for HAART with at least one protease inhibitor; non-protease-inhibitor-based HAART (NPI-HAART) for HAART with no protease inhibitor; HAART-naïve group (HAART-N) for those who had never been on HAART; and an Off-HAART group for those who were not on HAART at the time of the survey but had been on HAART previously. HAART status changed over the period of follow-up and was treated as a time-varying variable.

Covariates

Covariates included gender (male/female), age, military rank (officer/warrant officer, enlisted and civilian/retired), marital status (married, not married), race/ethnicity (non-Hispanic white, non-Hispanic African-American, and others), plasma viral load (pVL), CD4+ count, medical and mental comorbidity (further elaborated below), diagnosis of AIDS defining illness, and time since HIV diagnosis (in years). CD4 cell count was categorized as '<200 cells/mm^3', '200–499 cells/mm^3', and '>499 cells/mm^3', while plasma viral load was categorized as >50 copies/mL (yes) or ≤ 50 copies/mL (no). The definition of AIDS used the 1993 Centers for Disease Control and Prevention-revised criteria, except for an isolated CD4 cell count <200 cells/mm^3, as CD4 cell count was analyzed separately. Medical and mental comorbidity referred to chronic medical or mental conditions and were classified as having no comorbidity or having one or more comorbidity. Both medical and mental comorbidities were extracted from the participants' medical record using the central electronic health-records system of the US Military and through coordinator interview. Mental comorbidity was similarly classified. Further subcategorizations of medical and mental comorbidities were also analyzed to better delineate the data and to improve our understanding of their role in HRQOL. The medical subcategories were diabetes mellitus (DM), myocardial infarction/cardiovascular diseases (MI/CVD), cancers, and other chronic medical conditions. The subcategories of the mental comorbidities

were major-depressive disorder (MDD), anxiety/bipolar disorder, alcohol abuse, and other mental comorbidities. The subcategory of other mental comorbidities included drug abuse and post-traumatic stress disorder (PTSD), but these were grouped with the other mental comorbidities because of their smaller numbers.

Inclusion and exclusion criteria

All participants aged 18 years and above who completed the HRQOL survey questionnaires in 2006 for the first time were considered for inclusion into the current study. Participants on non-HAART antiretroviral therapy ($n = 14$) were excluded.

Statistical analyses

Baseline (2006) characteristics of participants were tabulated using proportions for count variables and medians and interquartile ranges for numeric variables. Bar charts displayed percentages of participants by HAART groups for categorical variables while graphs displayed the means and their corresponding 95% confidence intervals for numeric variables. Random effects model (REM) estimated the beta (β) coefficients and corresponding 95% confidence intervals for the variables. Restricted maximum likelihood (REML) estimated β using an unstructured covariance structure [21] to account for correlation of the random effects. As in the baseline study, different models for PCS and MCS were constructed. For each outcome variable, we conducted univariate analysis for the explanatory variables; variables that achieved $a < 0.2$ significance level were included for the final multivariate analyses. For interaction terms, we strictly followed the P-value < 0.05 for inclusion into the multivariate model as our current study was not aimed at addressing any specific effect modification (or interaction) between covariates and time. However, interaction terms that were marginally non-significant (P values between 0.05 and 0.08) were included one at a time to see if they had significant effects in the multivariate models and removed if they continued to remain non-significant. All variables except race, gender, and age at baseline (2006) were treated as time-varying covariates. Participants' age at baseline was used to avoid collinearity between age and time. Time was analyzed as continuous. Further testing for multicollinearity was done for covariates in the multivariate models using the variance inflation factor (VIF) in multiple regressions for every given time point (2006 through 2010) since the VIF option is not supported in the proc mixed procedure in SAS. We found no evidence of multicollinearity in our models based on this approach. Several sensitivity analyses were conducted to test how robust our final models were. Two influential observations were excluded from the PCS model and five from the MCS model. Both the PCS and MCS models were slightly right skewed; however, we compared the results of the original PCS and MCS models to a normalized PCS model after a cubic transformation of the dependent variable with no significant changes in the p-values, so we have reported results for the original untransformed data. All statistical analyses and graphs were performed using SAS 9.3/9.4 [SAS Institute Inc., Cary, NC].

Results

There were 812 participants in 2006 (baseline) who met the study eligibility criteria, and their characteristics are displayed in Table 1. Participants were mostly male (95%), with Caucasian and African-American making up 48% and 40%, respectively. Twenty-seven percent of participants had mental comorbidity (including major depressive disorder, generalized anxiety disorder, bipolar disorder, alcohol abuse, and others), 16% had medical comorbidity [including cancers (basal cell carcinoma of the skin, squamous cell carcinoma of the skin, anal cancer, prostate cancer, and Hodgkin's and Non-Hodgkin's lymphoma), diabetes mellitus, chronic kidney disease, coronary heart disease with and without myocardial infarction, and others], and 10% had a diagnosis of AIDS defining illness at baseline. The median age at baseline was 42 years (interquartile range [IQR] 37–47), and median PCS and MCS at baseline were 54.41 (IQR 45.95–57.48) and 50.77 (IQR 44.06–54.05), respectively. Supplemental Table 1 shows the number of participants per HAART group per year of follow-up, participants who responded to the SF-36 questionnaire in any given year, non-responders, and participants with missing values for one or more variables among responders.

In the univariate PCS analyses, there was no significant interaction between treatment (HAART) and time variables, $P = 0.6$ (Table 2, Fig. 1a–d). In addition, treatment had no significant effect on changes in PCS over the period of follow-up ($P = 0.7$). Compared to participants in the PI-HAART group, PCS of participants in the HAART-naïve and NPI-HAART groups were higher by 3.81 (95% CI 2.56–5.06) and 2.09 (95% CI 0.99–3.20), respectively (Table 2, Fig. 1a–c). However, there was no significant difference in PCS between the Off-HAART and PI-HAART groups (Table 2, Fig. 1d). Table 2 shows the univariate results for all covariates on PCS including subcategories of medical and mental comorbidities. In the univariate MCS model, we noted no significant interaction between treatment (HAART) and time variables and no significant treatment effects on changes in MCS over the follow-up period (Table 3, Fig. 2a–d). We also found no significant differences in MCS by HAART groups. Table 3 shows the univariate results for all the covariates on MCS. In the multivariate PCS model, the differences in scores were

Table 1 Baseline characteristics of participants in 2006

Characteristics	*N* (%)
Gender	
Male	771 (94.95)
Female	41 (5.05)
Race	
Non-Hispanic White	387 (47.66)
Non-Hispanic African-American	321 (39.53)
Hispanic/others	104 (12.32)
Rank	
Officer/warrant officer	61 (7.51)
Enlisted	374 (46.06)
Others (civilian/retired)	377 (46.43)
Married (yes)	270 (33.25)
Medical comorbidity (yes)	131 (16.13)
Diabetes	54 (6.65)
MI/CVD	11 (1.35)
Cancers	55 (6.77)
Other chronic medical conditions	11 (1.35)
Mental comorbidity (yes)	219 (26.97)
Major depressive disorder	150 (18.27)
Anxiety/bipolar disorders	32 (3.94)
Alcohol abuse	24 (2.96)
Other psychiatric disorders	13 (1.60)
AIDS-defining illness (yes)	82 (10.10)
HAART	
HAART-naïve	106 (13.05)
NPI-HAART	318 (39.16)
Off-HAART	100 (12.32)
PI-HAART	288 (35.47)
Plasma viral load > 50 copies/mL	
Yes	356 (43.84)
No	455 (56.03)
Missing	1 (0.12)
CD4 count groups (cells/mm^3)	
< 200	47 (5.79)
200–499	322 (39.66)
> 499	441 (54.31)
Missing	2 (0.25)
Age (years)—median (IQR)	42.00 (37.00–47.00)
CD4 Count ($\times 10^6$/L)—median (IQR)	524.00 (379.00–720.00)
Plasma viral load ($\log_{10}$)—median (IQR)	1.70 (1.70–3.56)
Time since HIV diagnosis (years)–median (IQR)	10.00 (5.00–16.00)
PCS—median (IQR)	54.41 (45.95–57.48)
MCS—median (IQR)	50.77 (44.06–54.05)

PCS physical component summary scores, *MCS* mental component summary scores, *HAART* highly active antiretroviral therapy, *PI-HAART* protease inhibitor-based HAART, *NPI-HAART* non-protease inhibitor-based HAART, *HAART-naïve* never received HAART, *Off-HAART* received HAART in the past but not currently on HAART, *IQR* interquartile range. AIDS-defining illness does not include CD4 < 200, *MI/CVD* myocardial infarction/cardiovascular disorders

1.58 (95% CI 0.14–3.03) and 1.10 (95% CI 0.18–2.04) for HAART-naïve and NPI-HAART, respectively, when compared to the PI-HAART but remained statistically significant (Table 4). Like in the univariate PCS model, there was no significant difference in scores between the Off-HAART and PI-HAART groups (Table 4). The change in PCS for every 1-year increment from baseline in the multivariate PCS model was −0.92 ($P = 0.001$) (Table 4).

Also independently predictive of PCS were CD4 count < 200 cells/mm^3 (β −2.90; 95% CI −4.60 to −1.21), CD4 count 200–499 cells/mm^3 (β −0.80; 95% CI −1.47 to −0.14), AIDS-defining illness (β −3.41; 95% CI −5.02 to −1.80), medical comorbidity (β −3.71; 95% CI −5.27 to −2.12), mental comorbidity (β −3.23; 95% CI −4.18 to −2.27), and age with every 5-year increment in participants' age leading to a reduction in PCS by −0.81 (95% CI −1.16 to −0.46). We found significant interaction between medical comorbidity and time (β 0.71, 95% CI 0.30–1.12) as well as between rank and time with every year of being a civilian or being retired leading to a 0.72 points improvement in PCS (95% CI 0.12–1.31) and every year of being an enlisted resulting in a 0.84 improvement in PCS (95% CI 0.25–1.44). Although time since HIV diagnosis was predictive of PCS in the univariate analysis, it was not significantly predictive after adjustment in the multivariate model. Similarly, being married was marginally non-significant in the multivariate PCS model (β −0.85; 95% CI −1.74 to 0.03, $P = 0.058$). Independently predictive of MCS were being African American (β 2.45, 95% CI 1.47–3.70), CD4 count < 200 cells/mm^3 (β −2.53, 95% CI −4.24 to −0.83), mental comorbidity (β −4.58, 95% CI −5.54 to −3.63), and rank (P value of the F statistics is 0.01). Being civilian/retired was −1.72 lower in MCS compared to officers (95% CI −3.73 to 0.29, $P = 0.09$), Table 4. In a separate analysis in which the referent group is changed to civilian/retired, the MCS of the enlisted was 1.56 points higher than the civilian/retired (95% CI 0.44–2.68, $P = 0.007$). Although plasma viral load > 50 copies/mL was predictive of MCS in the univariate REM, it was not statistically significant in the multivariate model (β −0.51, 95% CI −1.28 to 0.26, $P = 0.20$). Medical comorbidity was further subcategorized to diabetes, cardiovascular diseases including myocardial infarction, cancer, and other chronic medical conditions. While all these comorbidities contributed to lower PCS in the univariate models, diabetes (β −3.44, 95% CI −5.74 to −1.15).), MI/CVD (β −10.59, 95% CI −15.01 to −6.18) and cancers (β −3.19, 95% CI −5.52 to −0.86) were significant in the multivariate model. Significant interactions were noted with cardiovascular disease and the diabetes subcategories with yearly improvements in PCS by 2.10 and 0.65, respectively. PCS in those with cancers improved at a yearly rate of 0.55 but this marginally non-significant with a P value of 0.08 (Table 5). Subcategories of mental comorbidities all decreased PCS by approximately 3

Table 2 Univariate analyses for PCS with/without treatment-time and covariates-time interaction terms

Variable	PCS model with interaction term				PCS model without interaction term			
	β	SE	95% CI	P value	β	SE	95% CI	P value
HAART				0.0002[$$]				< 0.0001[$$]
HAART-naïve	4.05	0.97	2.14 to 5.95	< 0.0001	3.81	0.63	2.56 to 5.06	< 0.0001
NPI-HAART	1.99	0.69	0.63 to 3.34	0.004	2.09	0.56	0.99 to 3.20	0.0002
Off-HAART	0.59	0.98	-1.33 to 2.51	0.55	0.37	0.74	-1.08 to 1.82	0.62
PI-HAART	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	− 0.04	0.13	− 0.30 to 0.21	0.73	− 0.09	0.08	− 0.25 to 0.07	0.26
HAART × time				0.57[$$]				
HAART-naïve × time	− 0.48	0.35	− 1.17 to 0.21	0.17				
NPI-HAART × time	− 0.01	0.18	− 0.35 to 0.34	0.97				
Off-HAART × time	0.02	0.33	− 0.63 to 0.67	0.95				
PI-HARRT × time	Ref.	Ref.	Ref.	Ref.				
Intercept for HAART	49.66	0.53	48.62 to 50.70	< 0.0001	49.70	0.50	48.72 to 50.68	< 0.0001
Race/ethnicity								0.36[$$]
Non-hispanic African-American					0.89	0.63	− 0.34 to 2.13	0.16
Others including hispanics					0.33	0.92	− 1.47 to 2.13	0.72
Non-hispanic white					Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)					− 0.12	0.08	− 0.27 to 0.04	0.14
Intercept for race/ethnicity					50.63	0.46	49.72 to 51.54	< 0.0001
Male					1.02	1.35	− 1.63 to 3.67	0.45
Time (1-yearly increment)					− 0.12	0.08	− 0.27 − 0.04	0.13
Intercept for male					50.05	1.33	47.44 to 52.66	< 0.0001
Rank				< 0.0001[$$]				< 0.0001[$$]
Civilian/not active duty	− 5.43	1.31	− 7.99 to − 2.87	< 0.0001	− 3.27	1.09	− 5.41 to − 1.14	0.003
Enlisted	− 2.26	1.31	− 4.84 to 0.32	0.09	− 0.29	1.10	− 2.45 to 1.87	0.79
Warrant officer/officer	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	− 0.89	0.28	− 1.44 to − 0.35	0.001	− 0.09	0.08	− 0.25 to 0.06	0.25
Rank × time				0.01[$$]				
Civilian/not active duty × time	0.90	0.30	0.31 to 1.49	0.003				
Enlisted × time	0.83	0.30	0.24 to 1.43	0.006				
Warrant officer/officer	Ref.	Ref.	Ref.	Ref.				
Intercept for rank	54.57	1.22	52.18 to 56.96	< 0.0001	52.66	1.04	50.62 to 54.70	< 0.0001
Married	− 1.16	0.63	− 2.39 to 0.07	0.07	− 0.92	0.47	− 1.85 to 0.01	0.052
Time (1-yearly increment)	− 0.15	0.10	− 0.34 to 0.04	0.11	− 0.12	0.08	− 0.27 to 0.04	0.13
Married × time	0.10	0.17	− 0.24 to 0.44	0.56				
Intercept for married	51.40	0.40	50.61 to 52.19	< 0.0001	51.32	0.38	50.58 to 52.07	< 0.0001
Medical comorbidity	− 5.06	0.80	− 6.63 to − 3.50	< 0.0001	− 2.75	0.53	− 3.79 to − 1.70	< 0.0001
Time (1-yearly increment)	− 0.21	0.09	− 0.38 to − 0.03	0.02	− 0.05	0.08	− 0.21 to 0.10	0.50
Medical comorbidity × time	0.79	0.20	0.39 to 1.19	< 0.0001				
Intercept for medical comorbidity	51.79	0.37	51.07 to 52.52	< 0.0001	51.38	0.35	50.69 to 52.07	< 0.0001
Mental comorbidity	− 3.89	0.67	− 5.21 to − 2.57	< 0.0001	− 3.77	0.50	− 4.74 to − 2.79	< 0.0001
Time (1-yearly increment)	− 0.07	0.09	− 0.26 to 0.11	0.43	− 0.06	0.08	− 0.22 to 0.09	0.44
Mental comorbidity × time	0.05	0.18	− 0.30 to 0.39	0.79				
Intercept for mental comorbidity	51.98	0.38	51.23 to 52.73	< 0.0001	51.95	0.36	51.2 4 to 52.65	< 0.0001
Baseline age (5-yearly intervals)					− 1.22	0.15	− 1.52 to − 0.92	< 0.0001
Time (1-yearly increment)					0.11	0.08	− 0.27 to 0.05	0.17
Intercept for age					61.25	1.33	58.64 to 63.87	< 0.0001
Time since HIV diagnosis (5-yearly)	− 1.90	0.27	− 2.43 to − 1.36	< 0.0001	− 1.54	0.23	− 1.98 to − 1.09	< 0.0001
Time (one yearly increment)	− 0.21	0.18	− 0.57 to 0.15	0.25	0.17	0.09	− 0.002 to 0.35	0.053
Time since HIV diagnosis × time	0.15	0.06	0.03 to 0.27	0.02				
Intercept for time since HIV diagnosis	54.82	0.66	53.53 to 56.11	< 0.0001	53.96	0.55	52.87 to 55.04	< 0.0001
pVL > 50 copies/mL	0.66	0.56	− 0.44 to 1.75	0.23	0.12	0.33	− 0.53 to 0.76	0.72
Time (1-yearly increment)	− 0.04	0.10	− 0.24 to 0.15	0.65	− 0.11	0.08	− 0.27 to 0.05	0.18
pVL × time	− 0.23	0.19	− 0.59 to 0.14	0.23				
Intercept for pVL	50.78	0.41	49.97 to 51.59	< 0.0001	50.97	0.38	50.22 to 51.72	< 0.0001
CD4 category				0.03[$$]				< 0.0001[$$]
CD4 count < 200	− 2.87	1.39	− 5.59 to − 0.02	0.04	− 3.61	0.88	− 5.34 to − 1.88	< 0.0001
CD4 count 2–499	− 1.18	0.59	− 2.33 to 0.76	0.047	− 0.96	0.34	− 1.63 to − 0.29	0.005
CD4 count > 499	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	0.003	0.10	− 0.20 to 0.21	0.98	− 0.17	0.08	− 0.32 to − 0.01	0.04
CD4 category × time				0.50[$$]				
CD4 count < 200 × time	− 0.004	0.47	− 0.93 to 0.93	0.99				
CD4 count 2–499 × time	− 0.22	0.19	− 0.15 to 0.58	0.25				
CD4 count > 499 × time	Ref.	Ref.	Ref.	Ref.				
Intercept for CD4 category	48.39	0.42	47.56 to 49.22	< 0.0001	51.67	0.38	50.91 to 52.42	< 0.0001
AIDS defining illness	− 6.31	1.08	− 8.42 to − 4.20	< 0.0001	− 5.53	0.83	− 7.16 to − 3.90	< 0.0001
Time (1-yearly increment)	− 0.13	0.08	− 0.30 to 0.03	0.11	− 0.10	0.08	− 0.26 to 0.05	0.19
AIDS defining illness × time	0.30	0.27	− 0.22 to 0.83	0.26				
Intercept for AIDS defining illness	51.63	0.36	50.92 to 52.33	< 0.0001	51.55	0.35	50.86 to 52.24	< 0.0001
Med comorbidity category				< 0.0001[$$]				< 0.0001[$$]
Diabetes	− 4.74	1.19	− 7.07 to − 2.42	< 0.0001	− 2.52	0.84	− 4.16 to − 0.88	0.003

Table 2 (continued)

CV disorder/MI	− 11.80	2.27	− 16.25 to − 7.35	< 0.0001	− 4.28	1.12	− 6.46 to − 2.11	0.0001
Cancers	− 4.60	1.19	− 6.95 to − 2.26	0.0001	− 3.09	0.82	− 4.70 to − 1.47	0.0002
Other chronic medical conditions	− 2.50	2.11	− 6.64 to 1.63	0.24	− 0.89	1.19	− 3.22 to 1.44	0.45
No med comorbidity category	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	− 0.21	0.09	− 0.38 to − 0.03	0.02	− 0.05	0.08	− 0.21 to 0.10	0.52
Med comorbidity category × time				0.0001[$$]				
Diabetes × time	0.78	0.30	0.19 to 1.38	0.01				
CV disorder/MI × time	2.23	0.58	1.08 to 3.37	0.0001				
Cancers × time	0.53	0.32	− 0.09 to 1.15	0.09				
Other chronic med conditions × time	0.54	0.54	− 0.52 to 1.61	0.32				
No med comorbidity category × time	Ref.	Ref.	Ref.	Ref.				
Intercept for med comorbidity category	51.80	0.37	51.08 to 52.51	< 0.0001	51.37	0.35	50.68 to 52.06	< 0.0001
Mental comorbidity category				< 0.0001[$$]				< 0.0001[$$]
MDD	− 3.84	0.76	− 5.33 to − 2.34	< 0.0001	− 3.60	0.56	− 4.70 to − 2.49	< 0.0001
Anxiety/bipolar disorders	− 5.90	1.42	− 8.68 to − 3.13	< 0.0001	− 4.21	0.85	− 5.88 to − 2.55	< 0.0001
Alcohol abuse	− 2.10	1.55	− 5.14 to 0.93	0.17	− 4.08	1.06	− 6.15 to − 2.00	0.0001
Other psychiatric disorders	− 3.91	2.06	− 7.95 to 0.12	0.06	− 3.71	1.06	− 5.79 to − 1.63	0.0003
No psychiatric disorder	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	− 0.08	0.09	− 0.26 to 0.11	0.43	− 0.06	0.08	− 0.21 to 0.10	0.46
Mental comorbidity category × time				0.22[$$]				
MDD × time	0.09	0.21	− 0.32 to 0.51	0.66				
Anxiety/bipolar disorders	0.58	0.40	− 0.20 to 1.36	0.14				
Alcohol abuse × time	− 0.76	0.43	− 1.60 to 0.09	0.08				
Other psychiatric disorders × time	0.08	0.56	− 1.02 to 1.20	0.88				
No psychiatric disorder × time	Ref.	Ref.	Ref.	Ref.				
Intercept for mental comorbidity category	51.99	0.38	51.24 to 52.75	< 0.0001	51.94	0.36	51.23 to 52.65	< 0.0001

All covariates were treated as time varying except for gender (male), age at baseline and race/ethnicity

PCS physical component summary scores, *MCS* mental component summary scores, *HAART* highly active antiretroviral therapy, *PI-HAART* protease inhibitor-based HAART, *NPI-HAART* non-protease inhibitor-based HAART, *HAART-naïve* never received HAART, *Off-HAART* received HAART in the past but not currently on HAART, *β* beta, *SE* standard error, *95% CI* 95% confidence interval

[$$]*P*-value of *F*-statistics of type 3 tests of the fixed effects

to 3.8 points after adjustment (Table 5). Similarly, the mental comorbidities decreased MCS by 2.8 to approximately 5 points after adjustment (Table 5).

Discussion

The goals of this study were twofold: to better understand the long-term predictors of HRQOL and to evaluate if there were differences in HRQOL measures by HAART groups over time. Studies on HRQOL in HIV-infected individuals have generally been used to address whether HAART improves HRQOL [4, 22], and while it is generally agreed that HAART improves HRQOL in the short-term [4, 22, 23], the evidence of the impact of HAART on HRQOL in the long-term is unclear [4]. The overall effect of HAART on HRQOL has been described as a balance between improvements in HIV-related morbidity and better life-expectancy on one hand and adverse effects of medication on the other [3, 23]. This picture is further complicated by increasing age-associated comorbidities [5, 24] in HIV-infected populations, differential response to HAART by older individuals [25], and effects of aging on the individual including physical senescence [23].

Side effects of HAART known to adversely affect HRQOL include lipodystrophy, diarrhea, anemia, peripheral neuropathy, insulin resistance and metabolic syndrome, renal tubular toxicity, pancreatitis, and hypersensitivity reaction [6, 7, 26]. While side effects are not unique to a specific class of HAART medications, protease inhibitors have been implicated as having greater adverse effects, including morphological changes and metabolic disturbances [27]. Therefore, we grouped HAART into protease-inhibitor-based HAART (PI-HAART) and non-protease inhibitor HAART (NPI-HAART). For those not on HAART, we further differentiated between those who were off medications (Off-HAART) and those who had never been on HAART (HAART-naive).

In an earlier study [2], we did not find any statistically significant differences in PCS and MCS among the HAART groups in the multivariate models. In this study, we specifically investigated the treatment effect of being on NPI-HAART compared to PI-HAART but did not find any statistically significant difference due to the lack of significant interaction between NPI-HAART and time (Table 3) or near parallel lines of the treatment groups (Fig. 1a, b). There were also no significant interactions among HAART-naive and Off-HAART and time. This showed no treatment benefits of PI-HAART over these groups, although unmeasured selection effects may have confounded this subset analysis. Furthermore, PCS were on average stable for the four groups over the period of follow-up, which may partly be attributable to the mobility of participants not on treatment (HAART-naïve and Off-HAART groups) to those on

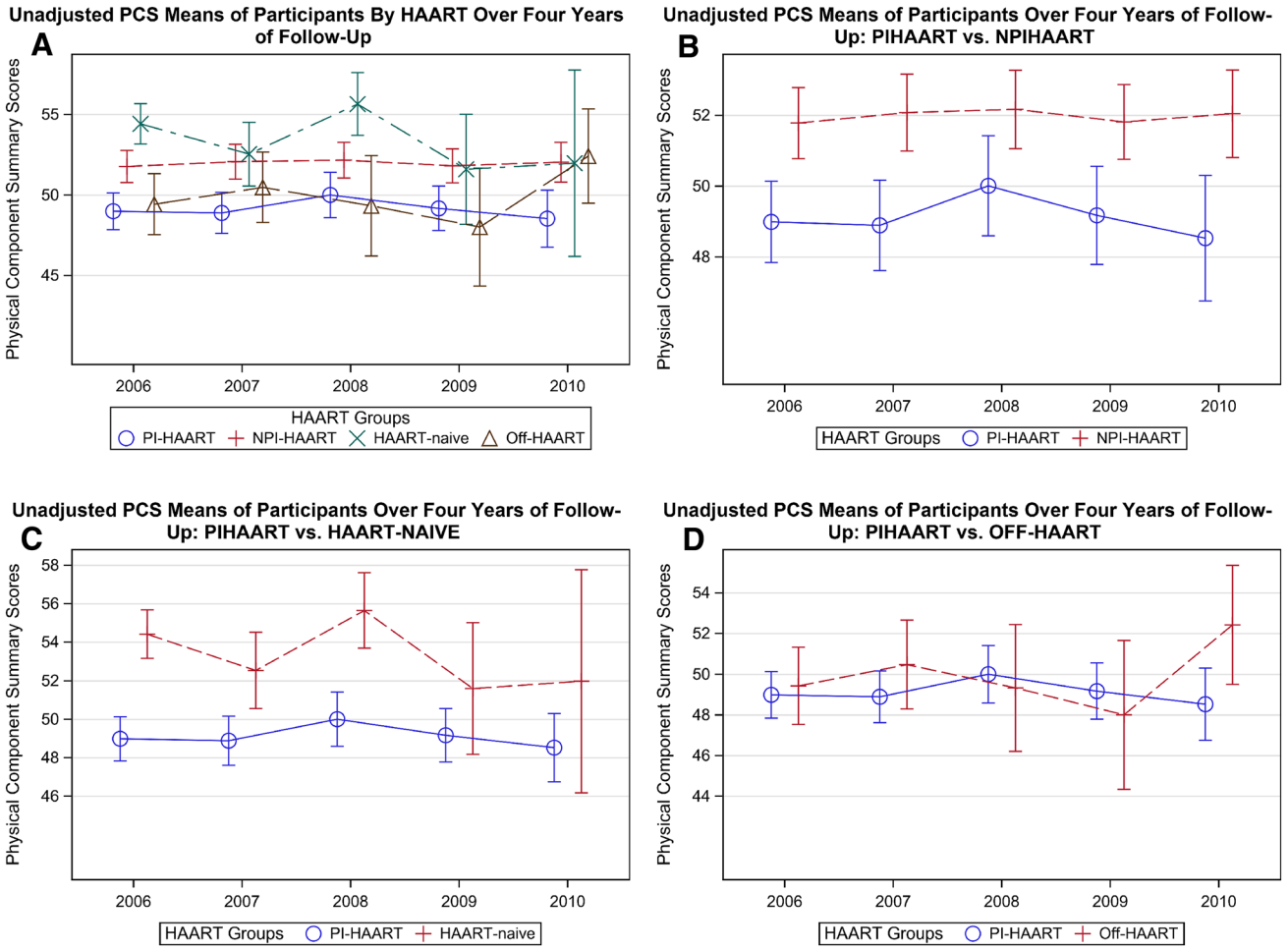

Fig. 1 **a–d** Physical component summary scores by HAART Group Over 4 years of follow-up. **a** Unadjusted PCS of participants by HAART group, **b** unadjusted PCS of participants on PI-HAART or NPI-HAART, **c** unadjusted PCS of participants on PI-HAART or HAART-NAÏVE, **d** unadjusted PCS of participants on PI-HAART or OFF-HAART; raw means are shown

treatment (PI-HAART and NPI-HAART groups) based on HIV-disease indicators or even among the treatment arms based on medication side-effect profiles or other clinical indications. Similar to PCS, we did not find any significant treatment benefit of NPI-HAART over PI-HAART for MCS. In addition, MCS in NPI-HAART, HAART-naïve, and Off-HAART groups were not significantly different from those of PI-HAART (Table 4).

In a 5-year longitudinal study of a French HIV-population on PI-HAART, Protopopescu et al. found that PCS improved in the first year following initiation of treatment but remained stable over the rest of the follow-up period [8]. Being that participants had already been on HAART for years before the HRQOL questionnaires were administered in the NHS cohort, it was not entirely surprising that we did not see any initial improvement in PCS. Our findings of no significant treatment benefit of NPI-HAART over PI-HAART on participants HRQOL scores is different from the findings of others [9, 27, 28] who reported improved quality of life in their studies. However, these studies varied with ours from a methodological standpoint and may partly explain the different results. For example, the work by Potard et al. [27] and Campo et al. [28] involved treatment switch without a concurrent PI-HAART comparison group while that by Fumaz et al. [9] involved 100 participants who had failed a PI-HAART regimen before randomization into another PI-HAART or efavirenz-based HAART groups.

Although PCS of the HAART-naïve group was still higher than that of the PI-HAART group in the multivariate model, there were no significant changes in the HAART-naive PCS over the follow-up period. This finding is not unexpected because in our cohort, participants are monitored regularly on a 6-monthly interval [29] for disease indicators (CD4-cell counts and plasma viral loads), and those with worsening disease indicators are placed on HAART. Therefore, the HAART-naive group may not reflect the

Table 3 Univariate analyses for MCS with/without treatment-time and covariates-time interaction terms

Variable	MCS model with treatment effect				MCS model without treatment effect			
	β	SE	95% CI	P value	β	SE	95% CI	P value
HAART				0.07[$$]				0.06[$$]
HAART-naïve	− 1.62	0.97	− 3.53 to 0.29	0.10	− 0.50	0.69	− 1.87 to 0.87	0.47
NPI-HAART	− 0.01	0.69	− 1.37 to 1.35	0.99	0.50	0.53	− 0.55 to 1.55	0.35
Off-HAART	− 1.98	0.99	− 3.92 to − 0.05	0.04	− 1.05	0.75	− 2.52 to 0.42	0.16
PI-HAART	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	− 0.04	0.14	− 0.31 to 0.22	0.76	0.10	0.08	− 0.06 to 0.25	0.24
HAART × time				0.25[$$]				
HAART-naïve × time	0.55	0.35	− 0.13 to 1.24	0.11				
NPI-HAART × time	0.09	0.18	− 0.26 to 0.45	0.61				
Off-HAART × time	0.50	0.34	− 0.16 to 1.16	0.14				
PI-HARRT × time	Ref.	Ref.	Ref.	Ref				
Intercept for HAART	48.24	0.53?	47.19 to 49.28	< 0.0001	47.73	0.48	46.79 to 48.67	< 0.0001
Race/ethnicity								< 0.0001[$$]
Non-hispanic African-American					2.71	0.60	1.54 to 3.88	< 0.0001
Others including hispanics					1.21	0.87	− 0.50 to 2.91	0.17
Non-hispanic white					Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)					0.11	0.08	− 0.05 to 0.27	0.17
Intercept for race/ethnicity					46.59	0.45	45.71 to 47.47	< 0.0001
Male					0.69	1.32	− 1.89 to 3.27	0.60
Time (1-yearly increment)					0.11	0.08	− 0.05 to 0.27	0.18
Intercept for male					47.16	1.30	44.61 to 49.71	< 0.0001
Rank				0.09[$$]				0.08[$$]
Civilian/not active duty	− 2.44	1.31	− 5.01 to 0.12	0.03	− 1.58	1.08	− 3.69 to 0.53	0.14
Enlisted	− 1.39	1.31	− 3.97 to 1.19	0.20	− 0.50	1.09	− 2.63 to 1.64	0.65
Warrant officer/officer	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	− 0.22	0.29	− 0.79 to 0.34	0.44	0.12	0.08	− 0.04 to 0.28	0.14
Rank × time				0.46[$$]				
Civilian/not active duty × time	0.36	0.31	− 0.24 to 0.97	0.07				
Enlisted × time	0.38	0.31	− 0.24 to 0.99	0.07				
Warrant officer/officer	Ref.	Ref.	Ref.	Ref.				
Intercept for rank	49.58	1.22	47.19 to 51.98	< 0.0001	48.77	1.03	46.75 to 50.79	< 0.0001
Married	− 0.26	0.63	− 1.49 to 0.97	0.68	0.50	0.47	− 0.42 to 1.41	0.29
Time (1-yearly increment)	− 0.01	0.10	− 0.19 to 0.20	0.95	0.11	0.08	− 0.05 to 0.27	0.18
Married × time	0.32	0.18	− 0.03 to 0.67	0.07				
Intercept for married	47.90	0.40	47.12 to 48.69	< 0.0001	47.65	0.37	46.92 to 48.39	< 0.0001
Medical comorbidity	− 0.76	0.81	− 2.35 to 0.83	0.35	− 0.60	0.54	− 1.65 to 0.45	0.26
Time (1-yearly increment)	0.11	0.09	− 0.07 to 0.29	0.22	0.12	0.08	− 0.04 to 0.28	0.13
Medical comorbidity × time	0.05	0.21	− 0.36 to 0.46	0.80				
Intercept for medical comorbidity	47.92	0.36	47.21 to 48.64	< 0.0001	47.89	0.35	47.21 to 48.58	< 0.0001
Mental comorbidity	− 4.90	0.67	− 6.21 to − 3.58	< 0.0001	− 4.75	0.49	− 5.70 to − 3.80	< 0.0001
Time (1-yearly increment)	0.16	0.10	− 0.03 to 0.35	0.10	0.17	0.08	0.02 to 0.33	0.03
Mental comorbidity × time	0.06	0.18	− 0.30 to 0.41	0.75				
Intercept for mental comorbidity	49.02	0.37	48.29 to 49.75	< 0.0001	48.97	0.35	48.29 to 49.66	< 0.0001
Baseline age (5-yearly increments)					0.24	0.15	− 0.06 to 0.54	0.11
Time (1-yearly increment)					0.11	0.08	− 0.05 to 0.27	0.18
Intercept for baseline age					45.78	1.34	43.16 to 48.40	< 0.0001
Time since HIV diagnosis (5-yearly increments)	− 0.24	0.27	− 0.77 to 0.29	0.38	− 0.22	0.23	− 0.66 to 0.22	0.33
Time (1-yearly increment)	0.13	0.18	− 0.23 to 0.49	0.48	0.15	0.09	− 0.03 to 0.33	0.10
Time since HIV diagnosis × time	0.01	0.06	− 0.12 to 0.13	0.91				
Intercept for time since HIV diagnosis	48.28	0.65	46.99 to 49.56	< 0.0001	48.23	0.55	47.16 to 49.31	< 0.0001
pVL > 50 copies/mL	− 1.65	0.56	− 2.76 to − 0.54	0.004	− 0.87	0.33	− 1.52 to − 0.22	0.009
Time (1-yearly increment)	− 0.03	0.10	− 0.23 to 0.16	0.73	0.06	0.08	− 0.10 to 0.22	0.46
pVL × time	0.32	0.19	− 0.05 to 0.70	0.08				
Intercept for pVL	48.49	0.41	47.69 to 49.29	< 0.0001	48.23	0.38	47.49 to 48.97	< 0.0001
CD4 category				0.03[$$]				0.005[$$]
CD4 count < 200	− 2.93	1.36	− 5.61 to − 0.26	0.03	− 2.77	0.87	− 4.48 to − 1.06	0.002
CD4 count 2–499	− 1.17	0.58	− 2.31 to − 0.03	0.04	− 0.54	0.34	− 1.21 to 0.13	0.11
CD4 count > 499	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	− 0.01	0.10	− 0.21 to 0.20	0.96	0.08	0.08	− 0.08 to 0.24	0.35
CD4 category × time				0.41[$$]				
CD4 count < 200 × time	0.07	0.45	− 0.81 to 0.96	0.87				
CD4 count 2–499 × time	0.25	0.18	− 0.11 to 0.61	0.18				
CD4 count > 499 × time	Ref.	Ref.	Ref.	Ref.				
Intercept for CD4 category	48.46	0.42	47.63 to 49.28	< 0.0001	48.22	0.38	47.48 to 48.97	< 0.0001
AIDS defining illness	− 1.57	1.10	− 3.72 to 0.58	0.15	− 0.82	0.85	− 2.49 to 0.85	0.34
Time (1-yearly increment)	0.08	0.08	− 0.08 to 0.25	0.34	0.11	0.08	− 0.05 to 0.27	0.17
AIDS defining illness × time	0.30	0.28	− 0.17 to 0.92	0.28				
Intercept for AIDS defining illness	47.97	0.36	47.27 to 48.67	< 0.0001	47.90	0.35	47.21 to 48.58	< 0.0001
Medical comorbidity category				0.83[$$]				0.35[$$]
Diabetes	− 1.42	1.19	− 3.75 to 0.90	0.23	− 0.63	0.83	− 2.26 to 0.99	0.45
CV disorder/MI	− 0.68	2.30	− 5.18 to 3.83	0.77	− 1.53	1.12	− 3.72 to 0.66	0.17
Cancers	− 0.29	1.24	− 2.73 to 2.14	0.81	− 0.94	0.84	− 2.58 to 0.70	0.26
Other chronic medical condition	− 0.27	2.12	− 4.44 to 3.89	0.90	1.11	1.17	− 1.18 to 3.41	0.34

Table 3 (continued)

No med comorbidity category	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	0.11	0.09	− 0.07 to 0.29	0.22	0.12	0.08	− 0.04 to 0.28	0.14
Medical comorbidity category × time				0.70[$$]				
Diabetes × time	0.28	0.31	− 0.32 to 0.89	0.36				
CV disorder/MI × time	− 0.25	0.59	− 1.41 to 0.91	0.67				
Cancers × time	− 0.24	0.33	− 0.89 to 0.41	0.47				
Other chronic medical condition × time	0.43	0.55	− 0.66 to 1.51	0.44				
No medical comorbidity × time	Ref.	Ref.	Ref.	Ref.				
Intercept for med comorbidity category	47.93	0.36	47.21 to 48.64	< 0.0001	47.90	0.35	47.21 to 48.59	< 0.0001
Mental comorbidity category				< 0.0001[$$]				< 0.0001[$$]
MDD	− 5.56	0.76	− 7.06 to − 4.06	< 0.0001	− 5.05	0.55	− 6.13 to − 3.96	< 0.0001
Anxiety/bipolar disorders	− 4.74	1.41	− 7.51 to − 1.96	0.0008	− 5.44	0.84	− 7.08 to − 3.79	< 0.0001
Alcohol abuse	− 2.59	1.59	− 5.70 to 0.52	0.10	− 3.48	1.05	− 5.54 to − 1.42	0.001
Other psychiatric disorders	− 2.27	2.07	− 6.32 to 1.78	0.27	− 3.09	1.05	− 5.16 to − 1.03	0.003
No psychiatric disorder	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	0.16	0.10	− 0.03 to 0.35	0.10	0.17	0.08	0.01 to 0.32	0.04
Mental comorbidity category × time				0.68[$$]				
MDD × time	0.21	0.22	− 0.22 to 0.64	0.33				
Anxiety/bipolar disorders	− 0.26	0.40s	− 1.05 to 0.53	0.52				
Alcohol abuse × time	− 0.34	0.45	− 1.22 to 0.54	0.45				
Other psychiatric disorders × time	− 0.24	0.57	− 1.36 to 0.88	0.67				
No psychiatric disorder × time	Ref.	Ref.	Ref.	Ref.				
Intercept for mental comorbidity category	49.02	0.37	48.29 to 49.75	< 0.0001	49.00	0.35	48.32 to 49.68	< 0.0001

PCS physical component summary scores, *MCS* mental component summary scores, *HAART* highly active antiretroviral therapy, *PI-HAART* protease inhibitor-based HAART, *NPI-HAART* non-protease inhibitor-based HAART, *HAART-naïve* never received HAART, *Off-HAART* received HAART in the past but not currently on HAART, *β* beta, *SE* standard error, *95% CI* 95% confidence interval, *pVL* plasma viral load, *Med* medical, *MDD* major depressive disorder, *CV* cardiovascular, *MI* myocardial infarction

[$$]*P*-value of *F*-statistics of type 3 tests of the fixed effects

expected downward trajectory in HRQOL [3] because of the steady movement of participants from this group to the treatment arms (PI-HAART and NPI-HAART). By the same token, it may be argued that the average improvements in HRQOL in the treatment arm may be blunted by additions of participants with less favorable HRQOL scores from the HAART-naïve or Off-HAART groups over time. The significant differences in PCS among the HAART groups may be explained by their baseline differences, residual confounding, and confounding by indication since the PI-HAART group had lived with HIV-infection longer and had more comorbidities including AIDS at baseline. The Off-HAART group also had a relatively stable PCS over the period of follow-up, similar to the findings by others [30, 31] but different from the SMART trial which found a decline in HRQOL among those on CD4 count-guided treatment interruption [32]. Like the HAART-naïve group, participants in the Off-HAART group with worsening disease indicators are often switched to either PI-HAART or NPI-HAART.

Another interesting finding in our current study was the interaction between time and medical comorbidity. While medical comorbidity was negatively predictive of PCS, we found that for every 1-year increment in study duration from baseline, the presence of medical comorbidity led to improvement in PCS by 0.7 points ($P = 0.005$). One likely explanation for this is that those who develop medical comorbidities were likely to have had more contact with the healthcare system, which may positively impact their PCS as their comorbid conditions improve or become stable. Furthermore, coping strategies used for their comorbidities may develop over time and also help lead to a net improvement in physical functioning. We also note an interaction between time and rank; those who were classified as either civilian/retired or enlisted had improvements in the PCS by 0.72 and 0.84, respectively, on a yearly basis compared to officers. This may be the result of becoming better adjusted to civilian life for the retired or disengaging in activities that may have been taxing on their physical functioning in later years. For the enlisted, it may be due to better adjustment to military life and possibly maintaining physical fitness to meet military standards.

Similar to the findings by other investigators and in keeping with clinical experience, we also found that lower CD4 counts [8, 13], AIDS diagnosis [8, 10], and mental comorbidities [10, 13] were negatively predictive of physical functional health in the long term. Increasing age was also a negative predictor of physical functional health similar to the findings of others [3, 8, 13]. Like in our cross-sectional study, being married was modestly negatively predictive of PCS. Time since HIV diagnosis, although significant in the univariate model, was not independently predictive of PCS, a finding that is similar to our baseline study and that of Jia et al. [11, 12].

Similar to our baseline study [2], four factors were independently predictive of mental functional health in our cohort: CD4 count < 200 cells/mm^3, mental comorbidity, older age at baseline, and being African-American. Additionally, the enlisted had higher MCS than civilian/retired by 1.56 times (95% CI 0.44–2.68). Although officers had 1.72 times higher MCS than civilian/retired, this was

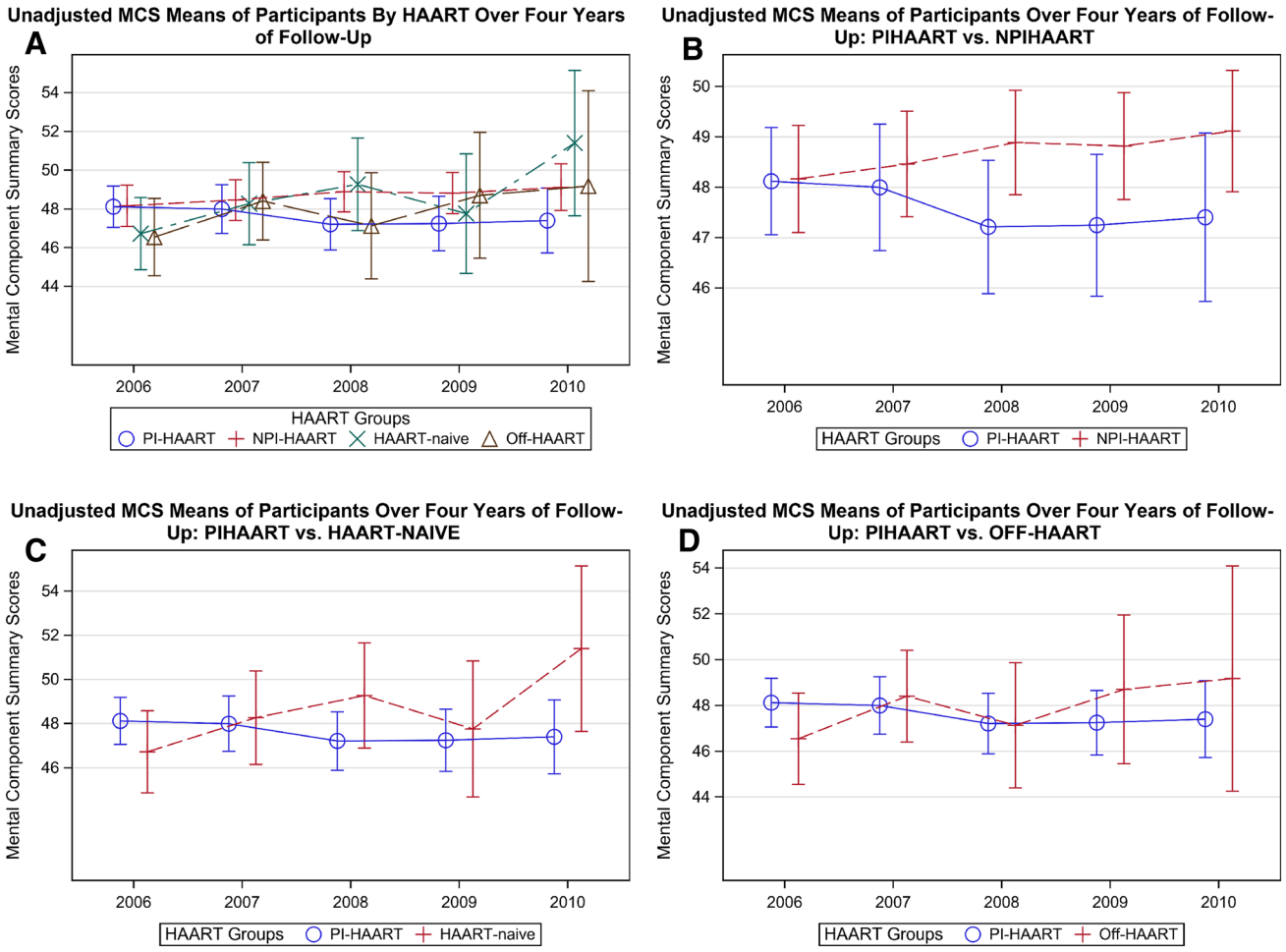

Fig. 2 **a**–**d** Mental component summary scores by HAART Group over 4 years of follow-up. **a** unadjusted MCS of participants by HAART group, **b** unadjusted MCS of participants on PI-HAART or NPI-HAART, **c** unadjusted MCS of participants on PI-HAART or HAART-NAÏVE, **d** unadjusted MCS of participants on PI-HAART or OFF-HAART; raw means are shown

marginally non-significant with a *P*-value of 0.09 but this could be attributable to the very small number of officers (61 at baseline). In this longitudinal study, every 5-year increment in age improved MCS by 0.55. Although the impact of mental comorbidity on mental functional health was not nearly as dramatic as we found in our baseline study (−3.23 vs. −6.15), it still remained the most significant predictor of MCS in our cohort and above the clinically meaningful threshold of 2–3 points difference [20]. Based on this current work and our previous work [2], we believe that there is a need to aggressively address the mental health needs of HIV-infected military personnel by both clinicians and policymakers in order to improve their overall quality of life.

Some of the limitations of our current study include the high percentage of missing HRQOL measures. Of the 812 eligible participants at baseline, 626 (77%) had HRQOL measures by the end of first year of follow-up but at the end of administrative censorship in September of 2010, there were only 362 (45%) participants with HRQOL measures. Participants with missing HRQOL measures were due to non-response to or improperly completed self-administered questionnaire or loss to follow-up. This loss has the potential to bias our results, but this is unlikely considering the consistency of the longitudinal results to the baseline findings for the entire cohort. In addition, the proportions of participants by demographic characteristics, HIV-disease indicators, and comorbidities were relatively consistent over time (Supplemental Figs. 1, 2). When we compared those who did not respond to the questionnaire for the period, we did not find any differences by demographic characteristics or HIV-disease indicators, but non-responders were less likely to have medical or mental comorbidity (data not shown).

Another limitation of our study is the predominantly male distribution of the cohort, which may limit the generalizability of our results. As we stated earlier, confounding by indication [33], which tends to be a major drawback to most clinical epidemiologic studies evaluating treatment benefits, may partly explain the better physical functional health we

Table 4 Multivariate predictors* of physical component summary scores (PCS) and mental component summary scores (MCS)

Variable	Adjusted model 1: PCS model				Adjusted model 2: MCS model			
	β	SE	95% CI	P value	β	SE	95% CI	P value
HAART								
HAART-naïve	1.58	0.74	0.14 to 3.03	0.03	− 0.83	0.76	− 2.33 to 0.67	0.28
NPI-HAART	1.10	0.48	0.18 to 2.04	0.02	− 0.13	0.47	− 1.05 to 0.79	0.78
Off-HAART	0.16	0.63	− 1.07 to 1.39	0.80	− 0.26	0.67	− 1.57 to 1.06	0.70
PI-HAART	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Age (years, 5-yearly increment)	− 0.81	0.18	− 1.16 to − 0.46	< 0.0001	0.55	0.16	0.23 to − 0.87	0.0007
CD4 category								
CD4 count < 200	− 2.90	0.87	− 4.60 to − 1.21	0.0008	− 2.53	0.87	− 4.24 to − 0.83	0.003
CD4 count 200–499	− 0.80	0.34	− 1.47 to − 0.14	0.02	− 0.49	0.34	− 1.16 to 0.18	0.15
CD4 count > 499	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Plasma viral load > 50 copies/mL					− 0.51	0.39	− 1.28 to 0.26	0.20
Time since HIV diagnosis (5-yearly)	0.18	0.28	− 0.37 to 0.72	0.53				
AIDS defining illness	− 3.41	0.82	− 5.02 to − 1.80	< 0.0001				
Medical comorbidity	− 3.71	0.80	− 5.27 to − 2.12	< 0.0001				
Mental comorbidity	− 3.23	0.49	− 4.18 to − 2.27	< 0.0001	− 4.58	0.49	− 5.54 to − 3.63	< 0.0001
Married	− 0.85	0.45	− 1.74 to 0.03	0.058				
Race/ethnicity								
Non-hispanic African-American					2.59	0.57	1.47 to 3.70	< 0.0001
Others					1.06	0.82	− 0.55 to 2.67	0.20
Non-hispanic white					Ref.	Ref.	Ref.	Ref.
Rank								0.01[$$]
Civilian/retired	− 3.40	1.29	− 5.94 to − 0.87	0.009	− 1.72	1.03	− 3.73 to 0.29	0.09
Enlisted	− 2.82	1.27	− 5.32 to − 0.33	0.03	− 0.16	1.04	− 2.20 to 1.88	0.88
Officer	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medical comorbidity × time	0.71	0.21	0.30 to 1.12	0.0007				
Rank × time								
Civilian/retired	0.72	0.30	0.12 to 1.31	0.018				
Enlisted	0.84	0.30	0.25 to 1.44	0.005				
Officer	Ref.	Ref.	Ref.	Ref.				
Time (1-yearly increment)	− 0.92	0.28	− 1.48 to − 0.37	0.001	0.11	0.08	− 0.05 to 0.28	0.18
Intercept	62.22	1.92	58.44 to 66.00	< 0.0001	44.82	1.79	41.31 to 48.33	< 0.0001

AIDS-defining illness does not include CD4 < 200

PCS physical component summary scores, *MCS* mental component summary scores, *HAART* highly active antiretroviral therapy, *PI-HAART* protease inhibitor-based HAART, *NPI-HAART* non-protease inhibitor-based HAART, *HAART-naïve* never received HAART, *Off-HAART* received HAART in the past but not currently on HAART,*β* beta, *SE* standard error, *95% CI* 95% confidence interval

*Gray = $P \geq 0.2$ in univariate analysis, so not included in model (Tables 2, 3)

$$*P*-value of *F*-statistics of type 3 tests of the fixed effects

observed in the HAART-naïve group over the PI-HAART group. In addition, residual confounding may have contributed to better physical functional health observed in these groups. Some of the ways to address these short-comings will be either through randomization or by propensity scoring, both of which are beyond the scope of our current research efforts but may be the subject for future research.

One of the important strengths of our study is the long follow-up period (over 4.5 years) enabling us to determine the long-term predictors of HRQOL in an observational study. To the best of our knowledge, this is the first study to evaluate the impact of specific HAART classes on HRQOL measures, including those who are HAART naïve and Off-HAART. Contrary to the view that PI-HAART is associated with more adverse effects, and therefore, will be more

Table 5 Multivariate* PCS and MCS models for categories for medical and mental comorbidities

Variable	Adjusted model 3: most parsimonious PCS model[a]				Adjusted model 4: most parsimonious MCS model[b]			
	β	SE	95% CI	P value	β	SE	95% CI	P value
Medical comorbidity categories								
Diabetes	− 3.44	1.17	− 5.74 to − 1.15	0.003				
MI and CV diseases	− 10.59	2.25	− 15.01 to − 6.18	< 0.0001				
Cancers	− 3.19	1.19	− 5.52 to − 0.86	0.007				
Other chronic medical disorders	− 0.84	2.10	− 4.97 to 3.28	0.69				
No chronic medical disorder	Ref.	Ref.	Ref.	Ref.				
Medical comorbidity categories × time								
Diabetes × time	0.65	0.31	0.04 to 1.25	0.04				
MI and CV diseases × time	2.10	0.58	0.96 to 3.25	0.0003				
Cancers × time	0.55	0.32	− 0.07 to 1.18	0.08				
Other chronic medical disorders × time	0.32	0.55	− 0.76 to 1.40	0.56				
No chronic medical disorder × time	Ref.	Ref.	Ref.	Ref				
Mental comorbidity categories								
Major depressive disorder	− 3.17	0.55	− 4.25 to − 2.09	< 0.0001	− 4.98	0.55	− 6.07 to − 3.90	< 0.0001
Anxiety/bipolar disorder	− 3.81	0.83	− 5.44 to − 2.17	< 0.0001	− 4.93	0.84	− 6.58 to − 3.28	< 0.0001
Alcohol abuse	− 3.14	1.04	− 5.19 to − 1.10	0.003	− 3.40	1.05	− 5.46 to − 1.35	0.001
Other mental comorbidities	− 2.99	1.05	− 5.05 to − 0.93	0.005	− 2.84	1.05	− 4.91 to − 0.78	0.007
No mental comorbidity	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (1-yearly increment)	− 0.76	0.29	− 1.33 to − 0.20	0.008	0.10	0.08	− 0.07 to 0.27	0.24
Intercept	61.50	1.89	57.78 to 65.22	< 0.0001	44.91	1.79	41.40 to 48.42	< 0.0001

*Gray = $P > 0.2$ in univariate analysis, so not included in model (see Tables 2, 3)

[a]Controlled for same set of covariates as in Table 4, Model 1

[b]Controlled for same set of covariates as in Table 4, Model 2

PCS physical component summary scores, *MCS* mental component summary scores, *HAART* highly active antiretroviral therapy, *PI-HAART* protease inhibitor-based HAART, *NPI-HAART* non-protease inhibitor-based HAART, *HAART-naïve* never received HAART, *Off-HAART* received HAART in the past but not currently on HAART, *β* beta, *SE* standard error, *95% CI* 95% confidence interval

detrimental to participants' HRQOL measures, we did not find treatment benefit of NPI-HAART over PI-HAART. This finding could be attributed to movement of participants within HAART groups and the use of newer PI-HAART medications with less toxicity compared to older PIs. In addition, those on HAART in our cohort had stable HRQOL scores over the follow-up period. Our study also shows that lower CD4 and mental comorbidities were the most important modifiable risk factors negatively affecting both PCS and MCS of participants while AIDS-defining illnesses and medical comorbidities specifically affect physical functional health. Addressing these risk factors would be expected to help improve the functional health of participants. Regarding mental comorbidities, MDD, anxiety/bipolar disorder and alcohol abuse were all independently predictive of MCS (Table 5, Model 4). Other mental comorbidities including drug abuse and PTSD among others were also predictive of MCS although we did not further categorize these separately due to their smaller numbers. Medical comorbidities were negatively predictive of only PCS (Table 5, Model 3). MI/CVD had the largest effect, followed by DM. Participants with MI/CVD had over a 10-point lower PCS compared to participants without MI/CVD but had a 2.1 annual improvement in scores over the period of follow up. This is not entirely surprising as these are serious medical conditions, but rapid improvement may be seen with prompt and adequate intervention. Those with DM also recorded an annual 0.65 improvement in scores over the period of follow-up.

Further improvement in mental functional health could be achieved through measures such as social support and active coping [11, 13] as well as ensuring timely and appropriate medical therapy. Incorporating a multidisciplinary, well-coordinated and targeted mental health intervention in this population once they enter the healthcare system may be beneficial in addressing their mental healthcare needs. Regular clinical monitoring of HIV-infected persons as well as testing for HIV disease indicators (CD4 cell count and plasma viral loads) were useful in deciding when to start HAART in the HAART-naïve at the time of this study, but ART initiation guidelines have since changed. In the United States, immediate initiation of ART followed the DHS guidelines in 2012 [34] while universal change for immediate initiation of ART followed the World Health Organization's guidelines in September 2015 [35]. But as some have noted, the treat all policy has its own challenges since a significant number of HIV-infected individuals do not know their status [36, 37] and will, therefore, not be receiving treatment. Related to this is late entry to treatment at which time individuals already have depressed immune system and clinical complications [36]. To overcome this challenge, testing needs to be scaled up and treatment capacity increased especially in resource-poor settings. In the NHS, however, testing is universal, and treatment is readily available. Therefore, the strategy at the time of closely monitoring the HAART-naïve and Off-HAART groups immunologically

and clinically contributed to the stable HRQOL scores in these groups as participants were moved to the PI or NPI treatment arms as their HIV-disease indicators worsened.

Conclusion

In this observational study, the effect of non-protease inhibitors on participants' mean HRQOL scores was not significantly different from that of participants on the protease inhibitors. In addition, there were no significant changes in HRQOL measures by HAART groups over the period of follow-up due to movement of participants from one treatment arm to the other, and therefore, justifying frequent monitoring CD4 counts and viral load. The long-term predictors of HRQOL in our cohort include medical and mental comorbidities, lower CD4 counts, AIDS defining illnesses, higher military rank, being African-American, and age at baseline. The impact of medical comorbidity on physical functional health diminished over time but that of mental comorbidity persisted. In addition, enlisted military personnel and civilian/retired saw an incremental, yearly improvement in their physical functional health over the period of follow-up. We believe that to improve the functional health of participants, there is a need to aggressively address the modifiable risk factors that predict low HRQOL, especially mental comorbidity and lower CD4 count.

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Data availability Data for this study are available from the Infectious Disease Clinical Research Program (IDCRP), headquartered at the Uniformed Services University of the Health Sciences (USU), Department of Preventive Medicine and Biostatistics. The Informed Consent Document under which the HIV Natural History Study data were collected specifies that each use of the data will be reviewed by the Institutional Review Board. Furthermore, the data set may include Military Health System data collected under a Data Assurance Agreement that requires accounting for uses of the data. Data requests may be sent to: Address: 11,300 Rockville Pike, Suite 600, Rockville, MD 20,852; Email: contactus@idcrp.org.

Compliance with ethical standards

Conflict of interest All of the authors declare no competing interests or financial interest in this work.

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