Health-Related Quality of Life in the Era of Highly Active Anti-Retroviral Therapy in a United States' Military Cohort of Individuals Living with Human Immunodeficiency Virus

A Thesis

Submitted to the Faculty

of

Drexel University

by

Leonard Emuren

in partial fulfilment of the

requirements for the degree

of

Doctor of Philosophy

May 2015

List of Tables

1. Table 1.1: AIDS defining opportunistic infections 26
2. Table 1.2: Antiretroviral Drugs Approved by the FDA 27
3. Table 1.3: Generic Measures of Health-Related Quality of Life 28
4. Table 1.4: HIV Disease-Specific Instruments 30
5. Table 1.5: SF-36 Health Status Scales and Interpretation of Low/High Scores 32
6. Table 1.6: The Short Form – 36 (SF-36) 33
7. Table 1.7: Reliability, Central Tendency, &Variability of Scales in the MOS 35
8. Table 1.8: Recoding Items (Step 1) 35
9. Table 1.9: Averaging Items to Form Scales (Step 2) 36
10. Table 1.10: Baseline Characteristics of the Cohort 36
11. Table 1.11: Health-Related Quality of Life Scores of Participants at Baseline 38
12. Table 1.11: Reliability of HRQOL Scores in the NHS & US Gen. Pop. 38
13. Table 2.1: Baseline Characteristics of Participants by HAART Group 65
14. Table 2.2: Factors Associated with PCS Scores at Baseline 67
15. Table 2.3: Factors Associated with PCS Scores at Baseline 69
16. Table 2.4: Factors Associated with PCS and MCS Scores at Baseline 71
17. Table 3.1.a: Baseline Characteristics of Participants in 2006 91
18. Table 3.1.b: HAART Groups of Participants from 2006 to 2010 92
19. Table 3.2.a: Univariate Analyses for PCS Scores 92
20. Table 3.2.b: Univariate Analyses for MCS Scores 93
21. Table 3.3.a: Multivariate Predictors of PCS Scores 94
22. Table 3.3.b: Multivariate Predictors of MCS Scores 94
23. Table 4.1: Characteristics of Participants 125
24. Table 4.2: Univariate Cox Regression Model for Hazard of Hospitalization 126
25. Table 4.3.a: Multivariate Cox Regression Model for Hazard of Hospitalization for Terciles of PCSS and MCSS 127
26. Table 4.3.b: Multivariate Cox Regression Model for Hazard of Hospitalization (PCSS and MCSS as Continuous Variables 128

List of Figures

1. Fig. 1.1: Structure of HIV ……..…….. 39
2. Fig. 1.2: Life Cycle of HIV …….……..……..... 40
3. Fig. 1.3.a: Monthly Return of Completed SF-36 by Calendar Year (2006-2008) … 41
4. Fig. 1.3.b: Monthly Return of Completed SF-36 by Calendar Year (2009-2010) … 41
5. Fig. 3.1.a: PCS Scores Over Four Years of Follow-up – All HAART Groups .....… 96
6. Fig. 3.1.b: PCS Scores Over Four Years of Follow-up – NPI/PI Groups ……..... 96
7. Fig. 3.1.c: PCS Scores Over Four Years of Follow-up – Naïve/PI Groups ….....… 97
8. Fig. 3.1.d: PCS Scores Over Four Years of Follow-up – Off/PI Groups ….....… 97
9. Fig. 3.2.a: MCS Scores Over Four Years of Follow-up – All HAART Groups .....… 98
10. Fig. 3.2.b: MCS Scores Over Four Years of Follow-up – NPI/PI Groups .....….... 98
11. Fig. 3.2.c: MCS Scores Over Four Years of Follow-up – Naïve/PI Groups ….....… 99
12. Fig. 3.2.d: MCS Scores Over Four Years of Follow-up ……..... 99
13. Fig. 3.3: Participants' Age by HAART Group Over Four Years of Follow-up …… 100
14. Fig. 3.4: CD4 Count by Treatment Group Over Four Years of Follow-up ……..... 100
15. Fig. 3.5: Viral Load by Treatment Group Over Four Years of Follow-up ...…..… 101
16. Fig. 3.6: HIV Duration by Treatment Group Over Four Years of Follow-up .....… 101
17. Fig. 3.7: CD4 Categories by Treatment Group Over Four Years of Follow-up 102
18. Fig. 3.8: pVL Categories by Treatment Group Over Four Years of Follow-up 102
19. Fig. 3.9: AIDS Diagnosis by Treatment Group Over Four Years of Follow-up 103
20. Fig. 3.10: Medical Comorbidity by Treatment Group Over Four Years of Follow-up …… 103
21. Fig. 3.11: Mental Comorbidity by Treatment Group Over Four Years of Follow-up …… 104
22. Fig. 3.12: Marital Status by Treatment Group Over Four Years of Follow-up .....… 104
23. Fig. 3.13: Race/Ethnicity by Treatment Group Over Four Years of Follow-up ….. 105
24. Fig. 4.1: Kaplan-Meier Survival Curve for PCSS ……. 129
25. Fig. 4.2: Minus-Log-Minus-Log Survival Curve for PCSS ……..……... 129
26. Fig. 4.1: Kaplan-Meier Survival Curve for MCSS ……..……. 130
27. Fig. 4.2: Minus-Log-Minus-Log Survival Curve for MCSS …...……..…….. 130
28. Fig. 5.1: Relationship among Measures of Patient Outcome in HRQOL Conceptual model …… 149

Dedication

To the memory of

my mother

Tumaye Grace Emuren

and my friend

Bokizibe Z. Avah, MBBS, MPH

whose clinical and outreach work among HIV-infected persons in my home state, Bayelsa, Nigeria first brought my attention to the burden of the disease.

Acknowledgements

Let me start by thanking all the members of my committee for the support and encouragement during the period of my dissertation, and for guiding me through this dissertation. They are: Seth Welles, PhD, ScD (Chair and Advisor); Brian Agan, MD (member, and Principal Investigator for the US Military HIV Natural History Study at the Infectious Disease Clinical Research Program [IDCRP]); Grace Macalino, PhD (member and Research Area Director, HIV/STI at IDCRP); Alison A. Evans, ScD (member); and Marcia Polansky, MS, ScD, MSW (member). Thank you all so much. I could not have asked for a better team. Thank you to Xiuping Chu, programmer analyst at IDCRP. To all the staff at the Department of Epidemiology and Biostatistics, Drexel School of Public Health (SPH), for being so supportive I say thanks. To my cohort at SPH, Neena, Bo and Jing thank you all for working as a team. To my professors at Drexel, I say thank you. Thanks also to my teachers at EVMS/ODU who laid a solid foundation for me to survive Drexel. To Dr. John Harrington for editorial help and suggestions, I say thank you.

Many thanks to my father and high school math teacher, Mr. Ebikapaye Emuren, for his support and encouragement. Thanks to Ebipere, my younger sister who has been immensely supportive during this time, and my mother-in-law, Mrs. Gladys Nwinee, for the help and support while I was at Philadelphia, away from the family. To my siblings, their families, and our extended families here and overseas, I say thank you. Thank you to Alex and Nma Nwokoji and family for ‘soft-landing’ us in the US, and by that act made this pursuit much easier. To all our friends who have been there for us this while, I say thank you. Finally, to my dear wife, Jane Barinua, for the love, support, patience and understanding, I say a big thank you. And to our kids, Tubolayefa, Dautari and Emmanuella for their patience and love. I love you all, and I thank God that I have you.

Table of Contents

List of Tables iii

List of Figures iv

Dedication v

Acknowledgements vi

1: Health-Related Quality of Life (HRQOL), Human Immunodeficiency Virus (HIV) and Highly Active Anti-Retroviral Therapy (HAART): The Example of the US Military HIV Natural History Study (NHS)

Part A: General Introduction to HRQOL, HIV and HAART 1

1.1: Introduction and Background 1

1.2: Human Immunodeficiency Virus (HIV) 2

1.2.1: HIV Life Cycle 2
1.2.2: HIV Natural History 3

1.3: Highly Active Anti-Retroviral Therapy (HAART) 4

1.4 Health-Related Quality of Life (HRQOL) 7

1.4.1: Definitions 7
1.4.2: Relevance of HRQOL 7
1.4.3: HRQOL Dimensions 9
1.4.4: HRQOL Instruments 10
1.4.5: The Medical Outcomes (MOS) Survey Short Form 36 (SF-36) 12
1.4.6: An Overview of Analytical Methods Used in HRQOL Research 13

1.5: HIV, HAART, and HRQOL 15

1.6: Gaps in the Literature 16

Part B: A General Descriptive Statistics of HRQOL of the NHS Cohort at Baseline ... 19

1.7: Methods 19

1.7.1: Study Cohort 19
1.7.2: Study Participants 20
1.7.3: Definitions and Variables Selection 20
1.7.3.1: Health-Related Quality of Life Scores 20
1.7.3.2: HAART (Treatment) Variable 21

1.7.3.3: Other Variables 21
1.7.4: Inclusion and Exclusion Criteria 22
1.7.5: Data Analysis 22

1.8: Results and Discussion 23

1.9: Conclusion 25

1.10: Tables 26

1.11: Figures 39

1.12: References 42

2: Baseline Factors Associated with Health-Related Quality of Life Among HIV-Infected Individuals in the HAART Era

Abstract 47

2.1: Introduction and Background 48

2.2: Methods 50

2.2.1: Study Cohort 50
2.2.2: Study Participants 51
2.2.3: Definitions and Variable Selection 51
2.2.3.1: Health-Related Quality of Life Scores 51
2.2.3.2: Treatment Variable 51
2.2.3.3: Covariates 52
2.2.4: Inclusions and Exclusions 53
2.2.5: Statistical Analysis 53

2.3: Results 54

2.4: Discussion 58

2.5: Conclusion 64

2.6: Tables 65

2.7. References 73

3: Predictors of Health-Related Quality of Life among HIV-infected Individuals in the HAART Era

Abstract 77

3.1: Introduction and Background 78

3.2: Methods 78

3.2.1: Study Participants and Cohort 78
3.2.2: Definitions and Variable Selection 79
3.2.2.1: Health-Related Quality of Life Scores 79
3.2.2.2: HAART (Treatment) Variable 79
3.2.3.3: Covariates 79
3.2.4: Inclusion and Exclusion Criteria 80
3.2.5: Statistical Analyses 80

3.3: Results 81

3.4: Discussion 83

3.5: Conclusions 90

3.6: Tables 91

3.7: Figures 96

3.8: References .....

4: Health Related Quality of Life and Risk of Hospitalization Among HIV-Infected Individuals

Abstract 108

4.1: Introduction and Background 109

4.2: Methods 111

4.2.1: Study Cohort 111
4.2.2: Study Participants 112
4.2.3: Definitions and Variable Selection 112
4.2.3.1: Hospitalization and Time from Completed Survey to Hospitalization 112
4.2.3.2: Health-Related Quality of Life Scores 113
4.2.3.3: Covariates 113
4.2.3.4: Time-Varying and Time-Invariant Covariates 114
4.2.3.5: Follow-Up Time 114
4.2.3.6: Censoring 114
4.2.4: Inclusion and Exclusion Criteria 115
4.2.5: Statistical Analyses 115

4.3: Results 116

4.4: Discussion 118

4.5: Conclusion 123

4.7: Tables 125

4.8: Figures 129

4.9: References 131

5: Conclusions and Recommendations

5.1: Conclusions 134

5.2: Recommendations 145

5.3: Figures 148

5.4: References 149

Vita 153

Chapter 1

Health-Related Quality of Life (HRQOL), Human Immunodeficiency Virus (HIV) and Highly Active Anti-Retroviral Therapy (HAART): The Example of the US Military HIV Natural History Study (NHS)

Part A: General Introduction to HIV, HAART and HRQOL

1.1: Introduction and Background

According to the World Health Organization (WHO), there were over 34 million people living with the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) globally at the end of 2011[1] .WHO also estimated that about 2.5 million new HIV infections occurred in 2011[1]. The parts of the world most severely affected by the HIV/AIDS pandemic are Sub-Saharan Africa (by far the most), the Caribbean, Eastern Europe and Central Asia[1]. It is worth noting that although the regional prevalence of HIV infection is about 25 times higher in sub-Saharan Africa than in Asia, almost 5 million people are living with HIV in South, South-East and East Asia combined[1]. AIDS-related mortality accounted for about 1.7 million deaths globally. While this represents a 24% decline from the 2005 peak, it sheds light on the burden of the disease at the global level. The greatest burden of the disease is felt in resource-poor countries where a significant number of infected persons still lack access to care despite a worldwide scale-up of anti-retroviral therapy (ART)[1].

In resource-rich countries, such as the United States of America, there is widespread availability of ARTs. The estimated annual number of persons aged 13 or older with newly diagnosed AIDS grew from 318 to 75,457 between 1981 and 1992[2]. Deaths from

AIDS also increased steadily from 451 to 50,628 between 1981 and 1995[2]. Following the introduction of highly active antiretroviral therapy (HAART), AIDS diagnoses and deaths declined significantly from 1995 to 1998, and remained stable from 1999 to 2008 at an average of 38,279 AIDS diagnoses and 17,489 deaths per year, respectively[2]. In the US men who have sex with men (MSM) and blacks bear the greatest burden of the disease[2,3]. At the end of 2008, there were over 1.1 million people living with HIV/AIDS in the United States[2]. The incidence of new HIV infections has remained stable at about 50,000 yearly[2]. Factors contributing to this are multiple and include continued high risk behavior among high risk groups – injection drug users (IDU), men who have sex with men (MSM), and sex workers; lack of awareness of infection status, access to or retention in HIV care and HIV-drug resistance[4].

1.2: Human Immunodeficiency Virus (HIV)

1.2.1: HIV Life Cycle

Figures 1 and 2 respectively show the structure of HIV and the HIV lifecycle. HIV is a retrovirus, a double-stranded ribonucleic acid (RNA) that employs the reverse transcriptase (RT) enzyme to transcribe the RNA into DNA in the cytoplasm of infected host's cell. Reverse transcription of the RNA core yields proviral DNA that may either reside in the cytoplasm in circular form or enter the cell nucleus and become integrated into host DNA[5]. Integrated viral DNA genes may remain latent, or, in response to viral and host regulatory proteins, may become activated. When the proviral DNA genes are activated, messenger RNA is transcribed leading to the formation of regulatory proteins such as *tat* and *rev*. These proteins, together with viral genomic RNA transcribed from

the integrated viral DNA, are assembled to form new HIV-1 viruses, which leave the infected cell and are available to attack new cells[5].

The major (glycol)-proteins to which humans infected with HIV produce antibodies are gp120, gp41, p16/p14, p27/p25 and p24. Both gp120 and gp41 are external envelope proteins that bind to receptors of host cells including CD4+ lymphocytes, macrophages, and monocytes; they are necessary for infectivity. However, gp120 attachment to CD4+ requires the presence of chemokine co-receptors such as CXCR4 or CCR5, which facilitate the process of cell binding and entry[5]. The p16/p14 tat proteins are found mostly in the nucleus and nucleolus of infected cells and function as an activator of viral transcription. The p19 rev protein is responsible for the transport and stability of the viral RNA, and travels between the cytoplasm and nucleolus of the infected cell. The p27/p25 *nef* proteins are active in the down regulation of CD4+ cells. They reside in the plasma membrane as well as the cytoplasm. The p24 gag protein functions in the core capsid and is found in the virion[5].

1.2.2: HIV Natural History

HIV infection is characterized by an acute (primary) phase, a clinical latency phase and a chronic infection phase including development of symptomatic disease and acquired immune disease (AIDS). Transmitted either sexually or parenterally, the HIV virus is detectable within 7-10 days of initial infection and viral antibodies detectable in 7-21 days later[5]. During this acute stage (acute HIV infection syndrome), viral load is usually high and infected individuals may present with flu-like symptoms such as fever, adenopathy, pharyngitis, and rash. Some may present with systemic symptoms including meningitis, Guillain-Barre syndrome, peripheral neuropathy and Bell's palsy[5].

Subsequent to and after destruction of gut-associated lymphoid tissue (GALT) that occurs a few weeks after the initial infection, the body's immune system responds via B-cell produced antibodies and CD8+ cells directed against the virus. At this point, the HIV viral level in the blood declines with a new viral set-point set in 3 to 4 months[5].

The clinical latency period is defined by a gradual decline in the level of CD4+ cells along with an increase in the CD8+ cells such that the ratio of CD4+/CD8+ drops below 1.0; the number of CD3+ cells remains relatively stable for several years. Destruction of the immune system continues and CD4+ cell level further declines as more viral particles are produced. Generally, CD4+ count indicates the degree of immunosuppression while the plasma viral load indicates the level of immune control versus viral replication and pathogenesis[5].

Several months prior to the development of clinical AIDS, a loss in T-cell homeostasis occurs as reflected by the rapid decline in CD3+ cells[5]. The above process is often accompanied by a change in the co-receptor utilization from CCR5 to CXCR-4 cell type. In rare situations where CXCR-4 predominates early in the infection, progression to clinical AIDS occurs more rapidly[5]. The median time from initial infection to development of clinical AIDS is about 10 years[5]. The Centers for Disease Control and Prevention (CDC) definition of AIDS include a laboratory confirmed HIV-infection and CD4+ T-lymphocyte count of less than 200cells/μL or with one of the AIDS defining opportunistic infections listed in table 1[6]. Pneumocystis jiroveci pneumonia, HIV wasting syndrome, Kaposi's sarcoma, oropharyngeal and esophageal candidiasis, extrapulmonary Cryptococcus, and tuberculosis are the commonly encountered opportunistic infections in the US[5].

1.3: Highly Active Anti-Retroviral Therapy (HAART)

There are currently over 25 antiretroviral drugs approved by the United States' Food and Drug Administration (Table 1.2). The six distinct classes of antiretroviral drugs are nucleoside reverse transcriptase inhibitors (NRTIs), Non-Nucleoside reverse Transcriptase Inhibitors (NNRTI), Protease Inhibitors (PIs), Integrase Inhibitors (INIs), Fusion Inhibitors and Small-Molecule CCR5 Antagonists[7]. Both fusion inhibitors and small-molecule CCR5 antagonists are referred to as Entry Inhibitors[7].

Before 1996, HIV/AIDS was treated with a single drug in the earlier period and later with two drugs. Because of resistance and the resultant treatment failure, and following the approval of the first protease inhibitors, combination therapy requiring at least two different classes of 3 different drugs were introduced with great success at maintaining virologic suppression beyond levels detectable by laboratory assays (< 50 copies per mL). The 3 drugs regimens came to be referred to as highly active antiretroviral therapy (HAART), usually requiring a protease inhibitor but because of toxicities non-nucleoside reverse transcriptase inhibitors (NNRTIs) were also used. Currently, HAART may be defined as a combination of at least three antiretroviral drugs from at least two classes. Preferred regimes include NNRTI-based regimen, PI-based regimes and INIs-based regimen[8].

NRTIs are reverse transcriptase (RT) inhibitors. They act by inhibiting DNA strand synthesis after being incorporated into the growing viral chain. Zidovudine (AZT, Retrovir), an NRTI, was the first anti-retroviral drug approved by the FDA in 1986. Other examples of NRTIs include stavudine (d4T, Zerit), didanosine, emtricitabine (FTC,

Emtriva), tenofovir disoprovil fumarate (TDF, Viread), abacavir (ABC, Ziagen), lamivudine (3TC, Epivir).

NNRTIs inhibit HIV-1 RT by binding and inducing the formation of a hydrophobic pocket proximal to, but not overlapping the active site[7]. The binding of NNTRIs changes the spatial conformation of the substrate-binding site and reduces polymerase activity[7]. Examples of NNRTIs are efavirenz, nevirapine, delaviridine, etravirine, and rilpivirine.

PIs block proteolysis of the viral polyprotein, a step required for the production of infectious particles[7]. PIs are among the most potent agents developed to date, but are large, peptide-like compounds that generally required co-administration of a boosting agent to inhibit their metabolism and enhance drug levels[7]. The HIV protease enzyme is responsible for the cleavage of the viral gag and gag-pol polyprotein precursors during virion maturation. Currently approved PIs include atazanavir (ATZ, Reyataz), darunavir (TMC114, Prezista), fosamprenavir (Lexiva), indinavir (IDV, Crixivan), lopinavir (LPV), nelfinavir (NFV, Viracept), ritonavir (RTV, Norvir), saquinavir (SQV, Fortovase/Invirase) and tipranavir (TPV, Aptivus)

First approved in 2007, integrase inhibitors (INIs or InSTIs) are the newest class of ARTs approved by the FDA[7]. They specifically inhibit strand transfer and block integration of the HIV DNA into the cellular DNA. All InSTIs are made up of two essential components: a metal-binding pharmacophore, which sequesters the active site magnesiums, and a hydrophobic group, which interacts with the viral DNA as well as the enzyme in the complex[7]. Examples of InSTIs are raltegravir and dolutegravir. Dolutegravir was approved in August, 2013[9].

Peptide fusion inhibitors were designed based on the discovery that two homologous domains in the viral gp41 protein must interact with each other to promote fusion, and that mimicry of one of one of these domains by a heterologous protein can bind and disrupt the intra-molecular interactions of the virus protein[7]. The only currently available fusion inhibitor is enfuvirtide (T-20) and is given by subcutaneous injection.

Small-molecule CCR5 antagonists carry out their anti-retroviral activity by binding to the hydrophobic pockets within the transmembrane helices of CCR5[7]. Also approved for the first time in 2007 by the FDA, maraviroc is the only available co-receptor CCR5 antagonist in the market.

There is drug resistance to virtually all available ARTs with cross-resistance among many of the drugs in the same class[7]. For the co-receptor CCR5 antagonist, resistance detection may be difficult to notice at the time of treatment failure making their use in clinical practice more complex compared to the other ARTs[7]. Because of resistance and drug toxicities, HIV-infected individuals may need to change medications from time to time[5].

1.4: Health-Related Quality of Life (HRQOL)

1.4.1: Definitions

The term health-related quality of life (HRQOL) is traceable to the 1948 definition of health[10] by the World Health Organization, which defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[11]. It is not surprising then that currently used definitions have towed similar concept of health. For example, Coons et al defined HRQOL as to "how well a person functions and to his or her perceptions of well-being in the physical, mental, and social

domains of life"[12]. The definition proposed by Wenger and Furberg and adopted by Naughton and Shumaker refers to HRQOL as "encompassing those attributes valued by patients, including their resultant comfort or sense of well-being; the extent to which they are able to maintain reasonable physical, emotional, and intellectual function; and the degree to which they retain their ability to participate in valued activities in the family, in the work-place, and in the community"[13,14]. The Centers for Disease Control and Prevention simply defines HRQOL as "encompassing those aspects of overall quality of life that can be clearly shown to affect health – either physical or mental"[15]. HRQOL therefore encompasses both the actual capabilities of the individual and his or her perceptions of activities the individual value as critical to assess[13]. Although quality of life (QOL) is often used synonymously with HRQOL in the literature (the older ones especially), QOL is an inclusive, broad concept that incorporates all factors affecting a person including economic status, social functioning, health status, life satisfaction and well-being, HRQOL focuses specifically on QOL as it relates to health.

1.4.2: Relevance of HRQOL

HRQOL is of particular importance in chronic illnesses, such as HIV/AIDS in which current therapeutic goals are not aimed at a cure but in halting disease progression, alleviating symptoms, improving functional capabilities and mitigating the adverse psychosocial consequences that may be associated with the disease[14]. Although often assessed in research settings, routine clinical assessment of health-related quality of life in persons with HIV infection has the potential to improve care by assessing and monitoring treatment effects, enhancing communication between patient and the provider, and tracking changes in functional status over time[10].

Given that there are HIV-naïve individuals who will eventually be requiring HAART, there is need to monitor the untreated course of the disease in order to allow intervention when it will be most beneficial to the infected individual. Also, the increased lifespan from HAART therapy also means that people living with HIV/AIDS (PLHA) are at potentially increased risk of prolonged morbidity due to medication adverse effects and age-associated comorbidity, such as diabetes, cancers, chronic obstructive pulmonary disease and heart diseases. HRQOL measures reflect the overall health status of the individual and with the increased survival in the HAART era non-AIDS comorbidities are now the principal diagnoses among those with HIV. Furthermore, resistance to medication, non-compliance, and future high risk behavior with acquisition of more virulent strains of the virus may further complicate the natural history of the disease with varying impact on the individual's well-being and quality of life. Finally, studies on HRQOL data can help identify subgroups with relatively poor perceived health and guide interventions to improve their situations and avert more serious consequences[15]. The interpretation and publication of these findings can help identify needs for health policies and legislation, help to allocate resources based on unmet needs, guide the development of strategic plans, and monitor the effectiveness of broad community interventions[15].

1.4.3: HRQOL Dimensions

The primary HRQOL dimensions are physical functioning, social functioning, psychological functioning, overall life satisfaction/well-being, and perception of health status[13]. Physical functioning refers to an individual's daily life activities. Social functioning is defined as a person's ability to interact with family, friends and the community[13]. Psychological functioning of a person refers to the individual's emotional

well[15]. Overall life satisfaction represents a person's perception of his or her overall sense of well-being[15]. Perceptions of health status is different from actual health but chronic illnesses or the acquisition of potentially deadly infection such as HIV may come with a period of adjustment, with individuals resetting their expectations and adapting to their new life situation. For HIV/AIDS, stigma and societal acceptability may all affect this process, as well as the availability and accessibility of therapy including psychological therapy.

Additional HRQOL dimensions that have been studied in the literature include neuropsychological functioning, personal productivity, intimacy and sexual functioning, sleep disturbance, pain and symptoms[15]. Neuropsychological functioning refers to the cognitive abilities of a person, such as memory, recognition, spatial skills and motor coordination[13]. HIV/AIDS may directly affect neurocognitive functioning, for example HIV dementia or it may be the complication of opportunistic infections such as toxoplasmosis or leukemia. Personal productivity includes paid and unpaid activities the individual is engaged in. Employment status is often affected by the disease. Sleep disturbance is often related to anxiety and depression and is a common finding among HIV-infected individuals; it has been shown to affect HRQOL[10]. Pain is a commonly assessed domain in HRQOL. HIV/AIDS patients may be plagued with chronic and debilitating pains such as HIV distal neuropathic pain that may significantly affect HRQOL[16]. Symptomatic HIV patients have poorer HRQOL compared to asymptomatic patients and symptom burden is a recognized contributor to the HRQOL of life of HIV-infected individuals[4,12,17-20].

1.4.4: HRQOL Instruments

Over the years several HRQOL instruments have been developed. There are two broad groups of HRQOL instruments – generic and disease specific. The generic instruments are designed to assess HRQOL in a broad range of populations and diseases while specific HRQOL instruments are designed to assess HRQOL in specific diseases such as HIV/AIDS. Examples of validated generic instruments include Medical Outcome Studies Short Form – 36 (MOS SF-36), Quality of Well-Being (QWB) Scale, Sickness Impact Profile (SIP), Nottingham Health Profile (NHP), the Cooperative Information Project (COOP) Charts, Time Trade Off (TTO), Standard Gamble (SG), Spitzer QL index, the World Health Organization Quality of Life Assessment Instrument (WHOQOL), the EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L), and Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST)[4,10]. Q-TWiST is regarded as a generic tool but was initially developed for HRQOL assessment in cancer clinical trials[21]. Examples of validated HIV-disease specific HRQOL instruments include Medical Outcome Study-HIV Health Survey (MOS-HIV), HIV Overview of Problems/Evaluation Systems (HOPES), HIV/AIDS-Targeted Quality of Life (HAT-QOL) and the AIDS Clinical Trial Group QOL Health survey (ACTG-QOL)[4,10,22]. Tables 3 and 4 respectively display the generic and HIV-disease specific HRQOL instruments, the dimensions examined by these tools, the approximate completion time, mode of administration as well as some of their advantages and disadvantages[10].

A good HRQOL instrument must be both valid and reliable[4,10]. Both the construct validity and the content validity must be established[4]. While the construct validity ensures that the instrument measures what it purports to measure the content validity

ensures that the tool measures all aspect of a given question[23]. Reliability refers to the degree to which the results obtained by a measurement, procedure can be replicated[23]. Reliability of the instruments is measured through their internal consistency using Cronbach's Alpha. A Cronbach's alpha of 0.7 and above is considered acceptable. Apart from validity and reliability, Grossman et al have proposed that an ideal instrument be self-administered, brief yet reasonably comprehensive, evaluates the most relevant aspects of HIV-related HRQOL, appropriate for the entire spectrum of the disease severity, responsive to clinically important changes in health status over time, easy to understand/appropriate for all literacy levels, sensitive to a wide range of patient cultural and ethnic backgrounds, available in appropriate translated versions, has wide patient acceptance/adherence, and allows easy data collection, scoring, and interpretation without the need to use a computer[10]. Finally, an ideal HRQOL tool must avoid the floor and ceiling effects in their scores[4]. Because no instrument meets all these criteria tradeoffs are usually made between the breadth and depth of the measuring tool[24]. Whereas breadth deals with the comprehensiveness of the tool, depth is concerned with the concept the instrument purportedly measures[25].

In our cohort, the SF-36 was used for obtaining HRQOL data. The SF-36 instrument has extensive usage in both cross-sectional and cohort studies. However, because it is a generic instrument its use in clinical trials is somewhat limited. In a systemic review of 24 clinical trials studies carried out by Gakhar et al, only 2 studies used the MOS SF-36 instrument while the MOS-HIV was used in 12 of those studies[4]. Shahriar et al compared the SF-36 and the MOS-HIV but did not find any unique value of the MOS-HIV over the SF-36. They concluded that although the SF-36 was a generic instrument, it may be a

preferable over the MOS-HIV because of the fewer ceiling effects, availability of national norms, and the vast amount of data for other populations in the U.S. and around the world[26].

1.4.5: The Medical Outcomes (MOS) Survey Short Form 36 (SF-36)

The precursor of the MOS SF-36 is the MOS Functioning and Well-Being Profile (MOSFWBP), an instrument that contains 149 items and requires 30 to 40 minutes to complete[10]. Because of its length, shorter versions of the instrument such as MOS SF-20, MOS SF-12, MOS SF-56, and the MOS SF-21 were developed from it[10,27]. An HIV-disease specific instrument is the MOS-HIV. The MOS was a 4 year observational study of the influence of characteristics of providers, patients, and health systems on outcomes of care[10]. The SF-36 is a generic, multi-purpose, short-form health survey with only 36 questions. It is a preference-based health utility index that has been used extensively in the US and internationally.

The SF-36 utilizes eight health concepts, namely physical functioning (PF), bodily pain (BP), role limitations due to physical health (RP), role limitations due to personal or emotional problems (RE), emotional well-being or mental health (MH), social functioning (SF), energy/fatigue or vitality (VT), and general health (GH) perceptions[4,10,22,28]. These concepts are further combined to form two summary scores known as the physical component summary (PCS) score (PF, BP, RP, and GH) and the mental component summary (MCS) score (MH, SF, RE and VT)[24]. Among the HRQOL domains that are included in other widely used surveys but not included in the SF-36 are sleep adequacy, cognitive functioning, sexual functioning, health distress, family

functioning, self-esteem, eating, recreation/hobbies, communication, and, by its generic nature, symptoms specific to one disease condition[24].

The MOS SF-36 is self-administered, takes about 10 minutes to complete and has been adapted in many cultures and translated into over 50 languages[10]. Table 5 shows the number of items in each concept, the levels and meaning of low and high scores of each concept[27]. The SF-36 instrument is displayed in Table 6[28]. The means and standard deviations of the PCSS and MCSS are both 50 and 10 respectively for the general US population. Table 7[22,28] shows the number of items in each subscale, their reliability (Cronbach's Alpha), means, and corresponding standard deviations for the general US population.

1.4.6: An Overview of Analytical Methods Used on HRQOL Research

HRQOL scores are generated as continuous variables usually in the global categories as mental component summary scale and physical component summary scale. In most cross-sectional studies on HRQOL, HRQOL is the outcome variable. Typically, in such studies HRQOL score is a continuous variable and analyses involves multivariate linear regression models to compute the beta coefficients of the explanatory variables. Because the SF-36 is a norm based scoring system, the HRQOL scores generated from this instrument for any given group can be directly compared to that of the US general population using the Z-test. In clinical trials, the baseline HRQOL scores are compared to that obtained at the end of follow-up using the t-test. The general approach in clinical trials is to use an intention-to-treat (ITT) analysis. In prospective cohort studies, t-test analysis are also used especially if when there are only two measurement points but studies using t-tests with more than two measurement points have also been done[29]. A

few prospective studies have used random effects regression model[30] in analyzing the impact of various explanatory variables on HRQOL, therefore accounting for time-varying covariates in the model which the earlier described approaches ignored.

Much fewer studies have used HRQOL as the explanatory variable in the literature, and such studies were mainly concerned with the ability of HRQOL to predict the utilization of healthcare resources[31,32] or mortality[33,34]. Survival analysis (Cox Proportional Hazard Regression models) has been used in assessing predictive value of HRQOL on survival[33,34]. Descriptive statistics have included Kaplan-Meier curves and the log-rank tests in these studies. In both studies HRQOL was divided into quartiles with the first quartile indicating worse HRQOL scores and the 4th quartile the best[33,34]. Cook et al[31] used random effects logistic regression model for their analysis while Royal et al[32] used multivariable logistic regression model in their analysis.

1.5: HIV, HAART and HRQOL

The diagnosis of HIV infection, in and of itself, can have deleterious impact on the psychological state of the individual and may negatively affect HRQOL especially for those with poor coping skills and with limited social support[10]. Both HIV-related symptoms and adverse effects from medications affect a wide range of the individual's quality of life and well-being[35]. Studies in the pre-HAART era generally revealed that HRQOL deteriorated over time for PLHA, especially for those who progressed to develop AIDS[35-37]. Others have found that HRQOL in asymptomatic HIV infection is comparable to that of the general population but as symptoms develop the HRQOL gradually declines[38]. Those with symptomatic AIDS generally have a much poorer

HRQOL score compared to asymptomatic HIV infected individuals or the general population[38,39].

Because those on HAART typically have a longer lifespan, they are potentially at increased risk of experiencing the adverse effects of the medications including diarrhea, anemia and lipodystrophy. Other side effects are peripheral neuropathy, insulin resistance, renal tubular toxicity, osteopenia, hepatotoxicity, pancreatitis, hypersensitivity reaction, hyperprolactinemia and neuropsychiatric disturbances[35]. It is estimated that three symptoms or side effects would result in deterioration in HRQOL by one standard deviation[35]. Assessing HRQOL in individuals with HIV disease on treatment is therefore very important as it is one of the only methods of reconciling the risks and benefits of prolonged therapies against a complex background of diverse morbidity[40].

1.6: Gaps in the Literature

The greater majority of research conducted on HRQOL in people living with HIV/AIDS are cross-sectional studies[29,38,41-48], and most of the longitudinal studies have been carried over relatively short periods of time, usually no longer than 1-year[36,49-54] or 2-year duration[55-57]. Also, most of these longitudinal studies were carried out in clinical trial settings as against a prospective cohort setting. Clinical trials findings may not always apply to non-clinical trial studies and the general population because of limited representation of minorities and disadvantaged groups in clinical trials. More so, clinical trials have strict inclusion criteria in order to decrease the probability of attrition or toxicity and maximize the likelihood of detecting a treatment effect. In their study to directly compare the HRQOL scores between clinical trial sample and non-clinical trial sample, Cunningham et al found that HRQOL scores were significantly lower in the non-

clinical trial group compared to the clinical trial group by about one standard deviation, even after direct adjustment for clinical and demographic characteristics, and also after comparison of the non-trial sample with the most symptomatic in the trial sample[58]. Some of the longitudinal studies involved the switching of drugs and did not have appropriate control group but uses the individual's baseline HRQOL score as basis for comparison[54].

The few prospective cohort studies on HRQOL also had problems with generalizability because they addressed specific groups or populations or had issues with sample size or were non-US based studies. For example, the work by Burgoyne et al had a 4-year follow-up but had only 41 patients making sub-analysis and the ability to detect effect size changes difficult[29]. They had enrolled 56 patients but lost 15 to follow-up and so issues of selection bias due to attrition may very well affect the interpretation of their results. The authors did not account for time varying covariates in their analysis. The study by Cook et al had only women[31]. Although the investigators used a random effects regression model, they only studied the impact of mental health quality of life on healthcare utilization[31]. The study by Liu et al studied only men who have sex with men, and so may not be generalizable to heterosexual men and women. The studies by Jia et al[53] and Lorenz et al[59] had only two measurement points, baseline and 12 months and baseline and 18 months respectively. Another study by Jia et al[60] also had two measurement points (baseline and 12 months), had only male participants and was drawn from 3 infectious disease clinics in one southern state, and would therefore not be considered representative of the entire country. The study by Cunningham et al used the Cox proportional hazards regression model to analyze the predictive value of HRQOL on mortality in a large representative HIV cohort but that study is over 9 years old and the

data was collected between January 1996 and December 1999[33]. Given that mortality is no longer a very common outcome among HIV-infected individuals in the US and other developed countries, other important end-points such as emergency room utilization and hospitalization may appear to be more relevant studies today. Another study that used the Cox regression model was that by De-Boer-van-der-Kolk et al; however, unlike the study by Cunningham et al, this study was based on a French population[34].

Protopopescu et al carried out a 5-year longitudinal study of the APROCO-COPILOTE cohort (ANRS CO-8) in which they compared the results of a random effect model (REM) to that of a joint model in their cohort when there is non-ignorable missing data[30]. They found similar results from both analytical models. The study evaluated the change in HRQOL (physical and mental component summary scores) in 1,000 participants who are on a PI-based HAART regime over a 5-year period. At the time of HAART initiation, 42.3% were HAART-naïve. Enrollment into this French cohort started in 1997 but the authors did not specify the time period they considered. These authors found that immune-depression and self-reported side effects were negative predictors of both physical and mental component summary scores. They also found that HRQOL improved after the first year of follow-up but stabilized thereafter. Because this was a PI-based HAART cohort, inferences may not be applicable to non-PI HAART cohort/population.

In the light of the aforementioned gaps in the literature, our proposed study provides us a unique opportunity to answer many of the questions on HRQOL in the HAART era in the United States, especially in the setting of equal access to health care. It allows us to compare the baseline predictors of HRQOL in our cohort to that of the general military population as reported in the Millennium cohort by Smith et al[61]. Other obvious

advantages the cohort provides us are its comprehensive and extensive follow-up periods and the large sample size. We would therefore be able to conduct analysis of the impact of specific HAART on HRQOL[62]; the impact of medical and mental comorbidities and AIDS-defining events on HRQOL[40], and the relationship between HRQOL and healthcare utilization, specifically hospitalizations.

Part B: A General Descriptive Statistics of HRQOL of the NHS Cohort at Baseline

1.7: Methods

1.7.1: Study Cohort

The U.S. Military HIV Natural History Study (NHS) is a prospective multicenter continuous enrollment observational cohort of HIV-infected active duty military personnel and other beneficiaries (spouses, adult dependents, and retired military personnel) from the Army, Navy/Marines and Air Force enrolled since 1986[63-66]. Participants are followed at five medical centers in the United States. Demographic data are collected at baseline and updated while medical and medication histories and standard laboratory studies are collected biannually. Blood samples obtained from participants in this cohort from scheduled visits are stored in a repository. Demographic information captured includes race/ethnicity (Caucasian, African American, Hispanic or Puerto Rican, Mexican, Asian, or Pacific Islander, Native American or Alaskan native, or other), age, gender, active duty, retired or dependent, and rank in military. Although not captured in the NHS database, injection drug use (IDU) has been reported to be very rare in this cohort[64,67]. All NHS participants provided informed consent, and approval for this research was obtained from the institutional review board at each participating site.

1.7.2: Study Participants

The RAND Short Form 36 (SF-36) questionnaires were administered annually to NHS participants from April 2006 to September 2010. However, a few participants had more than one completed questionnaire in a year, and for these participants the last completed questionnaire for that year was used. There were 1731 participants who completed the questionnaires over the period of the study. We used the CD4 count and HIV RNA levels closest in time to the HRQOL measure used.

1.7.3: Definitions and Variable Selections

1.7.3.1: Health-Related Quality of Life Scores

Baseline is defined as the first ever HRQOL measure irrespective of when the participant was enrolled in the study. As previously stated, there are eight health domains measured in the SF-36 questionnaires. These domains are further combined to produce two component summary scores – a physical component summary score (PCSS) and a mental component summary score (MCSS). We used the RAND 36-Item Health Survey 1.0[68] scoring system. This scoring system also includes a single item that provides an indication of perceived change in health but this item does not contribute to the score. The Rand Scoring System is a two-step process that is much easier to compute and differs from the MOS SF-36 Scoring System[68], although the instruments are the same. The first step is recoding of the pre-coded numeric values as shown in the scoring key in Table 1.8. All items are scored so that a high score defines a more favorable health state (see Table 1.3). Each item is scored on a 0 to 100 range so that the lowest and highest possible scores are set at 0 and 100, respectively (Table 1.9). Scores represent the

percentage of total possible scores achieved. In the second step, items in the same scale are averaged together to create the eight scale scores[68]. Only non-missing values are considered in calculating the scale scores[68]. For our dataset, we computed the eight health domain scores as well as the United States norm-based physical and mental components summary scores using the codes written by Ron Hays and available in his website[69].

1.7.3.2: HAART (Treatment) Variable

HAART is defined as a combination of at least three antiretroviral agents similar to previous investigations for this cohort[64]. HAART treatment is further divided into three groups: a protease inhibitor-based HAART (PI-HAART), for HAART with at least one protease inhibitor in the combined HAART regimen; a non-protease-inhibitor-based HAART (NPI-HAART), for HAART with at no protease inhibitor in the combined HAART regimen; and a HAART-naïve group (HAART-N) for those not on HAART. By HAART-naïve we mean participants had never been on HAART prior to completing the SF-36 questionnaire at baseline.

1.7.3.3: Other Variables

Variables considered for inclusion in the descriptive statistics and for the final models of the hypothesis-driven aims include HRQOL scores (PCSS and MCSS) and HAART treatment already defined above, gender (male/female), age, military rank (officer/warrant officer, enlisted and civilian/retired), marital status (married, not married), race/ethnicity, HIV RNA viral levels (measured in log base 10), CD4+ count, medical comorbidity, mental comorbidity, AIDS-defining illnesses, medication adherence, HIV duration, and calendar year. Calendar year is the year in which the

participant first completed the SF-36 questionnaire irrespective of when the participant was enrolled in the NHS.

Although AIDS-defining illnesses have declined significantly in the post-HAART era, AIDS definition will be in line with 1993 Centers for Disease Control and Prevention criteria, with the exception of an isolated CD4 count <200 cells/mm^3 as CD4 count will be analyzed separately. Race/ethnicity will be classified as non-Hispanic white, non-Hispanic African-American/black, and Others/Hispanic. Medical co-morbidity refers to chronic medical conditions, and will be classified as having no comorbidity or having one or more comorbidity. Mental comorbidity will be classified similarly. Adherence was classified as 'good' (yes) or 'poor' (no) with at least 90% adherence level required for classifying as good[56]

1.7.4: Inclusion and Exclusion Criteria

All participants in the US Military HIV NHS cohort who completed at least one HRQOL survey between 2006 and 2010 were included in the study. Exclusions will depend on the particular analysis and will be discussed in the relevant section.

1.7.5: Data Analysis

We computed scores of the eight health domains of HRQOL and the two norm-based summary scores (PCSS and MCSS) using the SAS codes provided Ron D. Hays.[69] We provided descriptive statistics using the proportions for count variables and means/standard deviations as well as the median/interquartile ranges for numeric variables including those for the eight health domains and the summary scores of the computed HRQOL measures. All statistical analyses were carried out using SAS version 9.3 [SAS Institute Inc., Cary, NC].

1.8: Results and Discussion

Figures 1.3.a and 1.3.b show the returns of completed survey questionnaires by month and year. There were 827 completed surveys in 2006 but returns were above 1000 from 2007 to 2010, with 2009 recording the highest number of completed surveys at 1284. Table 1.10 shows the descriptive statistics of the participants. Out of the 1730 participants who met our eligibility criteria, 826 (48%) were enrolled in the study for the first time in 2006, another 486 (28%) were enrolled in 2007 while the remaining 418 (24%) were enrolled in the study between 2008 and 2010. 42.54% were non-Hispanic African Americans, 41.79% non-Hispanic Whites and 15.66% comprising of other races/ethnic groups including Hispanics. Only 7% of the participants were female. 14.51% of the participants had one or more medical comorbidities while 25.78% had one or more mental comorbidities. By far the most common mental comorbidity in the cohort was major depressive disorder (60.59%) followed by general anxiety and bipolar disorders (17.53%) and alcohol abuse (11.98%). The common medical conditions were diabetes mellitus (33%), cancers (31%), cardiovascular diseases including coronary artery disease (11%) and kidney disease (9%). 11.56% of participants had AIDS at baseline with the median duration for the development of an AIDS-defining event being 7 years (interquartile range [IQR] of 1-12 years). About 24% of the cohort were HAART naïve at baseline while another 9% were off HAART at baseline, making the total percent of participants 'not on HAART' at baseline 35% (567). 529 participants (30.58%) were on a protease inhibitor based HAART (PI-HAART) while 35% of participants were on a non-protease inhibitor HAART (NPI-HAART). Of the 610 participants on NPI-HAART, 85% were on a non-nucleoside reverse transcriptase inhibitor (NNRTI) combination

therapy. 1.39% of participants were on a non-HAART antiretroviral therapy. Among those on HAART, 90% were adherent to their medication. The mean age of the participants was 40 years with about 38% being between 35 and 44 years, 3.64% older than 60 years, and about 8% being between 18 and 24 years. The mean CD4 count for the cohort was high at 537 cells/mm^3 with those having CD4 count <200 cells/mm^3 making up 7.5% of the cohort. The mean HIV RNA level was 2.74 in $\log_{10}$, with 50% of the cohort having a plasma viral load greater than 50 copies/mL. The median time from HIV diagnosis to baseline was 8 years (IQR: 2-15 years).

In table 1.11 we present the raw HRQOL scores of the eight health domain of the participants as well as their two summary scores, the physical component summary score (PCSS) and the mental component summary score (MCSS). Although the domain scores are linearly transformed T-scores, they were still highly skewed in our cohort (table 1.11), making the summary scores preferable in linear regression analyses. Furthermore, using the summary scores avoids the floor and ceiling effects associated with the domain scores[27]. Both PCSS and MCSS are norm-based scores and are comparable to the general US population which have a mean of 50 and a standard deviation of 10. At baseline, the NHS participants had a slightly higher physical functional health (51.52 vs. 50) and slightly lower mental functional health (47.58 vs. 50) when compared to the 1990 general US population. Compared to the Millennium Cohort of the US military, the NHS participants' physical components score was slightly lower (PCSS: 51.52 vs. 53.4) while the difference in the mental component score was more marked with a difference of over 5 (MCSS: 47.58 vs. 52.8). In general, it has been suggested that differences in HRQOL scores of 5 points or more in the health domains or 2 to 3 in the summary scores are

clinically and socially relevant[61,70]; however, even smaller point differences may be useful in risk stratification especially among those with advance disease[71].

The choice of HRQOL survey instrument has long been debated with many clinical trial studies preferring the HIV-specific HIV-MOS tool over the MOS SF-36 instrument that was used in our cohort. Earlier studies have demonstrated a high reliability of the MOS SF-36 in HIV population as well as in HIV-infected populations. In table 1.12 we displayed the reliability of the RAND SF-36 in NHS cohort as well as that of the general US population. The NHS participants' had slightly higher reliability (higher Cronbach alpha) in all eight health conceptual areas of the SF-36 questionnaire with the exception of emotional well-being.

1.9: Conclusion

In chapter 2 we will look at the baseline factors associated with health-related quality of life in the cohort. In chapter 3 we will take a longitudinal look at the changes in HRQOL measures for a nested cohort of the HRQOL study who were followed from 2006 to 2010. Finally, in chapter 4 we will examine whether HRQOL measures can predict hospitalization among cohort members using the Cox proportional hazard regression model. In chapter 5, our concluding chapter, we will summarize our major findings and make recommendations based on those. When we first conceived our various aims and hypotheses we thought the questionnaires were administered from the mid-1990s, and so we hoped to also examine the impact that serious non-AIDS and AIDS-defining events will have on HRQOL measures but those studies will no longer be meaningful since majority of the comorbidities and AIDS-defining events had already occurred at baseline.

1.10: Tables

Table 1.1: AIDS defining opportunistic infections

No	Infections
1	Candidiasis of bronchi, trachea, or lungs
2	Candidiasis, esophageal
3	Cervical cancer, invasive
4	Coccidioidomycosis, disseminated or extrapulmonary
5	Cryptococcosis, extrapulmonary
6	Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
7	Cytomegalovirus disease (other than liver, spleen, or nodes)
8	Cytomegalovirus retinitis (with loss of vision)
9	Encephalopathy, HIV-related
10	Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
11	Histoplasmosis, disseminated or extrapulmonary
12	Isosporiasis, chronic intestinal (greater than 1 month's duration)
13	Kaposi's sarcoma
14	Lymphoma, Burkitt's (or equivalent term)
15	Lymphoma, immunoblastic (or equivalent term)
16	Lymphoma, primary, of brain
17	Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
18	Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
19	Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
20	Pneumocystis carinii pneumonia
21	Pneumonia, recurrent
22	Progressive multifocal leukoencephalopathy
23	Salmonella septicemia, recurrent
24	Toxoplasmosis of brain
25	Wasting syndrome due to HIV

Source: CDC

Table 1.2: Antiretroviral Drugs Approved by the FDA

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Multi-class Combination Products (Combinatorial Pills)				
Atripla	Efavirenz, emtricitabine and tenofovir disoproxil fumarate	Bristol-Myers Squibb and Gilead Sciences	12-July-06	2.5 months
Complera	Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate	Gilead Sciences	10-August-11	6 months
Stribild	Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	Gilead sciences	27-August-12	6 months
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Emtriva	Emtricitabine, FTC	Gilead sciences	02-Jul-03	10 months
Epivir	Lamivudine, 3TC	GlaxoSmithKline	17-Nov-95	4.4 months
Hivid	Zalcitabine, dideoxycytidine, ddC (no longer marketed)	Hoffmann-La Roche	19-Jun-92	7.6 months
Retrovir	Zidovudine, azidothymidine, AZT	GlaxoSmithKline	19-Mar-87	3.5 months
Videx	Didanosine, dideoxyinosine, ddI	Bristol Myers-Squibb	9-Oct-91	6 months
Viread	Tenofovir disoproxil fumarate, TDF	Gilead	26-Oct-01	5.9 months
Zerit	Stavudine, d4T	Bristol Myers-Squibb	24-Jun-94	5.9 months
Ziagen	Abacavir sulfate, ABC	GlaxoSmithKline	17-Dec-98	5.8 months
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Edurant	Rilpivirine	Tibotec Therapeutics	20-May-11	10 months
Intelence	Etravirine	Tibotec Therapeutics	18-Jan-08	6 months
Rescriptor	Delavirdine, DLV	Pfizer	4-Apr-97	8.7 months
Sustiva	Efavirenz, EFV	Bristol Myers-Squibb	17-Sep-98	3.2 months
Viramune	Nevirapine, NVP	Boehringer Ingelheim	21-Jun-96	3.9 months
Protease Inhibitors (PIs)				
Agenerase	Amprenavir, APV (no longer marketed)	GlaxoSmithKline	15-Apr-99	6 months
Aptivus	Tipranavir, TPV	Boehringer Ingelheim	22-Jun-05	6 months
Crixivan	Indinavir, IDV	Merck	13-Mar-96	1.4 months
Invirase	Saquinavir mesylate, SQV	Hoffmann-La Roche	6-Dec-95	3.2 months
Kaletra	Lopinavir and ritonavir, LPV/RTV	Abbott Laboratories	15-Sep-00	3.5 months
Lexiva	Fosamprenavir Calcium, FOS-APV	GlaxoSmithKline	20-Oct-03	10 months
Norvir	Ritonavir, RTV	Abbott Laboratories	1-Mar-96	2.3 months
Prezista	Darunavir	Tibotech, Inc.	23-Jun-06	6 months
Reyataz	Atazanavir sulfate, ATV	Bristol Myers-Squibb	20-Jun-03	6 months
Viracept	Nelfinavir mesylate, NFV	Aguoron Pharmaceuticals	14-Mar-97	2.6 months
Fusion Inhibitors				

Fuzeon	Enfuvirtide, T-20	Hoffmann-La Roche & Trimeris	13-Mar-03	6 months
Entry Inhibitors – CCR5 co-receptor antagonist				
Selzentry	Miraviroc	Pfizer	06-August-07	8 months
HIV Integrase Strand Transfer Inhibitors				
Isentress	Raltegravir	Merck & Co., Inc.	12-Oct-07	6 months

Source: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118915.htm
Last updated: 02/08/2013; Accessed 08/07/2013

Table 1.3. Generic Measures of Health-Related Quality of Life (Source : Grossman)

Instrument	**Dimensions examined**	**Length; time to complete**	**Administration**	**Advantages**	**Disadvantages**
SIP	Physical: ambulation, mobility, body care Psychosocial: social interaction, communication, alertness, emotional behavior Other: sleep/rest, eating, work, home management, recreation and pastimes	136 items; ≈20 min	Self-administered or interviewer	Results can be presented as subscale and summary scores; no floor effects	Not HIV-specific; takes longer to administer; emphasis on physical dysfunction
QWB	Self-care, mobility, institutionalization, social activities, reports of symptoms and problems (physical and mental)	50 items; ≈20 min	Interviewer; self-administered version	Can be used to calculate cost-utility	Not HIV-specific; takes longer to administer; single score only
MOS SF-36	Physical functioning, role limitations caused by physical problems, social functioning, body pain, general mental health, role limitations caused by emotional problems, vitality, general health perceptions	36 items; 10 min	Self-administered	Culturally adapted and translated into > 50 languages	Not HIV-specific
LASA	Energy level, daily activity, overall QOL	3 items; 1 - 2 min	Self-administered	Short administration time; easy to administer	Not HIV-specific; not as reliable as multi-item measures; may

					not be truly linear
NHP	6 domains of experience: pain, physical mobility, sleep, emotional reactions, energy, social isolation 7 domains of daily life: employment, household work, relationships, personal life, sex, hobbies, vacations	45 items; 5 - 15 min	Self-administered	Evaluates areas pertinent to HIV disease	Not HIV-specific; items negatively worded
Spitzer QOL index	Activity, daily living, health, support, outlook on life	5 items; 10 min	Self-administered	Relatively short administration time	Not HI-specific; questionable reliability and sensitivity in HIV patients
MHIQ	Physical: mobility, self-care, communication, global physical functioning Social: general well-being, work/social role performance, social support and participation, global social functioning	≈ 59 items; 20 minutes	Self-administered or interviewer	Has been used in a variety of disease states and settings	Not HIV-specific; takes longer to administer; limited reliability
COOP Charts	Physical condition, emotional condition, daily work, social activities, overall condition, change in condition, pain, general HRQOL	9 items; 5 minutes	Interviewer	Short administration time; easy to administer to patients with limited education	Not HIV-specific

SIP, Sickness Impact Profile; QWB, Quality of Well-Being scale; MOS SF-36, Medical Outcomes Study Short Form-36; LASA, Linear Analogue Self-Assessment; QOL, quality of life; NHP, Nottingham Health Profile; MHIQ, McMaster Health Index Questionnaire; COOP, Cooperative Information Project; HRQOL, health-related quality of life.

Table 1.4: HIV Disease-Specific HRQOL Instruments (Source: Grossman[10])

Instrument	Dimensions Examined	Length; Time to Complete	Administration	Advantages	Disadvantages
MOS-HIV	General health perceptions, physical functioning, role functioning, pain, social functioning, mental health, energy, health distress, cognitive functioning, QOL, health transition	35 items; 5 min	Self-administered or interview	Shorter administration time; available in > 20 languages	Does not evaluate all areas pertinent to HIV; some ceiling and floor effects
HIV-QL31	Sexual life/activity, pain, psychological aspects (general feeling of well-being, depression), relationships, aspects connected with disease activities (denial of disease, obsession with disease), somatic aspects (diet, fatigue, sleep), impact of treatment and care (housing/accommodation and finance)	31 items; moderate	Self-administered	Based on patient-reported concerns	Not widely studied; responsiveness to change unknown
FAHI	Physical well-being, function and global well-being, emotional well-being/living with HIV, social well-being, cognitive functioning	44 items; lengthy	Self-administered	None beyond being HIV-specific	Takes longer to administer; not extensively used
HAT-QOL	Overall function (combination of physical, role, and social function), sexual function, disclosure worries, health worries, financial worries, HIV mastery, life satisfaction, medication concerns, provider trust	42 items; lengthy	Self-administered	Based on patient-reported concerns	Takes longer to administer; lower reliability
EORTC QLQ-C30	Physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, pain, fatigue, nausea and vomiting, overall HRQOL + AIDS module	30 items + 20 (AIDS module); lengthy	Self-administered	Widely used; translated into several languages	Takes longer to administer

GHSA	General health perception, physical functioning, role/social functioning, HIV-related symptoms, health care utilization	49 items; moderate	Self-administered or interview	None beyond being HIV-specific	Not studied longitudinally
HOPES	Physical: 8 subscales related to physical and daily functioning problems Psychosocial: 9 subscales related to emotional functions, communication, interaction problems Medication interaction: 3 subscales related to communication and interaction with health care providers Sexuality: 2 subscales related to sexual interest, activities, functioning Partner: 5 subscales related to communication and interaction problems with partner(s) Miscellaneous: 6 subscales	142 items; 15 - 30 min	Self-administered	Assesses many dimensions	Takes longer to administer; possible response bias
AIDS-HAQ	Disability, general health perception, social functioning, mental health, cognitive functioning, energy/fatigue, pain, disease worry, symptoms	30 items; lengthy	Self-administered	Studied longitudinally	Long administration time; not used extensively since the advent of HAART
MQOL-HIV	Mental health, physical health, physical functioning, social functioning, social support, cognitive functioning, financial status, partner intimacy, sexual functioning, medical care	40 items; 10 min	Self-administered or interview	Studied longitudinally; less susceptible to ceiling effects	Less reliable and less responsive to change than MOS-HI

MOS-HIV, Medical Outcomes Study HIV; QOL, quality of life; HIV-QL31, HIV-QOL Questionnaire; FAHI, Functional Assessment of HIV Infection; HAT-QOL, HIV/AIDS Quality of Life; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; HRQOL, health-related quality of life; GHSA, General Health Self-Assessment; HOPES, HIV Overview Problems Evaluation System; AIDS-HAQ, AIDS Health Assessment Questionnaire; MQOL-HIV, Multidimensional Quality of Life Questionnaire for HIV/AIDS.

Table 1.5: SF-36 Health Status Scales and the Interpretation of Low and High Score[&]

Concepts	**No. of Items**	**No. of Levels**	**Meaning of Scores**	
			Low	**High**
Physical functioning (PF)	10	21	Limited a lot in performing all physical activities including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role limitations due to physical problems (RP)	4	5	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health, past 4 weeks
Social Functioning (SF)	2	9	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems, past 4 weeks
Bodily pain (BP)	2	11	Very severe and extremely limiting pain	No pain or limitations due to pain, past 4 weeks
General mental health (MH)	5	26	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time, past 4 weeks
Role limitations due to emotional problems (RE)	3	4	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems, past 4 weeks
Vitality (VT)	4	21	Feels tired and worn out all	Feels full of pep and energy of the time all of the time, past 4 weeks
General health perceptions (GH)	5	21	Believes personal health is poor and likely to get worse	Believes personal health is excellent

[&](Source: Ware[25])

Table 1.6: Short Form – 36 (SF-36) (Source: www.rand.org/health/survey_tools/mos)

1. In general, would you say your health is:			
Excellent			1
Very good			2
Good			3
Fair			4
Poor			5
2. Compared to one year ago, how would you rate your health in general now?			
Much better now than one year ago			1
Somewhat better now than one year ago			2
About the same			3
Somewhat worse now than one year ago			4
Much worse now than one year ago			5
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much			
	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. *Vigorous activities*, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. *Moderate activities*, such as moving a table, pushing a vacuum, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing *several* flights of stairs	1	2	3
7. Climbing *one* flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking more than a mile	1	2	3
10. Walking several blocks	1	2	3
11. Walking one block	1	2	3
12. Bathing or dressing yourself	1	2	3
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? **(Circle One Number on Each Line)**			
		Yes	No
13. Cut down the amount of time you spent on work or other activities		1	2
14. Accomplished less than you would		1	2
15. Were limited in the kind of work of other activities		1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)		1	2
During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)? **(Circle One Number on Each Line)**			
		Yes	No
17. **Cut down the amount of time you spent on work or other activities**		1	2
18. **Accomplished less than you would**		1	2
19. Didn't do work or other activities as carefully as usual		1	2
20. **During the *past 4 weeks*, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Circle One Number)**			
Not at all			1
Slightly			2
Moderately			3
Quite a bit			4
Extremely			5
21. How much bodily pain have you had during the past 4 weeks? (Circle One Number)			
None			1

Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

22. During the *past 4 weeks*, how much did pain interfere with your normal work (including both work outside the home and housework)? *(Circle One Number)*

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** . . . **(Circle One Number on Each Line)**

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. **During the *past 4 weeks*, how much of the time has your *physical health or emotional problems* interfered with your social activities (like visiting with friends, relatives, etc.)? (Circle One Number)**

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

How TRUE or FALSE is **<u>each</u>** of the following statements for you. **(Circle One Number on Each Line)**

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Table 1.7: Reliability, Central Tendency and Variability of Scales in the Medical Outcome Studies (Source: Ware)

Scale	**Item**	**Alpha**	**Mean**	**SD**
Physical Functioning	10	0.93	70.61	27.42
Role limitations due to physical health	4	0.84	52.97	40.78
Role limitations due to emotional problems	3	0.83	65.78	40.71
Energy/Fatigue	4	0.86	52.15	22.39
Emotional well-being	5	0.90	70.38	21.97
Social functioning	2	0.85	78.77	25.43
Pain	2	0.78	70.77	25.46
General health	5	0.78	56.99	21.11
Health Change	1	-----	59.14	23.12
Physical Component Summary Score	36	0.92	50.00	10.00
Mental Component Summary Score	36	0.88	50.00	10.00

Table 1.8: Recoding Items (Step 1) (Source: RAND)

Items Numbers	**Change Original response Category***	**To Recoded Value of:**
1, 2, 20, 22, 34, 36	1 →	100
	2 →	75
	3 →	50
	4 →	25
	5 →	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1 →	0
	2 →	50
	3 →	100
13, 14, 15, 16, 17, 18, 19	1 →	0
	2 →	100
21, 23, 26, 27, 30	1 →	100
	2 →	80
	3 →	60
	4 →	40
	5 →	20
	6 →	0
24, 25, 28, 29, 31	1 →	0
	2 →	20
	3 →	40
	4 →	60
	5 →	80
	6 →	100
32, 33, 35	1 →	0
	2 →	25
	3 →	50
	4 →	75
	5 →	100

*Precoded response choices as printed in the questionnaire

Table 1.9: Averaging Items to Form Scales (Step 2) (Source: RAND)

Scale	**Number of Items**	**After Recoding Per Table, Average the Following Items:**
Physical Functioning	10	3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Role limitations due to physical health	4	13, 14, 15, 16
Role limitations due to emotional problems	3	17, 18, 19
Energy/Fatigue	4	23, 27, 29, 31
Emotional well-being	5	24, 25, 26, 28, 30
Social functioning	2	20, 32
Pain	2	21, 22
General health	5	1, 33, 34, 35, 36

Table 1.10: Baseline Characteristics of the Cohort

Characteristics	**N (%)**
Gender	
Male	1610 (93.06)
Female	120 (6.94)
Race	
Non-Hispanic White	723 (41.79)
Non-Hispanic African American	736 (42.54)
Hispanic/Others	271 (15.66)
Rank	
Officer/Warrant Officer	128 (7.40)
Enlisted	920 (53.18)
Others (Retired/Dependents)	680 (39.31)
Missing	2 (0.12)
Marriage	
Yes	557 (32.20)
No	1173 (67.80)
Medical Comorbidity	
Yes	251 (14.51)
No	1479 (85.49)
Mental Comorbidity	
Yes	446 (25.78)
No	1284 (74.22)
AIDS	
Yes	200 (11.56)
No	1530 (88.44)
HAART	
PI-Based	529 (30.58)
Non-PI-Based	610 (35.26)
HAART-Naïve	411 (23.76)
Off-HAART	156 (9.02)
Non-HAART ART	24 (1.39)
Adherence (≥ 90%)	
Yes	1036 (90.96)
No	97 (8.52)
Missing	6 (0.53)
Age Groups	
Between 18 and 24 years	137 (7.92)

Between 25 and 34 years	375 (21.68)
Between 35 and 44 years	656 (37.92)
Between 45 and 60 years	499 (28.84)
Greater than 60 years	63 (3.64)
CD4 Count Groups	
CD4 Count Less than 200	115 (6.65)
CD4 Count Between 200 and 499	748 (43.24)
CD4 Count Greater Than 499	865 (50.00)
Missing	2 (0.12)
HIV RNA Level Greater than 50 Copies	
Yes	865 (50.00)
No	864 (49.94)
Missing	1 (0.06)
Calendar Year	
2006	826 (47.75)
2007	486 (28.09)
2008	147 (8.50)
2009	172 (9.94)
2010	99 (5.72)
Age (years)	
Mean ± SD (N)	40.09 ± 10.59 (1730)
Median (IQR)	40.00 (32.00 – 47.00)
CD4 Count (x 10^6/L)	
Mean ± SD (N)	537.29 ± 266.79 (1728)
Median (IQR)	500.00 (359.00 – 677.00)
HIV RNA Level (Log_{10})	
Mean ± SD (N)	2.75 ± 1.27 (1729)
Median (IQR)	1.71 (1.70 – 3.98)
Time from HIV Diagnosis (years)	
Mean ± SD (N)	8.86 ± 7.17 (1730)
Median (IQR)	8.00 (2.00 – 15.00)

Table 1.11: Health Related Quality of Life Scores of Participants at Baseline

HRQOL Scores	Mean ± SD (N)
Physical Functioning (PHYFUN10)	
Mean ± SD (N)	85.48 ± 24.57 (1730)
Median (IQR)	100.00 (80.00 – 100.00)
Role Limitations Due to Physical Health (ROLEP4)	
Mean ± SD (N)	82.34 ± 32.99 (1724)
Median (IQR)	100.00 (75.00 – 100.00)
Bodily Pain (PAIN2)	
Mean ± SD (N)	81.00 ± 22.97 (1727)
Median (IQR)	90.00 (67.50 – 100.00)
General Health (GENH5)	
Mean ± SD (N)	70.34 ± 21.12 (1730)
Median (IQR)	75.00 (60.00 – 85.00)
Emotional Well Being (EMOT5)	
Mean ± SD (N)	67.92 ± 14.36 (1727)
Median (IQR)	72.00 (60.00 – 80.00)
Role Limitations Due to Emotional Problems (ROLEE3)	
Mean ± SD (N)	83.02 ± 33.47 (1726)
Median (IQR)	100.00 (100.00 – 100.00)
Energy/Fatigue (ENFAT4)	
Mean ± SD (N)	59.30 ± 16.96 (1728)
Median (IQR)	60.00 (50.00 - 70.00)
Social Functioning (SOCFUN2)	
Mean ± SD (N)	81.54 ± 24.03 (1727)
Median (IQR)	100.00 (62.50 – 100.00)
Physical Component Summary Score (PCSS)[$]	
Mean ± SD (N)	51.52 ± 9.08 (1719)
Median (IQR)	54.88 (46.94 – 57.97)
Mental Component Summary Score (MCSS)[#]	
Mean ± SD (N)	47.58 ± 9.18 (1719)
Median (IQR)	50.31 (43.44 – 53.85)

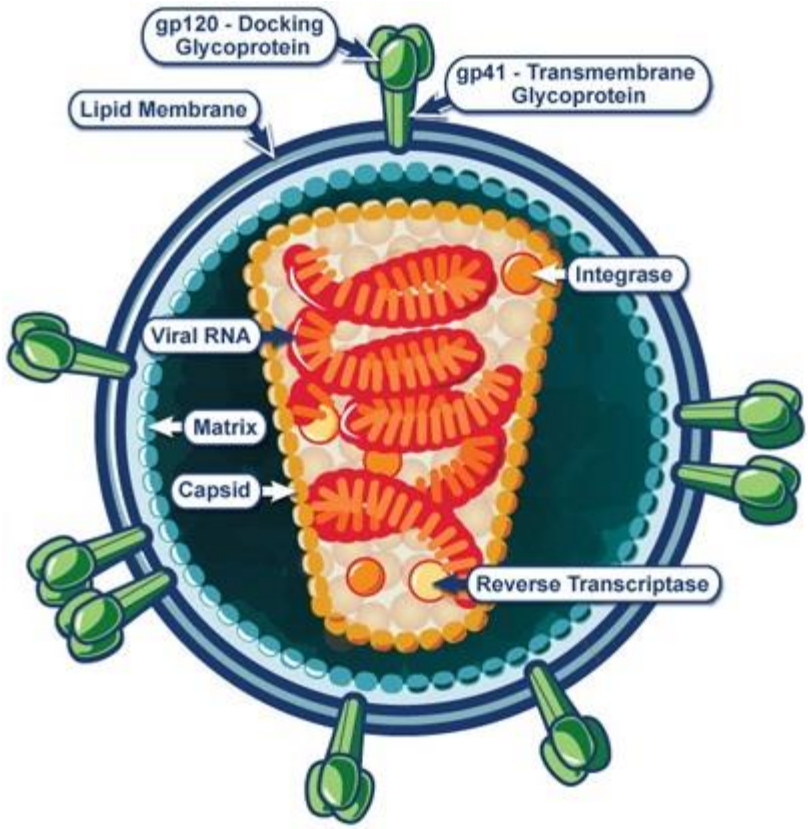
[$]PCSS (norm-based T score derived from PHYFUN10, ROLEP4, PAIN2 and GENH5)
[#] MCSS (norm-based T score derived from EMOT5 ROLEE3 ENFAT4 SOCFUN2)

Table 1.12: Comparison of Reliability of HRQOL Scores in the NHS Cohort and the US Gen. Population

HRQOL Scores	**Items**	**Alpha (NHS Cohort)**	**Alpha (US Population)**
Physical Functioning	10	0.96	0.93
Role Limitations – PH	4	0.89	0.84
Bodily Pain	2	0.86	0.78
General Health	5	0.83	0.78
Emotional Well-Being	5	0.84	0.98
Role Lim – Emot. Prob.	3	0.88	0.83
Energy/Fatigue	4	0.87	0.86
Social Functioning	2	0.86	0.85

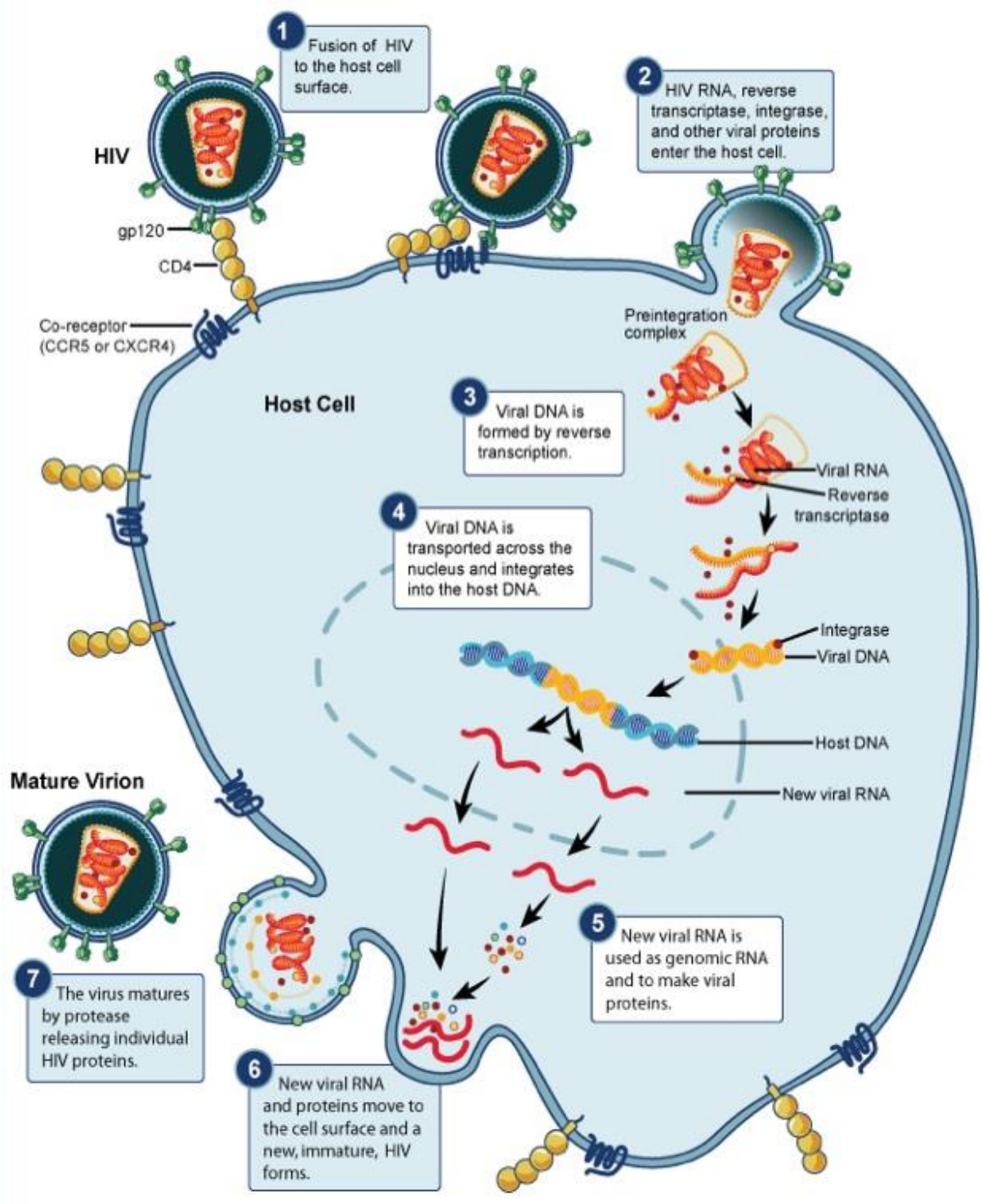
1.11: Figures

Figure 1.1: Structure of HIV



Source: http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/Pages/hivVirionLargeImage.aspx
Last updated: 01/05/2009; Accessed: 08/17/2013

Figure 1.2: Life cycle of HIV



Source: http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/Pages/hivReplicationCycle.aspx
Last updated: 04/03/2009; Accessed: 08/17/2013

Fig 1.3.a: Monthly Return of Completed SF-36 By Calendar Year (2006-2008)

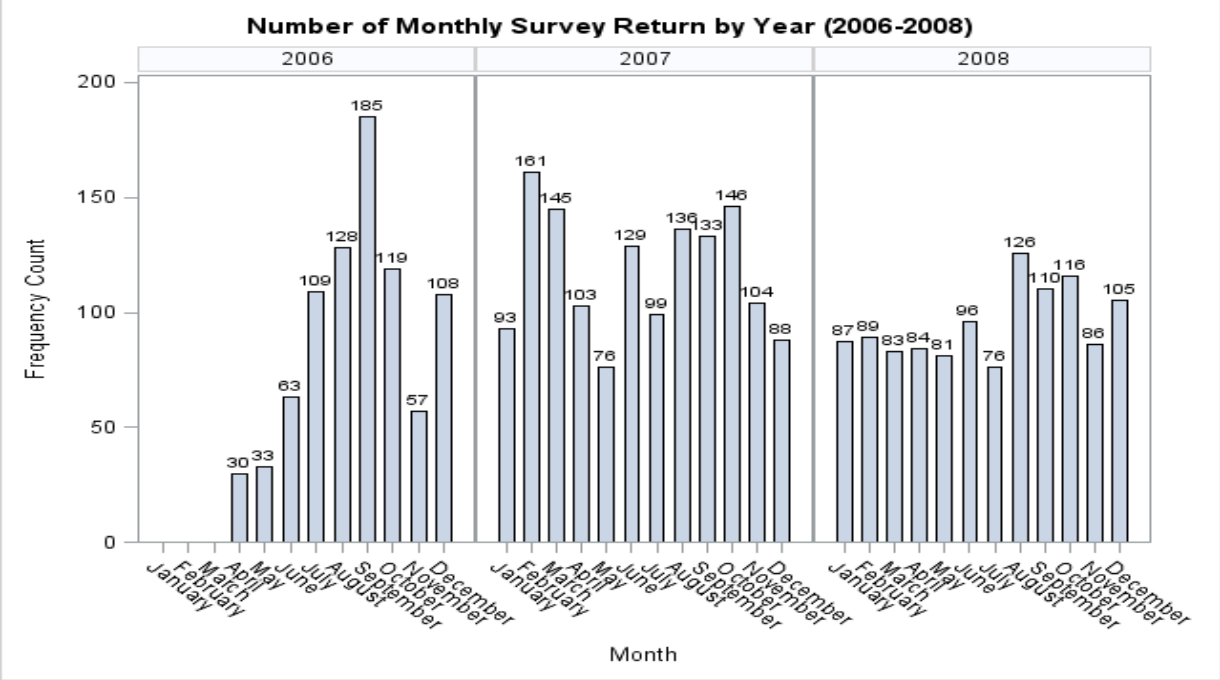
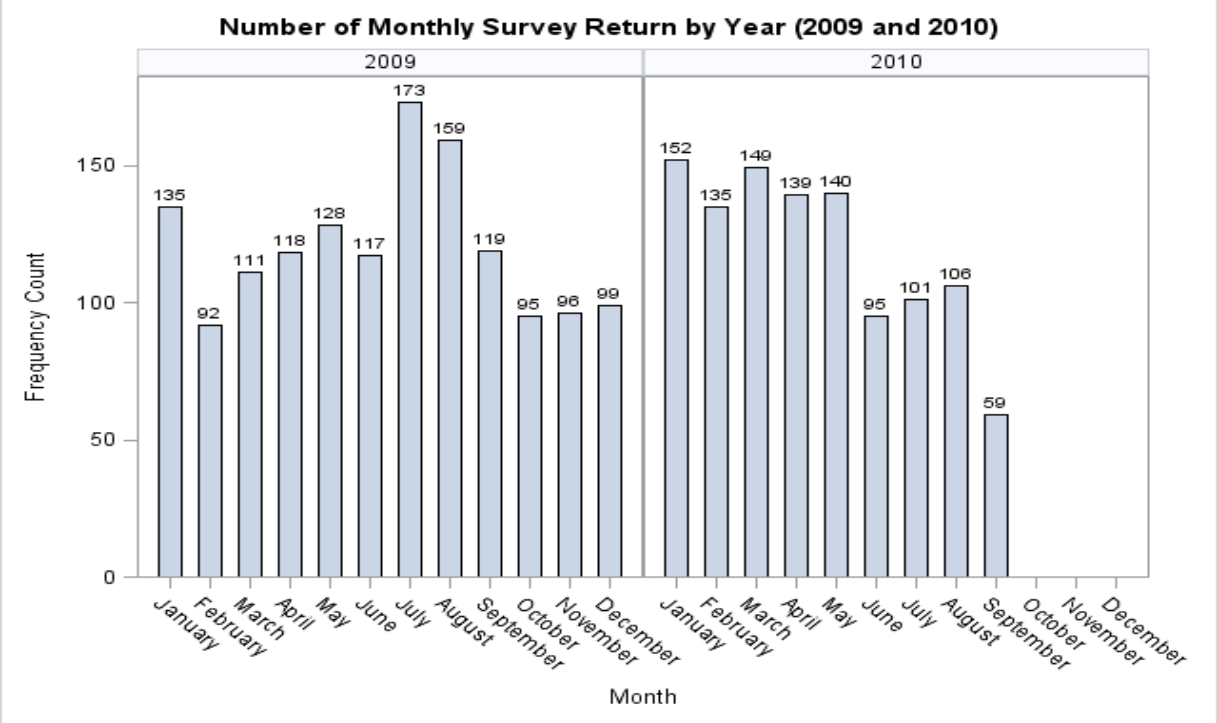


Fig 1.3.b: Monthly Return of Completed SF-36 By Calendar Year (2009 and 2010)



References

1. Joint United Nations Programme on HIV/AIDS. Global report: UNAIDS report on the global AIDS epidemic 2012 http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf.
2. Centers for Disease Control and Prevention (CDC). HIV surveillance - united states, 1981-2008. *MMRI.* 06/03/2011;60(21).
3. Centers for Disease Control and Prevention (CDC). HIV testing among men who have sex with men - 21 cities, united states, 2008. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6021a3.htm.
4. Gakhar H, Kamali A, Holodniy M. Health-related quality of life assessment after antiretroviral therapy: a review of the literature. *Drugs.* 2013;73(7):651-672.
5. Nelson KE, Celentano DD. Human immunodeficiency virus infections and the acquired immunodeficiency syndrome. In: Nelson KE, Willaims CM, eds. *Infectious disease epidemiology*. Third ed. Burlington, MA: Jones and Barlett Learning; 2013:651-721.
6. Centers for Disease Control and Prevention (CDC). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm. Accessed 8/18/2013.
7. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. *Cold Spring Harbor perspectives in medicine.* 2012;2(4):a007161.
8. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed 09/09/2013.
9. Food and Drug Administration (FDA). FDA approves new drug to treat HIV infection. August 12, 2013; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm364744.htm. Accessed 09/18/2013.
10. Grossman HA, Sullivan PS, Wu AW. Quality of life and HIV: current assessment tools and future directions for clinical practice. *The AIDS reader.* 2003;13(12):583-590, 595-587.
11. World Health Organization (WHO). Preamble to the constitution of the world health organization as adopted by the international health conference, new york, 19-22 june 1946, and entered into force on 7 april 1948.
12. Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. *PharmacoEconomics.* 2000;17(1):13-35.
13. Naughton MJ, Shumaker SA. Assessment of health-related quality of life in orthopaedic outcomes' studies. *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association.* 1997;13(1):107-113.
14. Wenger N, Furberg C. Cardiovascular disorders. *Quality of life assessment in clinical trials*. New York: Raven Press; 1990:335-345.
15. Centers for Disease Control and Prevention. Health-related quality of life (HRQOL). http://www.cdc.gov/hrqol/concept.htm. Accessed 08/9/2013.
16. Keltner JR, Vaida F, Ellis RJ, et al. Health-related quality of life 'well-being' in HIV distal neuropathic pain is more strongly associated with depression severity than with pain intensity. *Psychosomatics.* 2012;53(4):380-386.

17. Guaraldi G, Murri R, Orlando G, et al. Severity of lipodystrophy is associated with decreased health-related quality of life. *AIDS patient care and STDs.* 2008;22(7):577-585.
18. Guaraldi G, Murri R, Orlando G, et al. Lipodystrophy and quality of life of HIV-infected persons. *AIDS reviews.* 2008;10(3):152-161.
19. Luzi K, Guaraldi G, Murri R, et al. Body image is a major determinant of sexual dysfunction in stable HIV-infected women. *Antiviral therapy.* 2009;14(1):85-92.
20. Guaraldi G, Orlando G, Murri R, et al. Quality of life and body image in the assessment of psychological impact of lipodystrophy: validation of the Italian version of assessment of body change and distress questionnaire. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2006;15(1):173-178.
21. Clayson DJ, Wild DJ, Quarterman P, Duprat-Lomon I, Kubin M, Coons SJ. A comparative review of health-related quality-of-life measures for use in HIV/AIDS clinical trials. *PharmacoEconomics.* 2006;24(8):751-765.
22. Hays RD, Shapiro MF. An overview of generic health-related quality of life measures for HIV research. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 1992;1(2):91-97.
23. A dictionary of epidemiology. In: Last JM, ed. Fourth ed. New York: Oxford University Press; 2001.
24. Ware J. SF-36 health survey update. . http://www.sf-36.org/tools/sf36.shtml#VERS2. Accessed 5/28/2013.
25. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical care.* 1992;30(6):473-483.
26. Shahriar J, Delate T, Hays RD, Coons SJ. Commentary on using the SF-36 or MOS-HIV in studies of persons with HIV disease. *Health and quality of life outcomes.* 2003;1:25.
27. Wu AW, Hays RD, Kelly S, Malitz F, Bozzette SA. Applications of the Medical Outcomes Study health-related quality of life measures in HIV/AIDS. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 1997;6(6):531-554.
28. RAND. Scoring instructions for the 36-item short form survey (SF-36). http://www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html. Accessed 05/5/2013.
29. Burgoyne RW, Rourke SB, Behrens DM, Salit IE. Long-term quality-of-life outcomes among adults living with HIV in the HAART era: the interplay of changes in clinical factors and symptom profile. *AIDS and behavior.* 2004;8(2):151-163.
30. Protopopescu C, Marcellin F, Spire B, et al. Health-related quality of life in HIV-1-infected patients on HAART: a five-years longitudinal analysis accounting for dropout in the APROCO-COPILOTE cohort (ANRS CO-8). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2007;16(4):577-591.
31. Cook JA, Cohen MH, Burke J, et al. Effects of depressive symptoms and mental health quality of life on use of highly active antiretroviral therapy among HIV-seropositive women. *Journal of acquired immune deficiency syndromes (1999).* 2002;30(4):401-409.
32. Royal SW, Kidder DP, Patrabansh S, et al. Factors associated with adherence to highly active antiretroviral therapy in homeless or unstably housed adults living with HIV. *AIDS care.* 2009;21(4):448-455.
33. Cunningham WE, Crystal S, Bozzette S, Hays RD. The association of health-related quality of life with survival among persons with HIV infection in the United States. *Journal of general internal medicine.* 2005;20(1):21-27.

34. de Boer-van der Kolk IM, Sprangers MA, Prins JM, Smit C, de Wolf F, Nieuwkerk PT. Health-related quality of life and survival among HIV-infected patients receiving highly active antiretroviral therapy: a study of patients in the AIDS Therapy Evaluation in the Netherlands (ATHENA) Cohort. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2010;50(2):255-263.
35. Burgoyne RW, Tan DH. Prolongation and quality of life for HIV-infected adults treated with highly active antiretroviral therapy (HAART): a balancing act. *The Journal of antimicrobial chemotherapy.* 2008;61(3):469-473.
36. Revicki DA, Wu AW, Murray MI. Change in clinical status, health status, and health utility outcomes in HIV-infected patients. *Medical care.* 1995;33(4 Suppl):As173-182.
37. Wu AW, Rubin HR, Mathews WC, et al. Functional status and well-being in a placebo-controlled trial of zidovudine in early symptomatic HIV infection. *Journal of acquired immune deficiency syndromes (1999).* 1993;6(5):452-458.
38. Hays RD, Cunningham WE, Sherbourne CD, et al. Health-related quality of life in patients with human immunodeficiency virus infection in the United States: results from the HIV Cost and Services Utilization Study. *The American journal of medicine.* 2000;108(9):714-722.
39. Tran BX, Ohinmaa A, Nguyen LT. Quality of life profile and psychometric properties of the EQ-5D-5L in HIV/AIDS patients. *Health and quality of life outcomes.* 2012;10:132.
40. Anis AH, Nosyk B, Sun H, et al. Quality of life of patients with advanced HIV/AIDS: measuring the impact of both AIDS-defining events and non-AIDS serious adverse events. *Journal of acquired immune deficiency syndromes (1999).* 2009;51(5):631-639.
41. Armon C, Lichtenstein K. The associations among coping, nadir CD4+ T-cell count, and non-HIV-related variables with health-related quality of life among an ambulatory HIV-positive patient population. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2012;21(6):993-1003.
42. Bastardo YM, Kimberlin CL. Relationship between quality of life, social support and disease-related factors in HIV-infected persons in Venezuela. *AIDS care.* 2000;12(5):673-684.
43. Bing EG, Hays RD, Jacobson LP, et al. Health-related quality of life among people with HIV disease: results from the Multicenter AIDS Cohort Study. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2000;9(1):55-63.
44. Doyle K, Weber E, Atkinson JH, Grant I, Woods SP. Aging, prospective memory, and health-related quality of life in HIV infection. *AIDS and behavior.* 2012;16(8):2309-2318.
45. O'Cleirigh C, Skeer M, Mayer KH, Safren SA. Functional impairment and health care utilization among HIV-infected men who have sex with men: the relationship with depression and post-traumatic stress. *Journal of behavioral medicine.* 2009;32(5):466-477.
46. Rodriguez-Penney AT, Iudicello JE, Riggs PK, et al. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. *AIDS patient care and STDs.* 2013;27(1):5-16.
47. Preau M, Protopopescu C, Spire B, et al. Health related quality of life among both current and former injection drug users who are HIV-infected. *Drug and alcohol dependence.* 2007;86(2-3):175-182.
48. Wu AW, Huang IC, Gifford AL, Spritzer KL, Bozzette SA, Hays RD. Creating a crosswalk to estimate AIDS Clinical Trials Group quality of life scores in a nationally representative sample of persons in care for HIV in the United States. *HIV clinical trials.* 2005;6(3):147-157.

49. Weinfurt KP, Willke RJ, Glick HA, Freimuth WW, Schulman KA. Relationship between CD4 count, viral burden, and quality of life over time in HIV-1-infected patients. *Medical care.* 2000;38(4):404-410.
50. Low-Beer S, Chan K, Wood E, et al. Health related quality of life among persons with HIV after the use of protease inhibitors. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2000;9(8):941-949.
51. Cohen C, Revicki DA, Nabulsi A, Sarocco PW, Jiang P. A randomized trial of the effect of ritonavir in maintaining quality of life in advanced HIV disease. Advanced HIV Disease Ritonavir Study Group. *AIDS (London, England).* 1998;12(12):1495-1502.
52. Revicki DA, Chan K, Gevirtz F. Discriminant validity of the Medical Outcomes Study cognitive function scale in HIV disease patients. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 1998;7(6):551-559.
53. Jia H, Uphold CR, Zheng Y, et al. A further investigation of health-related quality of life over time among men with HIV infection in the HAART era. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2007;16(6):961-968.
54. Potard V, Chassany O, Lavignon M, Costagliola D, Spire B. Better health-related quality of life after switching from a virologically effective regimen to a regimen containing efavirenz or nevirapine. *AIDS care.* 2010;22(1):54-61.
55. Lorenz KA, Shapiro MF, Asch SM, Bozzette SA, Hays RD. Associations of symptoms and health-related quality of life: findings from a national study of persons with HIV infection. *Annals of internal medicine.* 2001;134(9 Pt 2):854-860.
56. Jayaweera D, Dejesus E, Nguyen KL, Grimm K, Butcher D, Seekins DW. Virologic suppression, treatment adherence, and improved quality of life on a once-daily efavirenz-based regimen in treatment-Naive HIV-1-infected patients over 96 weeks. *HIV clinical trials.* 2009;10(6):375-384.
57. Malan DR, Krantz E, David N, et al. 96-week efficacy and safety of atazanavir, with and without ritonavir, in a HAART regimen in treatment-naive patients. *Journal of the International Association of Physicians in AIDS Care (Chicago, Ill. : 2002).* 2010;9(1):34-42.
58. Cunningham WE, Bozzette SA, Hays RD, Kanouse DE, Shapiro MF. Comparison of health-related quality of life in clinical trial and nonclinical trial human immunodeficiency virus-infected cohorts. *Medical care.* 1995;33(4 Suppl):As15-25.
59. Lorenz KA, Cunningham WE, Spritzer KL, Hays RD. Changes in symptoms and health-related quality of life in a nationally representative sample of adults in treatment for HIV. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2006;15(6):951-958.
60. Jia H, Uphold CR, Wu S, Chen GJ, Duncan PW. Predictors of changes in health-related quality of life among men with HIV infection in the HAART era. *AIDS patient care and STDs.* 2005;19(6):395-405.
61. Smith TC, Zamorski M, Smith B, et al. The physical and mental health of a large military cohort: baseline functional health status of the Millennium Cohort. *BMC public health.* 2007;7:340.
62. Campo RE, Cohen C, Grimm K, Shangguan T, Maa J, Seekins D. Switch from protease inhibitor- to efavirenz-based antiretroviral therapy improves quality of life, treatment satisfaction and adherence with low rates of virological failure in virologically suppressed patients. *International journal of STD & AIDS.* 2010;21(3):166-171.
63. Chun HM, Fieberg AM, Hullsiek KH, et al. Epidemiology of Hepatitis B virus infection in a US cohort of HIV-infected individuals during the past 20 years. *Clinical infectious*

diseases : an official publication of the Infectious Diseases Society of America. 2010;50(3):426-436.

64. Chun HM, Roediger MP, Hullsiek KH, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. *The Journal of infectious diseases.* 2012;205(2):185-193.
65. Pelak K, Goldstein DB, Walley NM, et al. Host determinants of HIV-1 control in African Americans. *The Journal of infectious diseases.* 2010;201(8):1141-1149.
66. Spaulding AB, Lifson AR, Iverson ER, et al. Gonorrhoea or chlamydia in a U.S. military HIV-positive cohort. *Sexually transmitted infections.* 2012;88(4):266-271.
67. Brodine SK, Starkey MJ, Shaffer RA, et al. Diverse HIV-1 subtypes and clinical, laboratory and behavioral factors in a recently infected US military cohort. *AIDS (London, England).* 2003;17(17):2521-2527.
68. RAND. Scoring instructions for the 36-item short form survey (SF-36). http://www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html. Accessed 1/15/2015.
69. Hays RD. SAS code for scoring 36-item health survey 1.0. Accessed 9/5/2014.
70. Hopman WM, Berger C, Joseph L, et al. Health-related quality of life in Canadian adolescents and young adults: normative data using the SF-36. *Canadian journal of public health = Revue canadienne de sante publique.* 2009;100(6):449-452.
71. Jacobson DL, Wu AW, Feinberg J. Health-related quality of life predicts survival, cytomegalovirus disease, and study retention in clinical trial participants with advanced HIV disease. *Journal of clinical epidemiology.* 2003;56(9):874-879.

Chapter 2

Baseline Factors Associated with Health-Related Quality of Life among HIV-infected Individuals in the HAART Era

Abstract

Objective: *The aims of this study were: (i). to determine the factors associated with HRQOL at baseline in our cohort, and (ii). to evaluate if there are differences in baseline HRQOL measures by HAART groups.*

Methods: *The RAND Short Form 36 (SF-36) was administered between 2006 and 2010 among members of the NHS cohort, and participants who completed the SF-36 were included in the study. Physical component summary (PCSS) and mental component summary (MCSS) scores were computed based on standard algorithms. Multivariate linear regression models were constructed for PCSS and MCSS to estimate the association between highly active anti-retroviral therapy (HAART) and HRQOL scores while controlling for demographic characteristics and other covariates.*

Results: *HAART was not independently associated with HRQOL scores. Factors independently associated with PCSS were CD4 count < 200 cells/mm^3 (β= -5.87, 95% CI: -7.66, -4.08), mental comorbidity (β= -2.77, 95% CI: -3.73, -1.80), medical comorbidity (β= -2.68, 95% CI: -3.92, -1.44), AIDS diagnosis (β= -3.32, 95% CI: -3.72, -0.92). Others were gender, rank, marital status, and age. Factors independently associated with MCSS were CD4 count < 200 cells/mm^3 (β= -2.77, 95% CI: -3.73, -1.80), mental comorbidity (β= -6.24, 95% CI: -7.24, -5.24), age and being African American.*

Conclusion: *Modifiable factors associated with HRQOL measures at baseline were mental comorbidity, low CD4 count, medical comorbidity and AIDS diagnosis. Efforts should be made to address these risk factors in order to improve the functional status of HIV-infected individuals in the NHS cohort.*

Chapter 2

Baseline Factors Associated with Health-Related Quality of Life among HIV-infected Individuals in the HAART Era

2.1: Introduction and Background

The annual estimated rate of new human immunodeficiency virus (HIV) infections in the United States between 2008 and 2011 remained stable at 15.8 per 100,000 while the rate for HIV stage 3 or acquired immune deficiency syndrome (AIDS) was 10.3 per 100,000 in the same period[1]. Death from HIV/AIDS has continued to decline since the mid-1990s with the introduction of highly active antiretroviral therapy (HAART)[2,3]. By 2010, the Centers for Disease Control and Prevention (CDC) estimated that the all-cause mortality in people infected with HIV in the United States was 6.3 per 100,000 and the all-cause mortality in those with a diagnosis of AIDS was 5.0 per 100,000[1]. Given the stable incidence of HIV/AIDS in the US and the declining mortality among infected individuals, greater reliance is now being placed on other end-point measures both in clinical and public health settings, such as health-related quality of life, in assessing the well-being of individuals living with HIV/AIDS[4,5].

Health-related quality of life (HRQOL) is a multidimensional and dynamic concept that is well recognized as an end-point in assessing the well-being of individuals living with HIV/AIDS[5-9]. Several factors have been established as determinants of HRQOL in HIV-infected populations but these determinant are partly influenced by the population being studied, the HRQOL instrument used and the country of study among other factors[10,11]. Some of the determinants of HRQOL in HIV-infected individuals in the United States and other high-income countries[12] are age[13,14], race/ethnicity[13], gender[7,8,12,15], educational

level[13], income level[13,14], socioeconomic status[16], access to health insurance[17], being on antiretroviral therapy (ART) or highly active antiretroviral therapy (HAART)[9,10], injection drug use[18], the presence of mental and medical comorbidities[14,19], presence of AIDS-defining illnesses[13,20], CD4 count[13,21], viral load[21], and less frequently captured variables such as coping style/ability[17,22,23] and social support[22] among others.

The relationship between HIV/AIDS, HAART and HRQOL is a complex one. While HAART helps to prevent disease progression and results in better quality of life and well-being in HIV-infected individuals, the prolonged use of medication that is necessary to continually keep viral suppression below detection levels, often leads to adverse effects that may then worsens the individual's quality of life. Some of the recognized side effects of HAART are diarrhea, anemia, lipodystrophy, peripheral neuropathy, insulin resistance and metabolic syndrome, renal tubular toxicity, pancreatitis, and hypersensitivity reaction. Lipodystrophy, diarrhea and other medication-related symptoms have been shown to affect quality of life[24-26]. Although, side effects are not specific to one class of HAART medications, protease inhibitors have been implicated as having greater adverse effects including morphological changes and metabolic disturbances[27]. However, most studies evaluating the impact of different HAART regimen on HRQOL have been in clinical trials[10,28-31] or following a switch from protease inhibitor-based regimen to a non-protease-inhibitor regimen without the benefit of an appropriate control group[27].

We also note that some of the predictors of HRQOL in HIV-infected individuals in the general US population, such as lack of access to healthcare due to lack of insurance, access to and maintenance of anti-retroviral medications, and injection drug use may not play an equally important role as determinants of HRQOL of HIV-infected individuals in

the United States Military. This is because of the universal access to healthcare in this population and the rarity of injection drug use among military personnel[32,33]. The aims of this study were: (i). to determine the factors associated with HRQOL at baseline in our cohort, and (ii). to evaluate if there are differences in baseline HRQOL measures by HAART groups.

2.2: Methods

2.2.1: Study Cohort

The U.S. Military HIV Natural History Study (NHS) is a prospective multicenter continuous enrollment observational cohort of HIV-infected active duty military personnel and other beneficiaries (spouses, adult dependents, and retired military personnel) from the Army, Navy/Marines and Air Force enrolled since 1986[32,34-36]. Participants are followed at five medical centers in the United States. Demographic data are collected at baseline and updated while medical and medication histories and standard laboratory studies are collected biannually. Blood samples obtained from participants in this cohort from scheduled visits are stored in a repository. Demographic information captured includes race/ethnicity (Caucasian, African American, Hispanic or Puerto Rican, Mexican, Asian, or Pacific Islander, Native American or Alaskan native, or other), age, gender, active duty, retired or dependent, and rank in military. Although not captured in the NHS database, injection drug use (IDU) has been reported to be very rare in this cohort[32,33]. All NHS participants provided informed consent, and approval for this research was obtained from the institutional review board at each participating site.

2.2.2: Study Participants

The RAND Short Form 36 (SF-36) questionnaires were administered annually to NHS participants from April 2006 to September 2010. However, a few participants had more than one completed questionnaire in a year, and for these participants the last completed questionnaire for that year was used. We used the CD4 count and viral load values closest in time to the HRQOL measure used. Baseline was defined as the first ever HRQOL measure irrespective of when the participant was first enrolled in the NHS.

2.2.3: Definitions and Variable Selections

Variable selection was based on the literature on HRQOL in HIV-infected individuals in the United States and other high income countries[5,10], on HRQOL in the US Military[37] and on variables captured in our cohort[32-35].

2.2.3.1: Health-Related Quality of Life Scores

We computed the norm-based the physical (PCS) and mental (MCS) component summary scores 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[38,39]. The PCS and MCS scores were the outcome variables in our analyses. Although we also calculated the raw and transformed T-scores of the eight health domain scores, we have reported only the summary scores here for ease of results interpretation and for comparison with other studies.

2.2.3.2: HAART (Treatment) Variable

HAART was defined as a combination of at least three antiretroviral agents similar to previous investigations for this cohort[32]. HAART treatment was the main explanatory

variable. HAART treatment was divided into four groups: protease inhibitor-based HAART (PI-HAART), for HAART with at least one protease inhibitor in the combined HAART regimen; non-protease-inhibitor-based HAART (NPI-HAART), for HAART with no protease inhibitor in the combined HAART regimen; HAART-naïve group (HAART-N) for those not on HAART; and, OFF-HAART group made up of participants who were not on HAART at the time of completing the survey but had prior use of HAART. We separated this group from the HAART-naïve group because of their different demographic and clinical characteristics (see result section).

2.2.3.3: Covariates

Covariates considered for inclusion in our models were based on previous studies as well as on the demographic and clinical characteristics that were captured in the NHS cohort. These covariates included gender (male/female), age, military rank (officer/warrant officer, enlisted and civilian/retired), marital status (married, not married), race/ethnicity, plasma viral load, CD4+ cell count, medical comorbidity, mental comorbidity, AIDS-defining illnesses, medication adherence, HIV duration, and calendar year. CD4 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 or ≤50 copies/mL. Although most of the participants were not new to the HIV Natural History Study (NHS) of the US Military, enrollment into the HRQOL study specifically began in 2006 and continued until 2010. We therefore included calendar year in order to adjust for any temporal variations in participants' entry into the HRQOL study.

Although AIDS-defining illnesses have declined significantly in the HAART era, AIDS definition was in line with the 1993 Centers for Disease Control and Prevention criteria,

with the exception of an isolated CD4 cell count <200 cells/mm^3 as CD4 was analyzed separately. Race/ethnicity was classified as non-Hispanic white, non-Hispanic African-American, and Others (including Hispanics). Medical co-morbidity referred to chronic medical conditions, and was classified as having no comorbidity or having one or more comorbidity. Mental comorbidity was classified similarly. Adherence was classified as good (yes) or poor (no) with an adherence level of at least 90%[30] required for classifying as good.

2.2.4: Inclusion and Exclusion Criteria

All participants aged 18 years and above who completed the HRQOL survey questionnaires between 2006 and 2010 were included. We excluded participants who had been on treatment for less than four weeks prior to taking the HRQOL survey since some of the questions in the questionnaire specifically asked for participants' functional health in the past four weeks. We further excluded participants who were on both PI-HAART and NPI-HAART within four weeks of taking the survey. We also excluded participants who were on a non-HAART antiretroviral therapy at the time of survey.

2.2.5: Statistical Analyses

We summarized the baseline characteristics of the participants who met our inclusion criteria by four HAART groups (PI-HAART, NPI-HAART, HAART-Naïve, and HAART-Missing). Proportions of participant's characteristics were compared using Chi-square tests and exact statistics while the medians of the numeric variables were compared using the Kruskal Wallis tests. Separate multivariate regression models were constructed for PCS and MCS scores. We tested the effect of covariates on participants' PCS and MCS scores in univariate analyses, and included those which achieved a

significance p-value of less than 0.2 in the multivariate analyses. Race/ethnicity, and gender were forced into all models. Using these criteria, calendar year, marital status, medical comorbidity, and duration of HIV (years) were not included in the multivariate MCS model. All covariates were eligible for inclusion into the multivariate PCS model. Furthermore, for variables that were not significant in the multivariate models we manually removed and re-entered them (one at a time) to determine the most parsimonious models by comparing their adjusted R-square and Mallow's cp. We also tested the effect on adherence on both physical and mental health scores of participants. In doing so we excluded participants in the HAART-naïve and OFF-HAART groups. In the final models chosen, we checked for evidence of multi-collinearity, and for interaction between the main independent variable, HAART Treatment, and the covariates. All statistical analyses were performed using SAS 9.3 [SAS Institute Inc., Cary, NC].

2.3: Results

Baseline demographic and clinical characteristics by HAART group for participants with SF-36 data are displayed in table 2.1. Of the 1730 eligible participants, 24 (1.4%) on a non-HAART antiretroviral therapy were excluded. We also excluded another 38 (2.2%) who were either on HAART for less than 4 weeks prior to the survey or on both PI/NPI-HAART within 4 weeks of survey completion. Participants were different on all demographic characteristics with the exception of gender and marital status (Table 2.1). Participants were also significantly different on all clinical characteristics, namely CD4 cell count, plasma viral load, time from HIV diagnosis, medical and mental comorbidities, AIDS diagnosis, and medication adherence.

Participants scores on both their physical and mental HRQOL measures (PCS and MCS scores) were also different by HAART groups. The HAART-Naïve group had the highest median PCS score while the PI-HAART group had the lowest median PCS score. On the other hand, the NPI-HAART group had the highest median MCS score and the HAART-Naïve group had the lowest median MCS score. The median age of participants on PI-HAART was 44 years (interquartile range [IQR]: 39-50) followed by the NPI-HAART group with a median age of 41 years (IQR: 35-47) while the HAART-naïve group was much younger with a median age of 29 years (IQR: 25-38). The median age for the HAART-off group was 40.5 years (IQR: 36-45). Because the initial definition of HAART required that at least a protease inhibitor in the combination therapy, the PI-HAART group had the longest duration of HIV infection (median 15 years, IQR of 10-19 years).

Table 2.2 shows the univariate and multivariate analyses for the physical HRQOL scores (PCS score). Compared to the PI-HAART, HAART-naivety was associated with a higher PCS scores by 4.59 (95% Confidence Limits [95% CL]: 3.44, 5.74) in the unadjusted model but this was no longer significant after adjusting for covariates (β = 0.11, 95% CL: -1.57, 1.78). Also, the PCS scores of participants in the NPI-HAART group were significantly higher than those in the PI-HAART group in the unadjusted model (β = 2.53, 95% CL: 1.48, 3.58) but not in the adjusted model. There were no statistical difference in PCS scores between the PI-HAART and the Off-HAART groups both in the unadjusted and adjusted models. Being male was significantly associated with higher PCS scores (β = 2.11, 95% CL: 0.49, 3.73). Compared to participants enrolled into the HRQOL study in 2006, those enrolled in 2007 had significantly higher PCs scores by 1.56 (95% CL: 0.59, 2.53).

Factors associated with lower physical HRQOL scores (PCS scores) were age, CD4 count <200 cells/mm^3, lower military rank or being civilian/retired, presence of medical and mental comorbidities, AIDS diagnosis, and being married. Every 5-year increment in age was associated with 0.51 point reduction in PCS score (95% CL: -0.78, -0.24). Compared to officers, the PCS scores of active duty enlisted participants was lower by l.90 (95% CL: -3.53, -0.27) and that for civilians/retired military personnel was lower by 3.30 (95% CL: -5.03, -1.56). Being married was also associated with a reduction in PCS score by 1.24 points (95% CL: -2.13, -0.36) in the adjusted model. Medical and mental comorbidities, and AIDS diagnosis were significantly associated with a reduction in PCS scores by 2.72 (95% CL: -3.96, -1.47), 2.84 (95% CL: -3.82, -1.86) and 2.34 (95% CL: -3.75, -0.93) respectively. After adjusting for covariates, the PCS score of participants with CD4 count <200 cells/mm^3 was lower than those with CD4 count >500 cells/mm^3 by 5.12 points (95% CL: -6.91, -3.33) but there was no difference between the PCS scores of participants with CD4 count of 200-499 cells/mm^3 and those whose CD4 count >500 cells/mm^3 either in the unadjusted or adjusted models. There was no statistically significant difference in PCS scores by plasma viral load category. Race/ethnicity was also not associated with PCS scores. Although duration of HIV (in years) was significantly associated with a reduction in PCS score by 0.29 points for every unit increase in years in the unadjusted model, there was no significant association after adjusting for covariates.

Table 3.3 shows the univariate and multivariate analyses for the mental HRQOL scores. There were no statistically significant differences between the four treatment groups on their mental HRQOL scores before and after adjusting for covariates. Increasing age and

being African American were associated with relatively higher mental HRQOL score (MCS scores). In the multivariate model, we found that every 5-year increment in age was associated with a 0.48 point higher MCS scores (95% CL: 0.22, 0.74). Compared to Caucasians, being African-American was associated with a 1.54 point increase in MCS scores (95% CL: 0.61, 2.48). Having a CD4 count <200 cells/mm^3 ($\beta = 2.19$; 95% CL: -4.08, -0.31) significantly associated with lower MCS scores but not CD4 count of 200-499 cells/mm^3 ($\beta = -0.78$; 95% CL: -1.70, 0.10) when compared to CD4 count >499 cells/mm^3. Mental comorbidities were significantly associated with lower MCS scores by 6.12 points after adjusting for covariates (95% CL: -7.32, -5.30). AIDS diagnosis and plasma vial load were only significantly associated with lower MCS scores in the unadjusted models but were no longer significant after adjusting for covariates. Gender, military rank, medical comorbidities, and HIV duration were not associated with MCS scores in the unadjusted models.

In separate models restricted to the PI/NPI-HAART groups, we tested the association between adherence to HAART medication and HRQOL measures. In the unadjusted models medication adherence was significantly associated with both PCS and MCS scores but in the adjusted models there was no longer a significant association between adherence and PCS scores or MCS scores (Tables 2.2 and 2.3). There were no evidence of multi-collinearity and no evidence of interaction. In table 2.4 we displayed the most parsimonious PCS and MCS models with results similar to the ones already provided above.

2.4: Discussion

Health-related quality of life (HRQOL) has not been previously evaluated in the U.S. Military HIV Natural History Study (NHS), which is one of the oldest open-enrollment dynamic HIV cohorts in the country. Our aims were therefore to assess factors associated with HRQOL at baseline and to determine whether HRQOL measures were different among the HAART groups including those not on HAART. Because the HAART-naïve group were very different from the Off-HAART group both in demographic and clinical characteristics we treated them as a separate groups (table 2.1). In this study we found that being HAART-naïve was associated with a higher perceived physical functional health in the unadjusted model but after controlling for covariates there was no significant difference between HAART-naivety and being on a PI-HAART, a finding that is similar to that of Preau et al[40]. We also did not find any differences in physical functional health between the Off-HAART and PI-HAART groups. NPI-HAART was associated with higher perceived physical health in the univariate model but not in the adjusted model. In a cross-sectional study of 159 participants by Armon et al[17] found that use of efavirenz based HAART (NPI-HAART) was associated with higher physical functional health but also found inverse relationship between nevirapine based HAART (also an NPI-HAART) and physical functional health. The authors argued that the lower physical functional health reported with nevirapine may be due to it being reserved for participants with more severe disease[17], an argument we believe should hold true for PI-HAART.

There are very few studies on the relationship between HRQOL and specific antiretroviral therapy (ART) regimens in the literature and most of these are in clinical

trials[10]. Comparison of study findings is further complicated by the various instruments used, some being HIV-disease specific while others are generic. Of the 26 articles recently reviewed by Gakhar et al only two articles used the SF-36 questionnaire, 12 used the MOS-HIV with other disease-specific and generic instruments making the rest[10]. The study by Hodder et al[41] which used the SF-36 investigated the benefit of switching from either a PI-based or an NNRTI-based HAART to a single tablet regimen of efavirenz, emtricitabine, and tenofovir DF, and the other study that used the MOS SF-36 had participants on a PI-based HAART regimen alone[6]. While these studies showed improvement in HRQOL they are not directly comparable to ours. However, two other studies[27,29] reported better HRQOL after switching from a PI-based HAART to an NNRTI-based HAART (specifically efavirenz and nevirapine), but these studies did not control for the PI-comparison group. Fumaz et al[28], on the other hand, reported better quality of life in participants who switched from PI-HAART to NNRTI (efavirenz) in comparison to those who remained on PI-HAART; however, they used a 5-point adaptation of the MOS-HIV questionnaire[28] making direct comparison difficult. It has been suggested that the better physical health found in the NPI-HAART group was attributable to the simpler regimen of the NPI-HAART regimen, fewer adverse events, and better physical and emotional status[28]. It is worth noting here that efavirenz is associated with high central nervous system side effects especially in the initial 2 to 3 weeks of treatment[42], and this was case with some of the participants in the study reported by Fumaz et al[28].

The other factors independently associated with physical HRQOL (PCS) scores in our cohort were age, military rank, marital status, gender, CD4 count less than 200, medical

and mental comorbidities, AIDS diagnosis, and baseline enrollment year being 2007. However, only age, being African-American, CD4 count <200 cell/mm^3, and mental comorbidity were independently associated with mental HRQOL (MCS) scores in our cohort. We did not find any differences in mental health by HAART group either in the unadjusted or adjusted models. Age has been reported in the literature to be negatively associated with PCS score in HIV-infected populations[14,15,18,40,43,44]. Also, Smith et al found age to be negatively associated with PCS in a non-HIV military population[37] which is consistent with our findings. There was, however, a positive association between increasing age and MCS in our cohort similar to that in the military[37] and in HIV-infected individuals[13]. The relationship between age and HIV is a complex one but it is clear that both increasing age and HIV infection lead to a gradual decline in immunity, and that older individuals have slower immune recovery and achieve less CD4 cell restoration with HAART[45]. Also, both HIV infection and aging are associated with increased medical comorbidities that could further negatively impact physical functional health[19]. Beyond that, physical senescence associated with older age may also contribute poorer physical functional health[5].

Akin to the literature, we found that CD4 count <200 cells/mm^3 was significantly associated with lower physical HRQOL score[13,21,46]. There was no significant difference in PCS scores of participants with CD4 count of 200-499 cells/mm^3 when compared to those with CD4 count >499 cells/mm^3, similar to findings by others[13,14]. The negative impact of CD4 count <200 cells/mm^3 on perceived physical health is likely attributable to the greater burden of the disease associated with CD4 counts <200 cells/mm^3, including the fact these individuals are more likely to have had HIV-infection for a longer period of

time, be older and may have more associated comorbidities as was the case in our cohort (data not shown). We also found that CD4 counts <200 cells/mm^3 independently associated with lower mental HRQOL score similar to the findings by others[8,17,47] but unlike the findings by Hays et al[13], which found a positive association between lower CD4 count and mental HRQOL scores. It has been suggested that because CD4 count <200 cells/mm^3 is associated with faster disease progression in HIV-infected individuals, this will tend to cause distress that may negatively impact perceived mental health[8]. In line with several studies in the HAART era we did not find any difference in both the PCS and MCS scores of participants of the NHS to be affected by viral load[14,48,49]. This is not entirely surprising since the effect of viral load on HRQOL may be partly explained by its effect on CD4 count, and as previously noted by other investigators, CD4 count is a better prognostic marker for disease progression for HIV-infected individuals on HAART[48,49]. Moreover, slightly over half of the NHS participants had plasma viral load ≤50 copies/mL, a level that reflects significantly suppressed viral activity.

The presence of medical comorbidities was negatively associated with physical functional health but not mental functional health similar to findings by others[7,14,19,20,22,40]. The presence of mental comorbidities, on the other hand, was negatively associated with both physical and mental functional health of participants, although the dramatic influence of mental comorbidity on MCS in our cohort (β: -6.12; 95% CL: -7.32, -5.30) clearly shows the need for greater attention by both clinicians and policy makers in addressing this issue in this population of military personnel. The need for frequent and regular evaluation of the mental health of participants is further supported by the high prevalence of mental comorbidity in our cohort (over 25%) (please

see chapter 1, table 1.10.). Although diverse psychological comorbidities have been shown to influence HRQOL, depression, which accounted for over 60% of the psychological comorbidity in our cohort, is by far the most predictive of physical and mental functional health[7,14,40].

Having ever been diagnosed with AIDS was negatively associated with physical health in our cohort similar to findings by others[13,40,50] The median duration of AIDS diagnosis in our cohort was 8 years (IQR: 2-12 years). In our cohort, only 12 participants (6.12% of all those with AIDS at baseline) had a recent AIDS diagnosis in the one year preceding enrollment into the study. In sensitivity analyses, we did not find any differences in result when we excluded these participants with a recent AIDS diagnosis. Also, similar to findings by others[17,51] we did not find the presence of AIDS diagnosis to be independently associated with mental functional health, which may further support the view that with time HIV-infected individuals may develop more effective coping strategies that could enhance their mental health[5,22].

Although HIV duration was negatively associated with perceived physical health in the unadjusted model, the association was no longer significant after adjusting for age and other covariates. Most likely, the apparent negative association may have been explained by other factors such as medical comorbidity and AIDS that are more likely with longer duration of the disease. Furthermore age is often correlated with duration of HIV infection in our cohort (correlation coefficient 0.62, $p<.0001$). Race/ethnicity was not associated with physical functional health in our cohort which may give credence to the view that with employment and/or equal access to healthcare (more likely to be skewed by race/ethnicity in the general population), race/ethnicity is not a significant predictor of

PCSS. In our cohort, being African-American was positively associated with higher mental functional health which is similar to the findings in a non-HIV Military cohort which reported a higher MCS score among African-Americans compared to Caucasians[37]. While there may be need for further validation of this finding we are not sure if this has any clinical correlations. We also found gender differences in physical functional health in our cohort. This is similar to what has been reported in other studies[7,8,12,15,52] including the US Military[37].

Some of the limitations of our study include its cross-sectional nature, which may preclude conclusions on causality. Our study population was also predominantly male (over 90%) so generalizability to female should be applied cautiously. We also did not control for variables such as route of transmission as this was not captured at the time the surveys were administered due to fear of participants' violation of the Uniform Code of Military Justice[36]. It is worth noting that previous studies have however, not found route of transmission to be independently associated with HRQOL[16,17,19,40]. Finally, the use of the RAND SF-36 questionnaire, a generic HRQOL instrument, does not allow us to capture some important HIV-disease specific dimensions on quality of life such as cognitive functioning or sleep problems.

Our study had some major advantages. One, we simultaneously examined the differences in HRQOL measures in a large cohort of individuals on PI-HAART and NPI-HAART, as well as those who were HAART-naïve or Off-HAART. Because of the large sample size, we were able to adjust for many important variables in our models. Other advantages of the cohort are its representation of minority groups including African-Americans, Hispanics and other races. Also, the use of a norm-based generic HRQOL

questionnaire (RAND SF-36) makes it easy for direct comparisons with different populations and settings including the general US population, non-HIV-infected US military population, other HIV cohorts as well as those of other chronic diseases that have used similar instruments.

2.5: Conclusion

In conclusion, there are several important findings from our study. One, physical functional health was better than mental functional health in our cohort. Two, our study showed no differences in both physical and mental functional health of participants by HAART groups. Three, the high negative impact of mental comorbidities on mental functional health in our cohort deserves the attention of both clinicians and policy makers in order to improve the self-reported health of HIV-infected individuals in the United States Military. Also, the complex interplay between age/HIV and HRQOL needs to be further studied in order for us to better understand why older age is negatively associated with physical functional health but positively associated with mental functional health. Finally, we believe this current study will serve as a reference for future longitudinal studies on HRQOL in our cohort.

2.6: Tables

Table 2.1: Baseline Characteristics of Participants by Highly Active Anti-Retroviral Therapy Group

Characteristics	PI-Based HAART N (%)	Non-PI-Based HAART N (%)	HAART-Naïve N (%)	Off-HAART N (%)	P-Value*
Gender					0.2257
Male	485 (93.45)	533 (91.58)	390 (94.89)	144 (92.31)	
Female	34 (6.55)	49 (8.42)	21 (5.11)	12 (7.69)	
Race/Ethnicity					**<.0001**
Non-Hispanic White	**234 (45.09)**	**253 (43.47)**	**145 (35.28)**	**69 (44.23)**	
Non-Hispanic African American	**223 (42.97)**	**251 (43.13)**	**164 (39.90)**	**65 (41.67)**	
Hispanic/Others	**62 (11.95)**	**78 (13.40)**	**102 (24.82)**	**22 (14.10)**	
Rank					**<.0001**
Officer/Warrant Officer	**25 (4.83)**	**44 (7.56)**	**41 (10.00)**	**11 (7.05)**	
Enlisted	**177 (34.17)**	**290 (49.83)**	**340 (82.93)**	**76 (48.72)**	
Civilian/Retired	**316 (61.00)**	**248 (42.61)**	**29 (7.07)**	**69 (44.23)**	
Marriage					0.1784
Yes	165 (31.79)	201 (34.54)	115 (27.98)	52 (33.33)	
No	354 (68.21)	381 (65.46)	296 (72.02)	104 (66.67)	
CD4 Groups					
CD4 Less Than 200	**62 (11.95)**	**18 (3.10)**	**8 (1.95)**	**14 (8.97)**	**<.0001**
CD4 Between 200 and 499	**213 (41.04)**	**192 (33.05)**	**227 (55.37)**	**81 (51.92)**	
CD4 Greater Than 499	**244 (47.01)**	**371 (63.86)**	**175 (42.68)**	**61 (39.10)**	
Viral Load Copies > 50 copies/mL					**<.0001**
Yes	**176 (33.98)**	**103 (17.70)**	**405 (98.54)**	**139 (89.10)**	
No	**342 (66.02)**	**479 (82.30)**	**6 (1.46)**	**17 (10.90)**	
Mental Comorbidity					**<.0001**
Yes	**190 (36.61)**	**150 (25.77)**	**36 (8.76)**	**54 (34.62)**	
No	**329 (63.39)**	**432 (74.23)**	**375 (91.24)**	**102 (65.38)**	
Medical Comorbidity					**<.0001**
Yes	**126 (24.28)**	**84 (14.43)**	**6 (1.46)**	**24 (15.38)**	
No	**393 (75.72)**	**498 (85.57)**	**405 (98.54)**	**132 (84.62)**	
AIDS					**<.0001**
Yes	**123 (23.70)**	**55 (9.45)**	**2 (0.49)**	**12 (7.69)**	
No	**396 (76.30)**	**527 (90.55)**	**409 (99.51)**	**144 (92.31)**	

Adherence (90%)					**<.0001**
Yes	**453 (87.62)**	**550 (94.66)**	**N/A**	**N/A**	
No	**64 (12.38)**	**31 (5.34)**	**N/A**	**N/A**	
Calendar Year					**<.0001**
Baseline Year 2006	**286 (55.11)**	**313 (56.09)**	**106 (25.79)**	**100 (64.10)**	
Baseline Year 2007	**168 (32.37)**	**157 (31.73)**	**107 (26.03)**	**35 (22.44)**	
Baseline Year 2008	**33 (6.36)**	**34 (5.84)**	**67 (16.30)**	**8 (5.13)**	
Baseline Year 2009	**24 (4.62)**	**48 (8.25)**	**79 (19.22)**	**10 (6.41)**	
Baseline Year 2010	**8 (1.54)**	**30 (5.15)**	**52 (12.65)**	**3 (1.92)**	
Age (years)					
Median (IQR)	**44.0 (39.0 – 50.0)**	**41.0 (35.0 – 47.0)**	**29.0 (25.0 – 38.0)**	**40.5 (36.0 – 45.0)**	**<.0001**
CD4 Cell Count (x 10^6/L)					
Median (IQR)	**477.0 (316.0 – 678.0)**	**570.0 (435.0 – 776.0)**	**466.0 (374.0 – 606.0)**	**450.0 (338.0 – 622.0)**	**<.0001**
Viral Load (Log_{10})					
Median (IQR)	**1.70 (1.70 – 2.26)**	**1.70 (1.70 – 1.70)**	**4.25 (3.73 – 4.73)**	**4.03 (3.29 – 4.46)**	**<.0001**
Time from HIV Diagnosis (years)					
Median (IQR)	**15.0 (10.0 – 19.0)**	**8.0 (4.0 – 14.0)**	**0.0 (0 – 1.0)**	**11.0 (7.0 – 15.0)**	**<.0001**
Physical Component Summary Score					
Median (IQR)	**52.90 (43.89 – 57.18)**	**55.45 (48.11 – 58.19)**	**56.26 (51.26 – 58.72)**	**(53.04, 45.15 – 57.39)**	**<.0001**
Mental Component Summary Score					
Median (IQR)	**50.36 (42.35 – 54.08)**	**51.26 (44.89 – 54.39)**	**48.81 (43.45 – 53.35)**	**50.12 (42.34 – 52.87)**	**0.0003**

*Chi-square test for count variable and Kruskal Wallis for numeric variable. N/A = Not Applicable. IQR = Interquartile Range

Table 2.2: Factors Associated with Physical Component Summary Scores at Baseline

Variable	Physical Component Summary Scores (n = 1652)							
	Unadjusted Model				Multivariate Model			
	β	SE	95% CI	P-Value	β	SE	95% CI	P-Value
HAART Status								
HAART Naïve	**4.59**	**0.59**	**3.44, 5.74**	**<.0001**	0.11	0.85	-1.57, 1.78	0.90
Non-PI-Based HAART	**2.53**	**0.54**	**1.48, 3.58**	**<.0001**	0.68	0.54	-0.38, 1.75	0.21
Off-HAART	0.81	0.81	-0.78, 2.40	0.32	-0.50	0.84	-2.15, 1.15	0.56
PI-Based HAART	-	-	-	-	-	-	-	-
Age (5-yearly Increment)	**-1.03**	**0.10**	**-1.23, -0.83**	**<.0001**	**-0.51**	**0.14**	**-0.78, -0.24**	**0.0002**
Race/Ethnicity								
Non-Hispanic African American	0.12	0.484	-0.83, 1.07	0.81	-0.373	0.462	-1.28, 0.53	0.42
Hispanic/Others	0. 38	0.653	-0.90, 1.66	0.56	-0.736	0.618	-1.95, 0.48	0.23
Non-Hispanic White	-	-	-	-	-	-	-	-
Gender								
Male	**2.97**	**0.87**	**1.27, 4.67**	**0.0006**	**2.11**	**0.83**	**0.49, 3.73**	**0.01**
Female	-	-	-	-	-	-	-	-
Rank								
Enlisted	**-2.07**	**0.84**	**-3.72, -0.42**	**0.01**	**-1.90**	**0.83**	**-3.53, -0.27**	**0.02**
Civilian	**-6.20**	**0.86**	**-7.89, -4.52**	**<.0001**	**-3.30**	**0.88**	**-5.03, -1.57**	**0.0002**
Officer/Warrant Officer	-	-	-	-	-	-	-	-
Marital Status								
Married	**-1.814**	**0.473**	**-2.74, -0.89**	**0.0001**	**-1.24**	**0.45**	**-2.13, -0.36**	**0.006**
Single	-	-	-	-	-	-	-	-
CD4 Count Groups								
<200 cells/mm^3	**-7.75**	**0.93**	**-9.58, -5.92**	**<.0001**	**-5.94**	**0.94**	**-7.78, -4.09**	**<.0001**
200-499 cells/mm^3	-0.64	0.45	-1.53, 0.24	0.15	-0.76	0.44	-1.62, 0.10	0.08
>499 cells/mm^3	-	-	-	-	-	-	-	-
Viral Load >50 copies/mL								
Yes	0.61	0.44	-0.26, 1.48	0.17	0.17	0.59	-0.99, 1.32	0.78
No	-	-	-	-	-	-	-	-
Medical Comorbidity								
Yes	**-5.21**	**0.62**	**-6.42, -4.00**	**<.0001**	**-2.72**	**0.63**	**-3.96, -1.47**	**<.0001**
No	-	-	-	-	-	-	-	-
Mental Comorbidity								
Yes	**-4.57**	**0.49**	**-5.54, -3.60**	**<.0001**	**-2.84**	**0.50**	**-3.82, -1.86**	**<.0001**
No	-	-	-	-	-	-	-	-
AIDS								
Yes	**-6.07**	**0.682**	**-7.40, -4.73**	**<.0001**	**-2.34**	**0.72**	**-3.75, -0.93**	**0.001**

No	-	-	-	-	-	-	-	-
Duration of HIV (years)	**-0.30**	**0.03**	**-0.36, -0.24**	**<.0001**	0.02	0.05	-0.07, 0.11	0.66
Adherence[##]	**2.14**	**1.01**	**0.16, 4.12**	**0.03**	1.58	0.95	-0.29, 3.44	0.10
Calendar Year								
2010	1.91	0.99	-0.02, 3.85	0.05	-0.37	0.96	-2.24, 1.51	0.70
2009	0.78	0.78	-0.74, 2.31	0.31	-0.35	0.75	-1.83, 1.13	0.64
2008	**2.62**	**0.82**	**1.01, 4.24**	**0.001**	1.48	0.79	-0.07, 3.02	0.06
2007	**1.10**	**0.52**	**0.07, 2.13**	**0.04**	**1.56**	**0.49**	**0.59, 2.53**	**0.002**
2006	-	-	-	-	-	-	-	-
Intercept	***NA***	***NA***	***NA***	***NA***	***57.84***	***1.70***	***54.52, 61.16***	***<.0001***

[##]Model with only PI-HAART and NPI-HAART. SE = Standard Error. β = Beta coefficient. CI = Confidence Interval

Table 2.3: Factors Associated with Mental Component Summary Scores at Baseline

Variable	Mental Component Summary Scores (n = 1652)							
	Unadjusted Model				Multivariate Model			
	β	SE	95% CI	P-Value	β	SE	95% CI	P-Value
HAART Status								
HAART Naïve	-0.51	0.61	-0.15, 2.02	0.40	-1.27	0.80	-2.85, 0.30	0.11
Non-PI-Based HAART	0.94	0.55	-0.15, 0.68	0.09	0.02	0.55	-1.05, 1.11	0.96
HAART Holiday	-1.41	0.83	-3.04, 0.23	0.09	-1.07	0.87	-2.78, 0.64	0.22
PI-Based HAART	-	-	-	-	-	-	-	-
Age (5-yearly Increment)	**0.25**	**0.11**	**0.04, 0.46**	**0.02**	**0.48**	**0.13**	**0.22, 0.74**	**0.0003**
Race/Ethnicity								
Non-Hispanic African American	**1.84**	**0.49**	**0.88, 2.79**	**0.0002**	**1.54**	**0.48**	**0.61, 2.48**	**0.001**
Hispanic/Others	-0.81	0.66	-2.10, 0.48	0.22	-0.71	0.64	-1.97, 0.55	0.27
Non-Hispanic White	-	-	-	-	-	-	-	-
Gender								
Male	0.84	0.88	-0.89, 2.57	0.34	1.11	0.85	-0.56, 2.78	0.19
Female	-	-	-	-	-	-	-	-
Rank								
Enlisted	-0.36	0.88	-2.08, 1.37	0.68	0.73	0.87	-0.97, 2.45	0.40
Civilian	-1.19	0.90	-2.95, 0.57	0.18	-0.32	0.90	-2.08, 1.45	0.72
Officer/Warrant Officer	-	-	-	-	-	-	-	-
Marital Status								
Married	-0.31	0.48	-1.26, 0.63	0.52				
Single	-	-	-	-				
CD4 Count Groups								
<200 cells/mm^3	**-3.07**	**0.96**	**-4.95, -1.19**	**0.001**	**-1.96**	**0.98**	**-3.87, -0.04**	**0.04**
200-499 cells/mm^3	**-1.04**	**0.46**	**-1.95, -0.13**	**0.02**	-0.80	0.46	-1.70, 0.10	0.08
>499 cells/mm^3	-	-	-	-	-	-	-	-
Viral Load >50 copies/mL								
Yes	**-1.46**	**0.45**	**-2.34, -0.58**	**0.001**	**-0.420**	**0.611**	**-1.62 – 0.78**	**0.49**
No	-	-	-	-	-	-	-	-
Medical Comorbidity								
Yes	0.71	0.64	-0.54, 1.97	0.26				
No	-	-	-	-				
Mental Comorbidity								
Yes	**-5.99**	**0.49**	**-6.96, -5.03**	**<.0001**	**-6.12**	**0.52**	**-7.13, -5.10**	**<.0001**
No	-	-	-	-	-	-	-	-
AIDS								
Yes	**-1.97**	**0.71**	**-3.36, -0.59**	**0.005**	-0.79	0.73	-2.23, 0.64	0.28

No	-	-	-	-	-	-	-	-
Duration of HIV (years)	0.003	0.03	-0.06, 0.06	0.91				
Adherence[##]	**2.30**	**0.98**	**0.37, 4.23**	**0.02**	1.77	0.93	-0.06, 3.59	0.06
Calendar Year								
2010	0.59	1.00	-1.37, 2.56	0.55				
2009	-0.28	0.79	-1.73, 1.34	0.72				
2008	-0.30	0.84	-1.83, 1.34	0.72				
2007	-0.45	0.53	-1.49, 0.60	0.40				
2006	-	-	-	-				
Intercept	***NA***	***NA***	***NA***	***NA***	***44.69***	***1.73***	***41.29, 48.09***	***<.0001***

[##]Model with only PI-HAART and NPI-HAART. SE = Standard Error. β = Beta coefficient. CI = Confidence Interval

Table 2.4: Factors Associated with Physical/Mental Component Summary Scores at Baseline

Variable	Physical/Mental Component Summary Scores (n = 1652)							
	Most Parsimonious Multivariate PCSS Model				Most Parsimonious Multivariate MCSS Model			
	β	SE	95% CI	P-Value	β	SE	95% CI	P-Value
HAART Status								
HAART Naïve	0.07	0.68	-1.25, 1.40	0.91	-1.14	0.79	-2.69, 0.41	0.15
Non-PI-Based HAART	0.61	0.53	-0.42, 1.64	0.25	0.08	0.55	-0.99, 1.16	0.88
HAART Holiday	-0.42	0.77	-1.94, 1.09	0.58	-1.05	0.87	-2.76, 0.67	0.23
PI-Based HAART	-	-	-	-	-	-	-	-
Age (5-yearly Increment)	**-0.48**	**0.13**	**-0.73, -0.22**	**0.0002**	**0.38**	**0.12**	**0.14, 0.61**	**0.002**
Race/Ethnicity								
Non-Hispanic African American					**1.60**	**0.47**	**0.67, 2.52**	**0.0007**
Hispanic/Others					-0.70	0.64	-1.95, 0.56	0.28
Non-Hispanic White					-	-	-	-
Gender								
Male	**2.14**	**0.82**	**0.53, 3.76**	**0.009**	1.22	0.84	-0.43, 2.88	0.15
Female	-	-	-	-	-	-	-	-
Rank								
Enlisted	**-1.99**	**0.82**	**-3.60, -0.39**	**0.02**				
Civilian	**-3.31**	**0.85**	**-4.98, -1.64**	**0.0001**				
Officer/Warrant Officer	-	-	-	-				
Marital Status								
Married	**-1.27**	**0.45**	**-2.16, -0.41**	**0.0041**				
Single	-	-	-	-				
CD4 Count Groups								
<200 cells/mm^3	**-5.87**	**0.91**	**-7.66, -4.08**	**<.0001**	**-1.96**	**0.98**	**-3.88, -0.05**	**0.04**
200-499 cells/mm^3	-0.74	0.43	-1.59, 0.11	0.09	-0.76	0.46	-1.66, 0.14	0.10
>499 cells/mm^3	-	-	-	-	-	-	-	-
Viral Load >50 copies/mL								
Yes					-0.42	0.61	-1.61 – 0.78	0.50
No					-	-	-	-
Medical Comorbidity								
Yes	**-2.68**	**0.63**	**-3.92, -1.44**	**<.0001**				
No	-	-	-	-				
Mental Comorbidity								
Yes	**-2.77**	**0.49**	**-3.73, -1.80**	**<.0001**	**-6.24**	**0.51**	**-7.24, -5.24**	**<.0001**
No	-	-	-	-	-	-	-	-
AIDS								
Yes	**-2.32**	**0.71**	**-3.72, -0.92**	**0.001**	-0.90	0.73	-2.33, 0.53	0.22

No	-	-	-	-	-	-	-	-
Duration of HIV (years)								
Adherence[##]	1.59	0.95	-0.27, 3.46	0.09	1.73	0.93	-0.09, 3.55	0.06
Calendar Year								
2010	-0.47	0.95	-2.24, 1.51	0.62				
2009	-0.44	0.75	-1.90, 1.03	0.56				
2008	1.40	0.78	-0.13 2.94	0.07				
2007	**1.52**	**0.49**	**0.56, 2.49**	**0.002**				
2006	-	-	-	-				
Intercept	***57.61***	***1.67***	***54.34, 60.87***	***<.0001***	***45.63***	***1.48***	***42.72, 48.53***	***<.0001***

[##]Model with only PI-HAART and NPI-HAART. SE = Standard Error. β = Beta coefficient. CI = Confidence Interval

2.7: References

1. Centers for Disease Control and Prevention (CDC). Rates of diagnoses of HIV infection among adults and adolescents, by area of residence, 2011—United States and 6 dependent areas. 2011; http://www.cdc.gov/hiv/pdf/statistics_2011_HIV_Surveillance_Report_vol_23.pdf. Accessed 01/26/2015.
2. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *The New England journal of medicine.* 1998;338(13):853-860.
3. Centers for Disease Control and Prevention (CDC). HIV surveillance - united states, 1981-2008. *MMRI.* 06/03/2011;60(21).
4. Murri R, Fantoni M, Del Borgo C, et al. Determinants of health-related quality of life in HIV-infected patients. *AIDS care.* 2003;15(4):581-590.
5. Degroote S, Vogelaers D, Vandijck DM. What determines health-related quality of life among people living with HIV: an updated review of the literature. *Archives of public health = Archives belges de sante publique.* 2014;72(1):40.
6. Carrieri P, Spire B, Duran S, et al. Health-related quality of life after 1 year of highly active antiretroviral therapy. *Journal of acquired immune deficiency syndromes (1999).* 2003;32(1):38-47.
7. Briongos Figuero LS, Bachiller Luque P, Palacios Martin T, Gonzalez Sagrado M, Eiros Bouza JM. Assessment of factors influencing health-related quality of life in HIV-infected patients. *HIV medicine.* 2011;12(1):22-30.
8. Protopopescu C, Marcellin F, Spire B, et al. Health-related quality of life in HIV-1-infected patients on HAART: a five-years longitudinal analysis accounting for dropout in the APROCO-COPILOTE cohort (ANRS CO-8). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2007;16(4):577-591.
9. Jin Y, Liu Z, Wang X, et al. A systematic review of cohort studies of the quality of life in HIV/AIDS patients after antiretroviral therapy. *International journal of STD & AIDS.* 2014;25(11):771-777.
10. Gakhar H, Kamali A, Holodniy M. Health-related quality of life assessment after antiretroviral therapy: a review of the literature. *Drugs.* 2013;73(7):651-672.
11. Grossman HA, Sullivan PS, Wu AW. Quality of life and HIV: current assessment tools and future directions for clinical practice. *The AIDS reader.* 2003;13(12):583-590, 595-587.
12. Rao D, Hahn EA, Cella D, Hernandez L. The health related quality of life outcomes of English and Spanish speaking persons living with HIV/AIDS from the continental United States and Puerto Rico. *AIDS patient care and STDs.* 2007;21(5):339-346.
13. Hays RD, Cunningham WE, Sherbourne CD, et al. Health-related quality of life in patients with human immunodeficiency virus infection in the United States: results from the HIV Cost and Services Utilization Study. *The American journal of medicine.* 2000;108(9):714-722.
14. Liu C, Johnson L, Ostrow D, Silvestre A, Visscher B, Jacobson LP. Predictors for lower quality of life in the HAART era among HIV-infected men. *Journal of acquired immune deficiency syndromes (1999).* 2006;42(4):470-477.
15. Ruiz Perez I, Rodriguez Bano J, Lopez Ruz MA, et al. Health-related quality of life of patients with HIV: impact of sociodemographic, clinical and psychosocial factors. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2005;14(5):1301-1310.

16. Degroote S, Vogelaers DP, Vermeir P, et al. Socio-economic, behavioural, (neuro)psychological and clinical determinants of HRQoL in people living with HIV in Belgium: a pilot study. *Journal of the International AIDS Society.* 2013;16:18643.
17. Armon C, Lichtenstein K. The associations among coping, nadir CD4+ T-cell count, and non-HIV-related variables with health-related quality of life among an ambulatory HIV-positive patient population. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2012;21(6):993-1003.
18. Fleming CA, Christiansen D, Nunes D, et al. Health-related quality of life of patients with HIV disease: impact of hepatitis C coinfection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2004;38(4):572-578.
19. Rodriguez-Penney AT, Iudicello JE, Riggs PK, et al. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. *AIDS patient care and STDs.* 2013;27(1):5-16.
20. Anis AH, Nosyk B, Sun H, et al. Quality of life of patients with advanced HIV/AIDS: measuring the impact of both AIDS-defining events and non-AIDS serious adverse events. *Journal of acquired immune deficiency syndromes (1999).* 2009;51(5):631-639.
21. Call SA, Klapow JC, Stewart KE, et al. Health-related quality of life and virologic outcomes in an HIV clinic. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2000;9(9):977-985.
22. Jia H, Uphold CR, Zheng Y, et al. A further investigation of health-related quality of life over time among men with HIV infection in the HAART era. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2007;16(6):961-968.
23. Langius-Eklof A, Lidman K, Wredling R. Health-related quality of life in relation to sense of coherence in a Swedish group of HIV-infected patients over a two-year follow-up. *AIDS patient care and STDs.* 2009;23(1):59-64.
24. Corless IB, Kirksey KM, Kemppainen J, et al. Lipodystrophy-associated symptoms and medication adherence in HIV/AIDS. *AIDS patient care and STDs.* 2005;19(9):577-586.
25. Nicholas PK, Kirksey KM, Corless IB, Kemppainen J. Lipodystrophy and quality of life in HIV: symptom management issues. *Applied nursing research : ANR.* 2005;18(1):55-58.
26. Burgoyne RW, Tan DH. Prolongation and quality of life for HIV-infected adults treated with highly active antiretroviral therapy (HAART): a balancing act. *The Journal of antimicrobial chemotherapy.* 2008;61(3):469-473.
27. Potard V, Chassany O, Lavignon M, Costagliola D, Spire B. Better health-related quality of life after switching from a virologically effective regimen to a regimen containing efavirenz or nevirapine. *AIDS care.* 2010;22(1):54-61.
28. Fumaz CR, Tuldra A, Ferrer MJ, et al. Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens. *Journal of acquired immune deficiency syndromes (1999).* 2002;29(3):244-253.
29. Campo RE, Cohen C, Grimm K, Shangguan T, Maa J, Seekins D. Switch from protease inhibitor- to efavirenz-based antiretroviral therapy improves quality of life, treatment satisfaction and adherence with low rates of virological failure in virologically suppressed patients. *International journal of STD & AIDS.* 2010;21(3):166-171.
30. Jayaweera D, Dejesus E, Nguyen KL, Grimm K, Butcher D, Seekins DW. Virologic suppression, treatment adherence, and improved quality of life on a once-daily efavirenz-based regimen in treatment-Naive HIV-1-infected patients over 96 weeks. *HIV clinical trials.* 2009;10(6):375-384.

31. van Leth F, Conway B, Laplume H, et al. Quality of life in patients treated with first-line antiretroviral therapy containing nevirapine and/or efavirenz. *Antiviral therapy.* 2004;9(5):721-728.
32. Chun HM, Roediger MP, Hullsiek KH, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. *The Journal of infectious diseases.* 2012;205(2):185-193.
33. Brodine SK, Starkey MJ, Shaffer RA, et al. Diverse HIV-1 subtypes and clinical, laboratory and behavioral factors in a recently infected US military cohort. *AIDS (London, England).* 2003;17(17):2521-2527.
34. Chun HM, Fieberg AM, Hullsiek KH, et al. Epidemiology of Hepatitis B virus infection in a US cohort of HIV-infected individuals during the past 20 years. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2010;50(3):426-436.
35. Pelak K, Goldstein DB, Walley NM, et al. Host determinants of HIV-1 control in African Americans. *The Journal of infectious diseases.* 2010;201(8):1141-1149.
36. Spaulding AB, Lifson AR, Iverson ER, et al. Gonorrhoea or chlamydia in a U.S. military HIV-positive cohort. *Sexually transmitted infections.* 2012;88(4):266-271.
37. Smith TC, Zamorski M, Smith B, et al. The physical and mental health of a large military cohort: baseline functional health status of the Millennium Cohort. *BMC public health.* 2007;7:340.
38. RAND. Scoring instructions for the 36-item short form survey (SF-36). http://www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html. Accessed 05/5/2013.
39. Hays RD. SAS code for scoring 36-item health survey 1.0. http://gim.med.ucla.edu/FacultyPages/Hays/utils/SF36/sf36.sas. Accessed 9/5/2014.
40. Preau M, Marcellin F, Carrieri MP, Lert F, Obadia Y, Spire B. Health-related quality of life in French people living with HIV in 2003: results from the national ANRS-EN12-VESPA Study. *AIDS (London, England).* 2007;21 Suppl 1:S19-27.
41. Hodder SL, Mounzer K, Dejesus E, et al. Patient-reported outcomes in virologically suppressed, HIV-1-Infected subjects after switching to a simplified, single-tablet regimen of efavirenz, emtricitabine, and tenofovir DF. *AIDS patient care and STDs.* 2010;24(2):87-96.
42. Bartlett JG GJ, Pham PA. *Medical Management of HIV Infection.* Knowledge Source Solutions; 2012.
43. Liu C, Ostrow D, Detels R, et al. Impacts of HIV infection and HAART use on quality of life. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2006;15(6):941-949.
44. Kowal J, Overduin LY, Balfour L, Tasca GA, Corace K, Cameron DW. The role of psychological and behavioral variables in quality of life and the experience of bodily pain among persons living with HIV. *Journal of pain and symptom management.* 2008;36(3):247-258.
45. Effros RB, Fletcher CV, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2008;47(4):542-553.
46. Gill CJ, Griffith JL, Jacobson D, Skinner S, Gorbach SL, Wilson IB. Relationship of HIV viral loads, CD4 counts, and HAART use to health-related quality of life. *Journal of acquired immune deficiency syndromes (1999).* 2002;30(5):485-492.
47. Preau M, Protopopescu C, Spire B, et al. Health related quality of life among both current and former injection drug users who are HIV-infected. *Drug and alcohol dependence.* 2007;86(2-3):175-182.

48. Anastos K, Barron Y, Cohen MH, et al. The prognostic importance of changes in CD4+ cell count and HIV-1 RNA level in women after initiating highly active antiretroviral therapy. *Annals of internal medicine.* 2004;140(4):256-264.
49. Tarwater PM, Gallant JE, Mellors JW, et al. Prognostic value of plasma HIV RNA among highly active antiretroviral therapy users. *AIDS (London, England).* 2004;18(18):2419-2423.
50. Rueda S, Raboud J, Mustard C, Bayoumi A, Lavis JN, Rourke SB. Employment status is associated with both physical and mental health quality of life in people living with HIV. *AIDS care.* 2011;23(4):435-443.
51. Zinkernagel C, Taffe P, Rickenbach M, et al. Importance of mental health assessment in HIV-infected outpatients. *Journal of acquired immune deficiency syndromes (1999).* 2001;28(3):240-249.
52. Lifson AR, Grandits GA, Gardner EM, et al. Quality of life assessment among HIV-positive persons entering the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. *HIV medicine.* 2015;16 Suppl 1:88-96.

Chapter 3

Predictors of Health-Related Quality of Life among HIV-infected Individuals in the HAART Era

Abstract

***Objective**: The aims of this study were: (i). to determine the long-term predictors of HRQOL in our cohort, and (ii). to evaluate the impact of HAART use on changes in HRQOL measures on the long-term.*

***Methods**: Study participants were a nested cohort of the NHS that responded to the SF-36 questionnaire in 2006 and annually thereafter until 2010. Physical component summary (PCSS) and mental component summary (MCSS) scores were computed based on standard algorithms. Mixed linear random effects model was used to estimate the changes in PCSS and MCSS over the four year period of follow-up.*

***Results**: There was no beneficial effect of being in one HAART group compared to the other, and HAART did not lead to changes in HRQOL scores over the period of follow-up. Factors independently predictive of PCSS were being on NPI-HAART (β= 1.13, 95% CI: 0.20, 2.05), being HAART-naïve (β= 1.55, 95% CI: 0.15, 2.95), CD4 count < 200 cells/mm^3 (β= -2.62, 95% CI: -4.31, -0.93), CD4 count 200-499 cells/mm^3 (β= -0.90, 95% CI: -1.57, -0.23), mental comorbidity (β= -3.24, 95% CI: -4.19, -2.29), medical comorbidity (β= -3.80, 95% CI: -5.38, -2.23), AIDS diagnosis (β= -3.38, 95% CI: -4.98, -1.78), 5-yearly increment in age (β= -0.83, 95% CI: -1.12, -0.54) and being married. Every one-year of follow-up also led to an improvement in PCSS for those with medical comorbidity. Factors independently associated with MCSS were CD4 count < 200 cells/mm^3 (β= -2.42, 95% CI: -4.13, -0.71), mental comorbidity (β= -4.38, 95% CI: -5.32, -3.43), and being African American (β= 2.45, 95% CI: 1.35, 3.56).*

***Conclusion**: There is an urgent need to address the modifiable factors predictive of physical and mental HRQOL measures in our cohort specifically mental comorbidity and low CD4 count. Our study did not find any treatment benefit of NPI-HAART over PI-HAART in the long term. Our study supports the frequency of testing for HIV-disease indicators, which informs the need for those not on treatment being placed on treatment or the need to change treatment among those already on treatment.*

Chapter 3

Predictors of Health-Related Quality of Life among HIV-infected Individuals in the HAART Era

3.1: Introduction and Background

In an earlier study (chapter 2), we determined the factors associated with health-related quality of life (HRQOL) measures at baseline for our cohort. In this current study we further investigate the long-term predictors of HRQOL in our cohort, and also examine the changes in HRQOL among participants on different classes of highly active anti-retroviral therapy (HAART) including those who were not on HAART. One major advantage of doing so is that it will be enable us to evaluate the HRQOL trajectory both for those on HAART and those not on HAART, assess the benefit of the frequency of testing for HIV disease indicators (CD4 cell count and plasma viral load) and compare treatment modalities in order to maximize HRQOL in HIV-infected individuals[1].

3.2: Methods

3.2.1: Study Participants and Cohort

The participants for the current study are a nested cohort of the larger Natural History Study cohort, which has been described elsewhere[2-5] (please see chapter 2). Briefly, the United States Military HIV Natural History Study (NHS) is a dynamic cohort of military personnel and their dependents who are followed at five medical centers. Participants included in the current study were those who completed the RAND Short Form 36 (SF-36) at baseline in 2006, and were subsequently followed through September, 2010. All

participants provided informed consent, and approval for this research was obtained from the institutional review board at each participating site.

3.2.2: Definitions and Variable Selections

3.2.2.1: Health-Related Quality of Life Scores

The norm-based the physical (PCS) and mental (MCS) component summary scores 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[6,7]. The PCS and MCS scores were the outcome variables in our analyses, and were measured over 5 yearly time points, 2006 to 2010.

3.2.2.2: HAART (Treatment) Variable

We defined HAART as a combination of at least three antiretroviral agents in line with previous investigations for this cohort[3]. In line with our baseline study, HAART treatment was categorized into four groups: (i) protease inhibitor-based HAART (PI-HAART), for HAART with at least one protease inhibitor in the combined HAART regimen; (ii) non-protease-inhibitor-based HAART (NPI-HAART), for HAART with no protease inhibitor in the combined HAART regimen; (iii) HAART-naïve group (HAART-N) for those who had never been on HAART; and (iv) an Off-HAART group, for those who were not on HAART at the time of survey but have had HAART in the past.

3.2.2.3: Covariates

Covariates selected were in line with those included for the cross-sectional study (please see chapter 2). These 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), viral load, CD4+ count, medical comorbidity, mental comorbidity, AIDS diagnosis, and HIV duration. 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 was in line with the 1993 Centers for Disease Control and Prevention criteria, with the exception of an isolated CD4 cell count <200 cells/mL as CD4 was analyzed separately. Medical co-morbidity referred to chronic medical conditions, and was classified as having no comorbidity or having one or more comorbidity. Mental comorbidity was classified similarly.

3.3: 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. Similar to the baseline study we excluded 14 participants on a non-HAART anti-retroviral therapy.

3.4: Statistical Analyses

We tabulated the baseline (2006) characteristics of participants using proportions for count variables and medians and interquartile ranges for numeric variables while we used bar charts and graphs to summarize the longitudinal data from 2006 to 2010. Bar charts were used to display percentages of participants by HAART groups for categorical variables while graphs displayed the means and their corresponding 95% confidence intervals for numeric variables. We used random effects model (REM) to estimate the

beta (β) coefficients and corresponding 95% confidence intervals for the variables. We used the restricted maximum likelihood (REML) estimation method to estimate β, and used an unstructured covariance structure[8] to account for correlation of the random effects. Like in the baseline study, we constructed different models for PCSS and MCSS. For each outcome variable, we first conducted univariate analysis for the explanatory variables and only variables that achieved <0.2 significance level were included for the final multivariate analyses. We further utilized the minus 2 log likelihood ratio (-2LLR) test to determine the number of variables that made the most parsimonious models. Variables with significant interaction with time in the univariate analyses were tested for significant interaction in the multivariate models. All variables, with the exception of race and gender, were treated as time-dependent variables. Time was treated as a numeric variable although we also compared the results with treating it as a discrete variable. All statistical analyses and graphs were performed using SAS 9.3 [SAS Institute Inc., Cary, NC].

3.3: Results

There were 812 participants in 2006 (baseline) who met the study eligibility criteria, and their characteristics are displayed in table 3.1a. Participants were mostly male (95%), with Caucasian and African-American making up 48% and 40% respectively. 27% of participants had mental comorbidity, 16% medical comorbidity and 10% had AIDS at baseline. The median age at baseline was 42 years (interquartile range [IQR]: 34-47), and the median physical and mental component summary scores were respectively 54.41 (IQR, 45.95 – 57.48) and 50.77 (IQR, 44.06 – 54.05). Table 3.1b shows the number of participants per HAART group per year of follow-up, the total number of participants who responded to the SF-36 questionnaire in any given year, the number of non-

responders, and the number of participants with missing values for one or more variables among responders.

In the univariate PCSS analyses, there was no significant interaction between the treatment (HAART) and time variables, p=0.6 (table 3.2.a, figures 3.1.a-d). Also, there was no significant effect of treatment on changes in PCS scores over the period of follow-up (p=0.7). Compared to participants in the PI-HAART group, the PCS scores of participants in the NPI-HAART and HAART-naïve groups were respectively higher by 3.6 (95% confidence interval [CI]: 2.11-5.94) and 2.11 (95%CI: 0.65-3.38) (tables 3.2.a. and figures 3.1.a-c). In the multivariate model (most parsimonious), the differences in scores were respectively 1.55 and 1.13 for HAART-naïve and NPI-HAART but remained statistically significant (table 3.3.a). There was no significant difference in PCS scores between the Off-HAART and PI-HAART groups both in the univariate and multivariate models (tables 3.2.a, 3.3.a, fig. 3.1.a, 3.1.d). The change in PCS scores for every one year increment from baseline in the multivariate PCSS model was -0.03 (p=0.8). In the univariate MCSS model, no significant interaction was noted between the treatment (HAART) and time variables, and there were no significant treatment effects on changes in MCS scores over the follow-up period (table 3.2.b and fig. 3.1.b). There was also no significant difference in MCS scores by HAART group.

Other factors that were independently predictive of physical functional health were CD4 count <200 cells/mm^3 (β: -2.62; 95%CI: -4.31 – -0.93), CD4 count 200-499 cells/mm^3 (β: -0.90; 95%CI: -1.57 – -0.23), AIDS diagnosis (β: -3.38; 95%CI: -4.98 – -1.78), medical (β: -3.80; 95%CI: -5.38 – -2.23), and mental (β: -3.24; 95%CI: -4.19 –

-2.29), comorbidities, being married (β: 0.99; 95%CI: -1.88 – -0.11), and age of participants with every 5 year increment in age leading to a reduction in PCS scores by -0.83 (95%CI: -1.12 – -0.54), . There was also significant interaction between medical comorbidity and time (β: 0.72, 95% CI: 0.32 – 1.13). Although the duration of HIV infection was predictive of physical functional health in the univariate analysis, it was not significantly predictive of physical functional health after adjusting for in the multivariate model. Factors that were independently predictive of mental functional health were being African American (β: 2.45, 95% CI: 1.35 – 3.56), CD4 count <200 cells/mm^3 (β: -2.42, 95% CI: -4.13 – -0.71), and mental comorbidity (β: -4.38, 95% CI: -5.32 – -3.43). Although plasma viral load >50 copies/mL was predictive of mental functional health in the univariate REM, this was no longer statistically significant in the multivariate model (β: -0.61, 95% CI: -1.28 – 0.05).

3.4: Discussion

The goals of this study were two-fold: 1) to determine the long-term predictors of HRQOL, and 2) to evaluate if there were differences in HRQOL measures by HAART groups. Studies on HRQOL in HIV-infected individuals have generally been used to address whether HAART improves HRQOL[9,10], and while it is generally agreed that HAART improves HRQOL in the short-term[9-11], the evidence of the impact of HAART on HRQOL on the long term is not clear[9]. The overall effect of HAART on HRQOL has been described as a balance between improvements in HIV-related morbidity and better life-expectancy on the one hand and medication adverse effects on the other hand[1,11]. This picture is further complicated by the increasing age-associated comorbidities[12,13] in

HIV-infected populations, the differential handling of HAART by older individuals[14] and the very effects of aging on the individual including physical senescence[11].

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[15-17]. (Also see chapter 2). While side effects are not unique to a specific class of HAART medications, the protease inhibitors have been implicated as having greater adverse effects including morphological changes and metabolic disturbances[18]. To that end, we grouped we 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) from those who had never been on HAART (HAART-naive).

In our earlier study (chapter 2), we did not find any statistically significant differences in physical or mental functional health among the HAART groups in the multivariate models although those in the NPI-HAART and HAART-naïve groups had significantly higher PCS scores compared to the PI-HAART group in univariate analyses. In this study we specifically investigated the treatment effect of being on NPI-HAART compared to being on PI-HAART but did not find any statistically significant difference as evidenced by the lack of significant interaction between NPI-HAART and time (table 3.2.a) or near parallel lines of the treatment groups (figures 3.1.a. and 3.1.b). There were also no significant interactions among HAART-naive and Off-HAART and time. Furthermore, PCS scores were on average stable for the four groups over the period of follow-up. However, while there was no PCS score difference between the PI-HAART and Off-

HAART groups, there were statistically significant differences in PCS scores in the HAART-naïve and NPI-HAART groups both in the univariate and multivariate models. Similarly, there were no significant treatment benefit of being in the other groups over PI-HAART in terms of MCS scores, and being in these groups did no lead to changes in MCS scores over time. Also, the MCS scores in NPI-HAART, HAART-naïve and Off-HAART groups were not significantly different from those of PI-HAART.

In a five year longitudinal study of a French HIV-population on PI-HAART, Protopopescu et al, found that PCS scores improved in the first year following initiation of treatment but remained stable over the rest of the follow-up period[19]. Being that participants had already been on HAART for years before the HRQOL questionnaires were administered in our cohort, it was not entirely surprising that we did not see any initial improvement in PCS scores. Our findings of no significant treatment benefit of NPI-HAART over PI-HAART on participants HRQOL scores is different from the findings of others[18,20,21] who reported improved quality of life in their studies. We note, however, that the studies by Potard et al[18] and Campo et al[21] involved treatment switch without the benefit of a concurrent PI-HAART comparison group while that by Fumaz et al[20] involved 100 participants who had failed a PI-HAART regime before randomization into another PI-HAART or efavirenz based HAART.

Although PCS score of the HAART-naïve group was still higher than that of the PI-HAART group in the multivariate model, those who were HAART naive showed an average decline in PCS scores by 0.5 points (p=0.5) over the follow-up period. This finding is not unexpected because in our cohort, participants are monitored regularly on a six-monthly interval[22] for disease indicators (CD4 cell counts and viral loads), and those

with worsening disease indicators are placed on HAART. Therefore, the HAART-naive group may not reflect the expected downward trajectory in HRQOL[1] because of the steady movement of participants in this group to the treatment arms (PI and NPI). By the same token, it may be argued that improvements in HRQOL may be blunted by additions of participants with less favorable HRQOL scores over time. The significant differences in PCS scores 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 scores over the period of follow-up similar to the findings by others[23,24] but different from the SMART trial which found a decline in HRQOL among those on CD4 count-guided treatment interruption[25]. Like the HAART-naïve group, participants with worsening disease indicators are also 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 scores, we found that for every one year increment in duration from baseline, the presence of medical comorbidity led to improvement in PCS score 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 contacts with the healthcare system and other specialists which may positively impact their PCS as their comorbid conditions improve or become stable. Furthermore, coping strategies used for their comorbidities may also help with their HIV-infection with net improvement in physical functioning. Similar to the findings by other investigators and in keeping with clinical experience, we also found

that lower CD4 counts[19,26], AIDS diagnosis[19,27], and mental comorbidities[26,27] were negatively predictive of physical functional health on the long term. Increasing age was also a negative predictor of physical functional health similar to the findings of others[1,19,26]. Like in our baseline study, being married was negatively predictive of physical functional health. HIV duration although significant in the univariate model was not independently predictive of PCS score, a finding that is similar to our baseline study and that of Jia et al[28,29].

Only three factors were independently predictive of mental functional health in our cohort, and these were CD4 count <200 cells/mm^3, mental comorbidity and being African-American, and these findings were similar to our baseline study (chapter 2). Although the impact of mental comorbidity on mental functional health was not nearly as dramatic as we found in our baseline study (-4.36 vs. -6.15), it still remained the most significant predictor of MCS scores in our cohort (chapter 2). Based on our current and baseline studies, we believe that there is a need to aggressively address the mental health needs of HIV-infected military personnel by both clinicians and policy makers 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 362 (45%) participants left 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 high percentage of dropout has the potential to bias our results but this is unlikely considering the similarity

of our current results to the baseline findings for the entire cohort. Also, the proportions of participants over the years did not seem to be affected by demographic characteristics, HIV-disease indicators or comorbidities (figures 3.3 to 3.11). 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). Investigators in a longitudinal French HIV cohort did not find any difference in their results between the traditional linear mixed random effects model (as in our current study) and the joint parameter-dependent selection model that accounted for non-ignorable dropout. We note here that the retention rate was much better with our cohort: 77% vs. 63.5% for the French study at the end of the first year of follow-up and 45% vs. 23.8% for the French study at the end of follow-up period.

Another limitation of our study is the predominantly male distribution of the cohort, which may limit the generalizability of our result. As we stated earlier, confounding by indication[30], which tends to be a major drawback to most clinical epidemiologic studies evaluating treatment benefits, may partly explain the better physical functional health we observed in the HAART-naïve group over the PI-HAART group. Also, residual confounding may have contributed to better physical functional health observed for these groups in our current study. Some of the ways to address these short-comings will be either through randomization, which is impossible being an observational study, or by propensity scoring, which is 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-based HAART are associated with more adverse effects and so will be more detrimental to participants HRQOL measures, we did not find treatment benefit of NPI-based HAART over PI-HAART. Also, those on HAART in our cohort had stable HRQOL scores over the period of follow-up. Our study also shows that lower CD4 count and mental comorbidities were by far the most important modifiable risk factors affecting the overall HRQOL (PCS and MCS) of participants while AIDS, and medical comorbidities specifically affected physical functional health. Addressing these risk factors will help improve the functional health of participants. Further improvement in mental functional health could be achieved through such measures as social support and active coping as suggested by previous investigators[26,28]. Regular clinical monitoring of HIV-infected persons as well as testing for HIV disease indicators (CD4 count and plasma viral loads) are useful in deciding when to start HAART in the HAART naïve. Furthermore, these measures are useful in determining those doing well on their treatment modalities, as well as in individuals who are off medications from various reasons including drug toxicities. The relatively stable HRQOL scores in the HAART naïve and the Off-HAART groups over time therefore supports the current monitoring strategy of the NHS as those with 'worsening' HIV-disease indicators are moved to either the PI or NPI treatment arms. However, because

this study is with a nested fixed cohort, further research on the entire dynamic cohort will be needed to corroborate these findings.

3.5: Conclusion

In this observational study, we found that the effect of non-protease inhibitors on participants' mean HRQOL scores was not significantly different from that of participants on the protease inhibitors. Also, there were no significant changes in HRQOL measures by HAART groups over the period of follow-up. The group differences in physical HRQOL scores is attributable to baseline measures, residual confounding and confounding by indication. We believe that to improve the functional health of participants, there is need to aggressively address the modifiable risk factors that predict low HRQOL especially mental comorbidity and lower CD4 count.

3.6: Tables

Table 3.1a: 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 (Retired/Civilians)	377 (46.43)
Married, Yes	270 (33.25)
Medical Comorbidity, Yes	131 (16.13)
Mental Comorbidity, Yes	219 (26.97)
AIDS, Yes	82 (10.10)
HAART	
PI-Based	288 (35.47)
Non-PI-Based	318 (39.16)
HAART-Naïve	106 (13.05)
Off-HAART	100 (12.32)
Viral Load > 50 copies/mL	
Yes	356 (43.84)
No	455 (56.03)
Missing	1 (0.12)
CD4 Count Groups	
<200 cells/mm^3	47 (5.79)
200-499 cells/mm^3	322 (39.66)
>499 cells/mm^3	441 (54.31)
Missing	2 (0.25)
Age (years) – Median (IQR)	42.00 (37.00 – 47.00)
CD4 Count (x 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 from HIV Diagnosis (years) – Median (IQR)	10.00 (5.00 – 16.00)
PCSS – Median (IQR)	54.41 (45.95 – 57.48)
MCSS – Median (IQR)	50.77 (44.06 – 54.05)

Table 3.1.b: HAART groups of participants from 2006 to 2010

Year	TPWCQOL	NPSNHSBNQ	MisValue	TP – Used	Off-HAART	HAART-Naive	NPI-HAART	PI-HAART
2006	812	0	9	803	100	104	315	284
2007	626	83	4	622	66	63	264	229
2008	535	78	3	532	50	33	254	195
2009	514	39	3	511	32	32	249	198
2010	362	66	7	355	22	13	186	136

TPWCQOL = Total Participants who Completed the SF-36 Questionnaire. Should equal sum of TP and MisVal.
NPSNHSBNQ = Number of Participants still in the NHS Cohort but did not complete the SF-36 Questionnaire. Based on having CD4 count and/or pVL
TP – Used = Total Participants Available for Statistical Analyses
MisVal = Missing one or more covariates

Table 3.2.a: Univariate Analyses for PCSS including Testing for Interaction Between HAART and Time

Variable	PCSS Model with Treatment Effect				PCSS Model without Treatment Effect			
	β	**SE**	**95%CI**	**P-Value**	**β**	**SE**	**95%CI**	**P-Value**
HAART								
HAART-Naïve	**4.02**	**0.98**	**2.11 – 5.94**	**<.0001**	**3.67**	**0.64**	**2.40 – 4.93**	**<.0001**
Non-PI-Based-HAART	**2.02**	**0.70**	**0.65 – 3.38**	**0.0038**	**2.11**	**0.56**	**1.01 – 3.20**	**0.0002**
Off-HAART	0.62	0.93	-1.33 – 2.56	0.5346	0.44	0.73	-1.00 – 1.88	0.5437
PI-Based-HAART	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (One-Yearly Increment)	-0.04	0.13	-0.31 – 0.22	0.7397	-0.09	0.08	-0.25 – 0.07	0.2653
HAART*Time								
HAART-Naïve*Time	-0.48	0.35	-1.17 – 0.21	0.49				
Non-PI-Based-HAART*Time	-0.004	0.18	-0.36 – 0.35	0.71				
Off-HAART*Time	0.03	0.34	-0.63 – 0.67	0.68				
PI-Based-HAART*Time	Ref.	Ref.	Ref.	Ref.				
Intercept	**49.59**	**0.54**	**48.54 – 50.64**	**<.0001**	**49.64**	**0.50**	**48.66 – 50.62**	**<.0001**

Table 3.2.b: Univariate Analyses for MCSS including Testing for Interaction Between HAART and Time

Variable	MCSS Model with Treatment Effect				MCSS Model without Treatment Effect			
	β	**SE**	**95%CI**	**P-Value**	**β**	**SE**	**95%CI**	**P-Value**
HAART								
HAART-Naïve	-1.54	0.99	-3.48 – 0.39	0.1184	-0.43	0.72	-1.84 – 0.98	0.5507
Non-PI-Based-HAART	-0.01	0.70	-1.38 – 1.36	0.9837	0.30	0.49	-0.66 – 1.25	0.5421
Off-HAART	-1.91	1.00	-3.88 – 0.05	0.0565	-0.69	0.64	-1.96 – 0.58	0.2851
PI-Based-HAART	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Time (One-Yearly Increment)	-0.04	0.14	-0.31 – 0.22	0.7467	0.09	0.08	-0.08 – 0.08	0.2926
HAART*Time								
HAART-Naïve*Time	0.56	0.36	-1.17 – 0.21	0.1167				
Non-PI-Based-HAART*Time	0.11	0.18	-0.36 – 0.35	0.5284				
Off-HAART*Time	0.53	0.34	-0.63 – 0.67	0.1198				
PI-Based-HAART*Time	Ref.	Ref.	Ref.	Ref.				
Intercept	**48.10**	**0.53**	47.05 – 49.15	<.0001	47.76	0.45	46.87 – 48.65	<.0001

Table 3.3.a: Multivariate Predictors of Physical (PCSS) and Mental (MCSS) Component Summary Scores

Variable	PCSS Model				Most Parsimonious PCSS Model			
	β	**SE**	**95%CI**	**P-Value**	**β**	**SE**	**95%CI**	**P-Value**
HAART								
HAART-Naïve	**1.52**	**0.74**	**0.08 – 2.97**	**0.0388**	**1.55**	**0.71**	**0.15 – 2.95**	**0.0299**
Non-PI-Based-HAART	**1.13**	**0.48**	**0.19 – 2.07**	**0.0187**	**1.13**	**0.47**	**0.20 – 2.05**	**0.0171**
Off-HAART	0.26	0.63	-0.97 – 1.50	0.6761	0.25	0.63	-0.98 – 1.49	0.6862
PI-Based-HAART	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Age (Years, 5-yearly Increment)	**-0.79**	**0.18**	**-1.14 – -0.43**	**<.0001**	**-0.83**	**0.15**	**-1.12 – -0.54**	**<.0001**
CD4 Category								
CD4 Count <200	**-2.61**	**0.86**	**-4.30 – -0.92**	**0.0025**	**-2.62**	**0.86**	**-4.31 – -0.93**	**0.0024**
CD4 Count 200 – 499	**-0.90**	**0.34**	**-1.57 – -0.23**	**0.0085**	**-0.90**	**0.34**	**-1.57 – -0.23**	**0.0084**
CD4 Count >499	**Ref**	**Ref**	**Ref**	**Ref.**	**Ref**	**Ref**	**Ref**	**Ref.**
Duration of HIV (Years)	0.03	0.06	-0.08 – 0.14	0.6268				
AIDS	**-3.36**	**0.83**	**-4.98 – -1.74**	**<.0001**	**-3.38**	**0.81**	**-4.98 – -1.78**	**<.0001**
Medical Comorbidity	**-3.83**	**0.80**	**-5.41 – -2.25**	**<.0001**	**-3.80**	**0.80**	**-5.38 – -2.23**	**<.0001**
Mental Comorbidity	**-3.19**	**0.49**	**-4.16 – -2.23**	**<.0001**	**-3.24**	**0.48**	**-4.19 – -2.29**	**<.0001**
Married	**-0.98**	**0.45**	**-1.87 – -0.09**	**0.0318**	**-0.99**	**0.45**	**-1.88 – -0.11**	**0.0277**
Rank								
Civilian/Retired	-1.67	1.07	-3.76 – 0.42	0.1178				
Enlisted	-0.91	1.05	-2.98 – 1.16	0.3892				
Officer	Ref.	Ref.	Ref.	Ref.				
Medical Comorbidity*Time	**0.73**	**0.21**	**0.33 – 1.14**	**0.0004**	**0.72**	**0.21**	**0.32 – 1.13**	**0.0005**
Intercept	**60.28**	**1.80**	**56.75 – 63.80**	**<.0001**	**59.72**	**1.33**	**57.12 – 62.32**	**<.0001**

Table 3.3.b: Multivariate Predictors of Mental Component Summary Scores (MCSS)

Variable	MCSS Model				Most Parsimonious MCSS Model			
	β	**SE**	**95%CI**	**P-Value**	**β**	**SE**	**95%CI**	**P-Value**
CD4 Category								
CD4 Count <200	**-2.34**	**0.87**	**-4.06 – -0.63**	**0.0074**	**-2.42**	**0.87**	**-4.13 – -0.71**	**0.0056**
CD4 Count 200 – 499	-0.55	0.35	-1.23 – 0.13	0.1153	-0.57	0.35	-1.24 – 0.11	0.1014
CD4 Count >499	Ref.	Ref.	Ref.	Ref.	Ref	Ref	Ref	Ref.
Plasma Viral Load >50copies/mL	-0.63	0.34	-1.29 – 0.04	0.0648	-0.61	0.34	-1.28 – 0.05	0.0717
Medical Comorbidity	-0.32	0.54	-1.34 – 0.70	0.5402				
Mental Comorbidity	**-4.26**	**0.49**	**-5.22 – -3.30**	**<.0001**	**-4.38**	**0.48**	**-5.32 – -3.43**	**<.0001**
Race/Ethnicity								
Non-Hispanic African-America	**2.54**	**0.57**	**1.41 – 3.66**	**<.0001**	**2.45**	**0.56**	**1.35 – 3.56**	**<.0001**
Others	0.87	0.83	-0.76 – 2.51	0.2952	0.89	0.82	-0.73 – 2.50	0.2832
Non-Hispanic White	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Rank								
Civilian/Retired	-1.25	1.03	-3.28 – 0.77	0.2237				
Enlisted	-0.69	1.04	-2.73 – 1.35	0.5034				
Officer	Ref.	Ref.	Ref.	Ref.				
Intercept	49.25	0.99	47.30 – 51.20	<.0001	48.37	0.49	47.41 – 49.34	<.0001

3.7: Figures

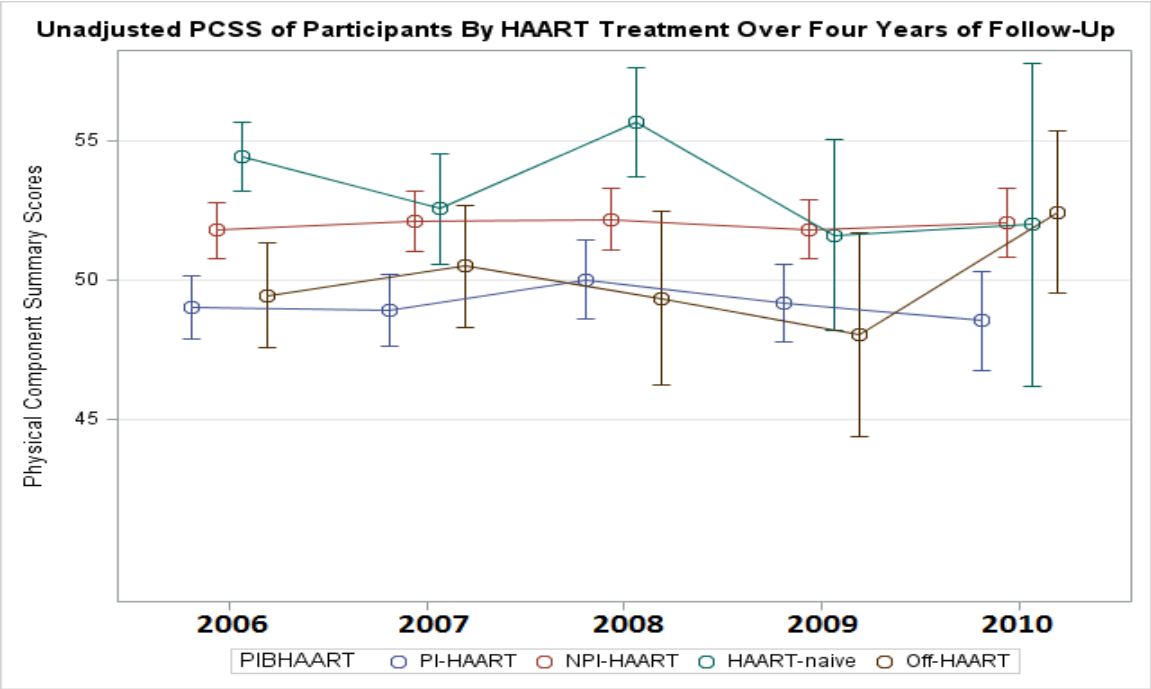


Fig. 3.1.a: Physical Component Summary Scores Over Four Years of Follow-Up

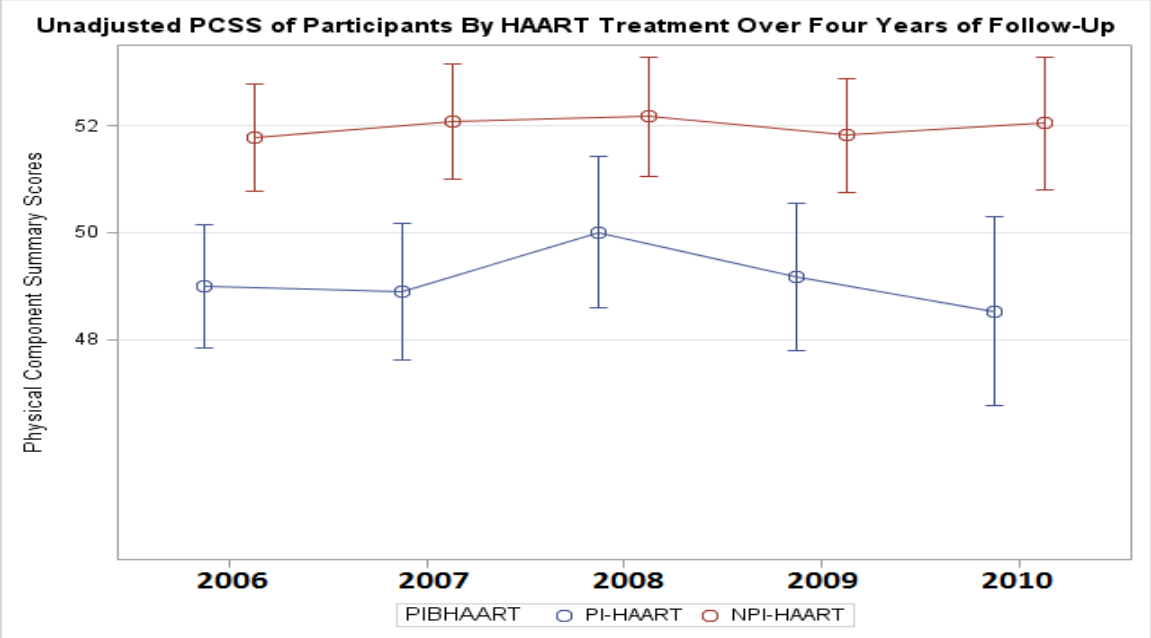


Fig. 3.1.b: Physical Component Summary Scores Over Four Years of Follow-Up: PI/NPI

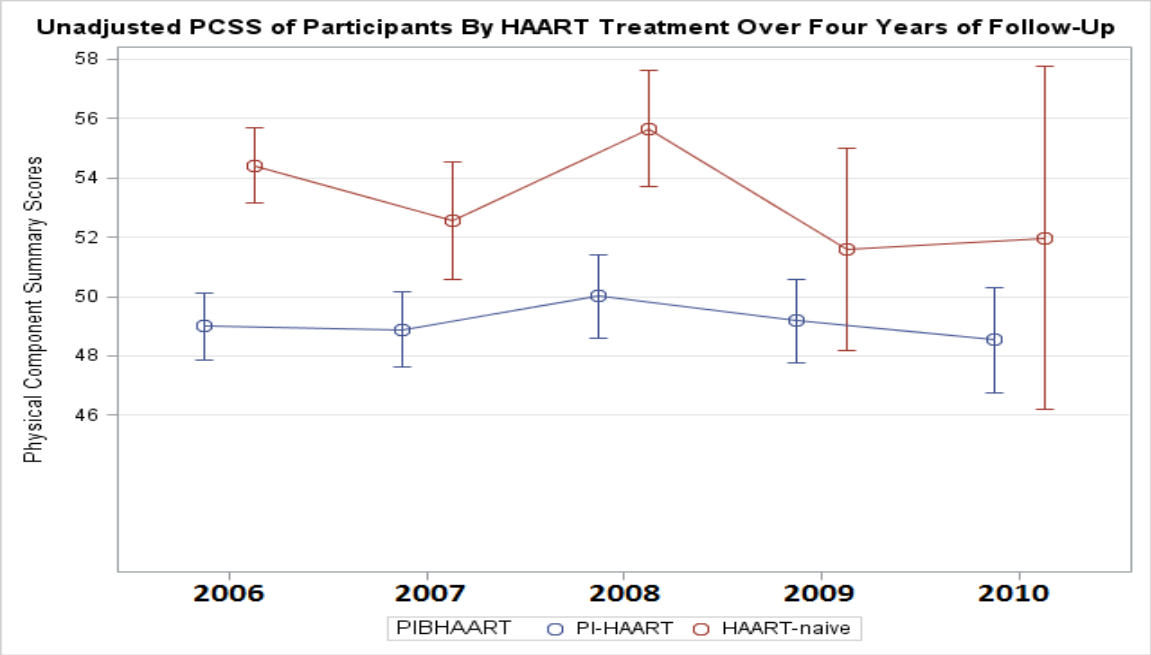


Fig. 3.1.c: Physical Component Summary Scores Over Four Years of Follow-Up: PI/Naïve

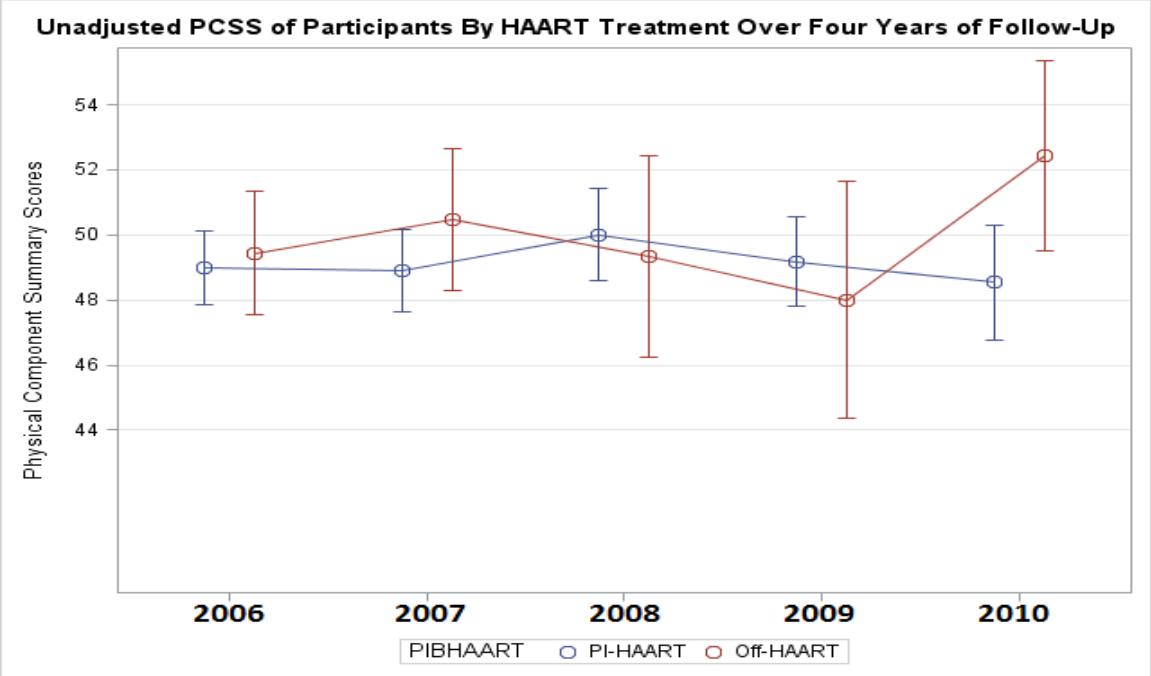


Fig. 3.1.d: Physical Component Summary Scores Over Four Years of Follow-Up: PI/Off

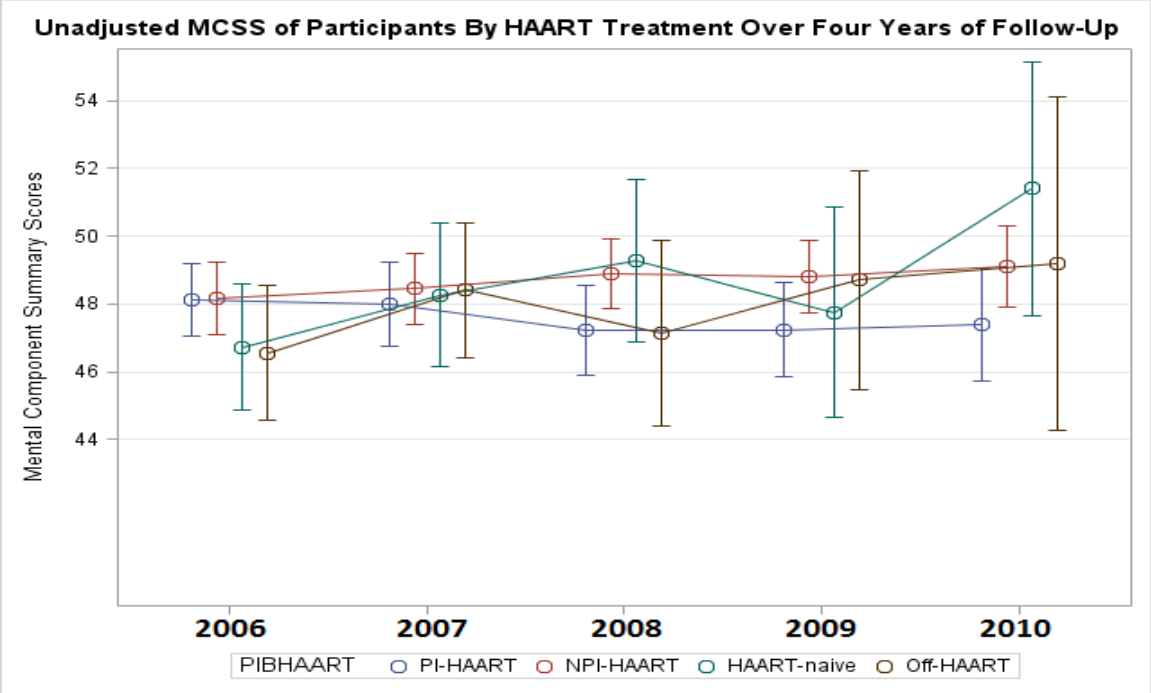


Fig. 3.2.a: Mental Component Summary Scores Over Four Years of Follow-Up

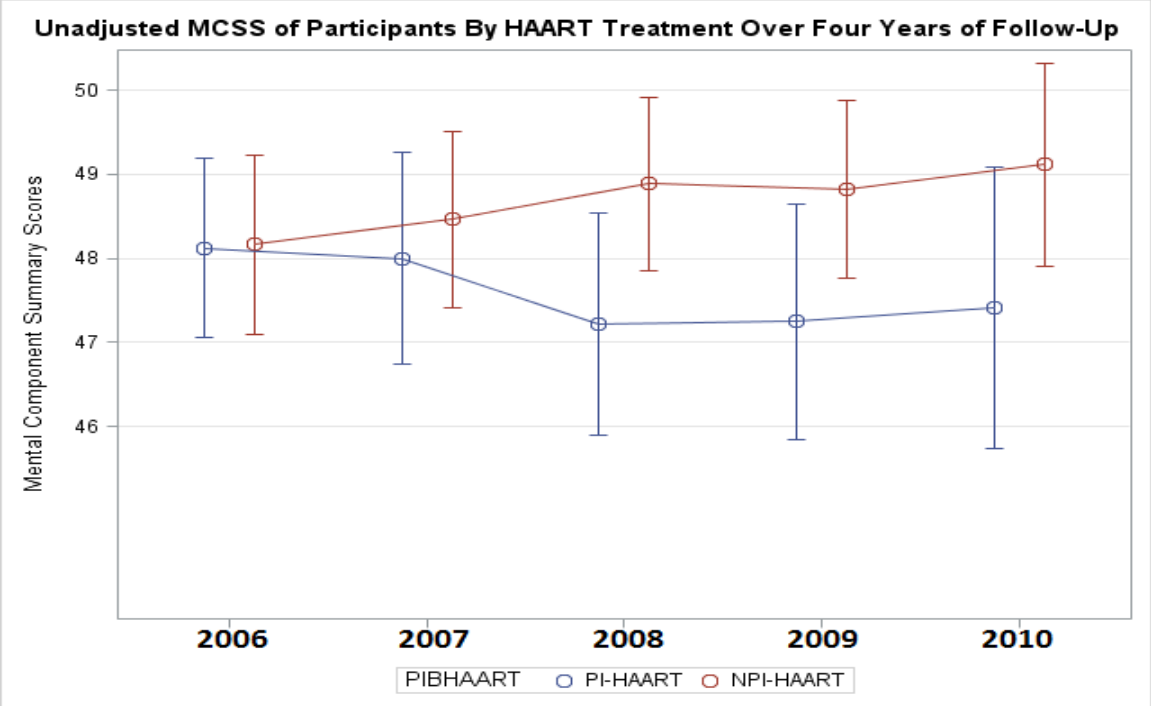


Fig. 3.2.b: Mental Component Summary Scores Over Four Years of Follow-Up: PI/NPI

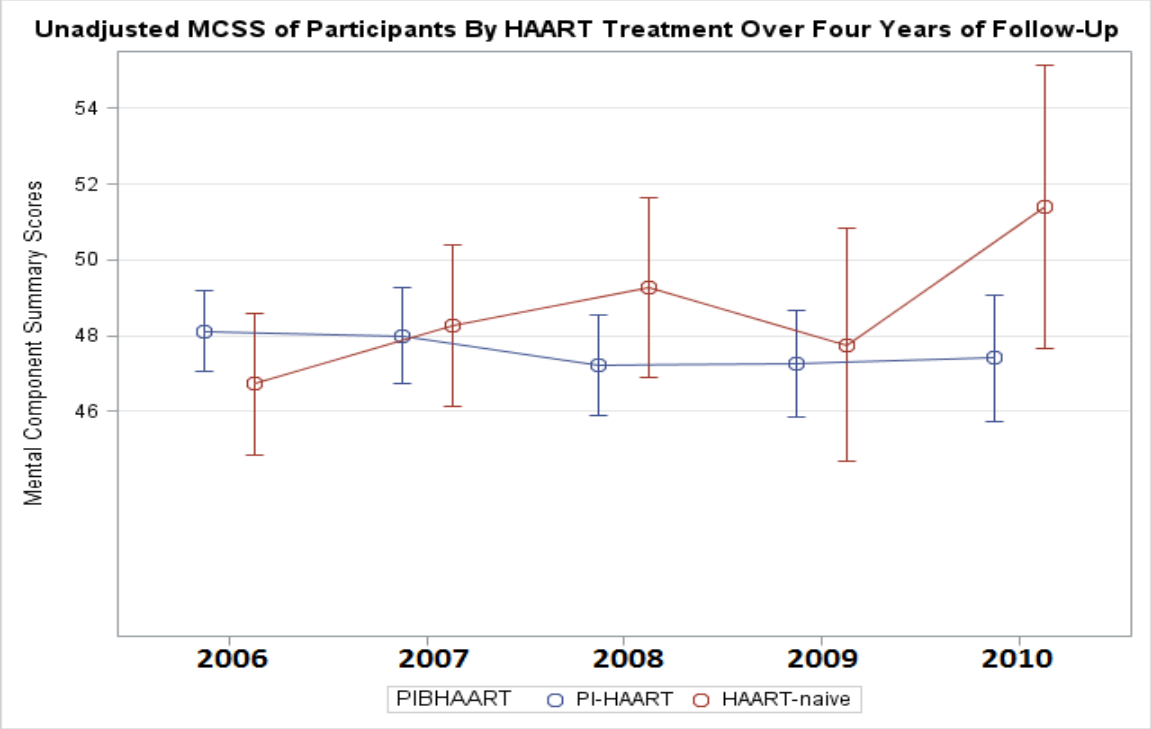


Fig. 3.2.c: Mental Component Summary Scores Over Four Years of Follow-Up: PI/Naïve

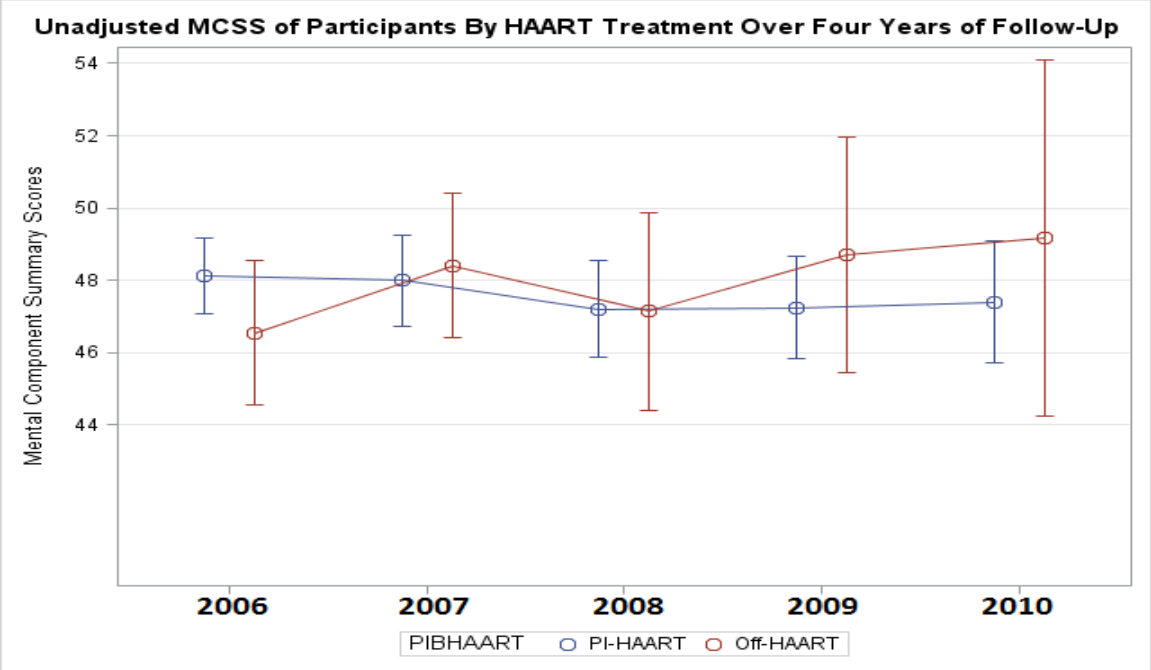


Fig. 3.2.d: Mental Component Summary Scores Over Four Years of Follow-Up: PI/Off

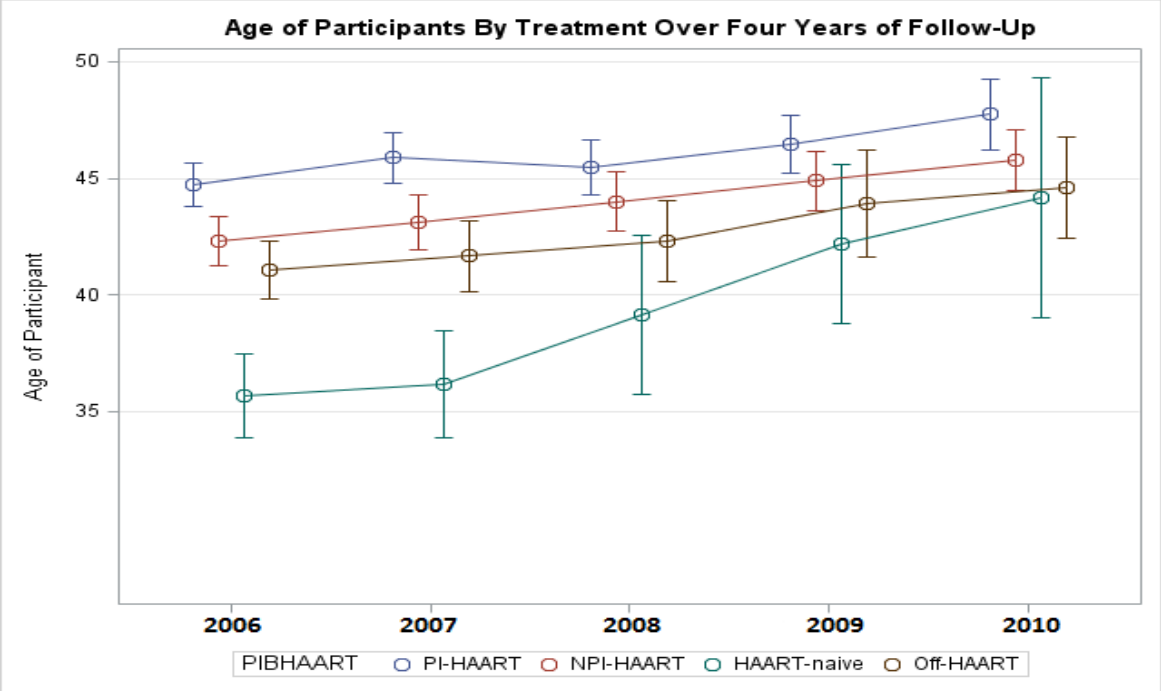


Fig. 3.3: Age of Participants by Treatment Groups Over Four Years of Follow-Up

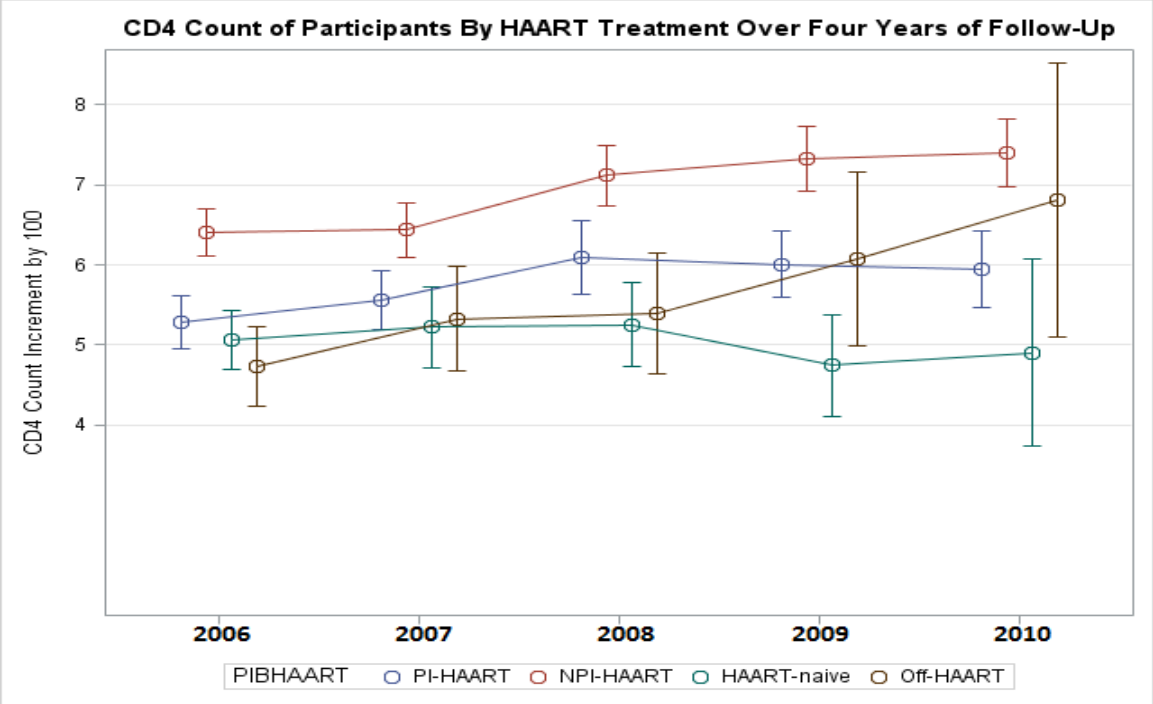


Fig. 3.4: CD4 Count (cells/mm^3) by Treatment Group Over Four Years of Follow-Up

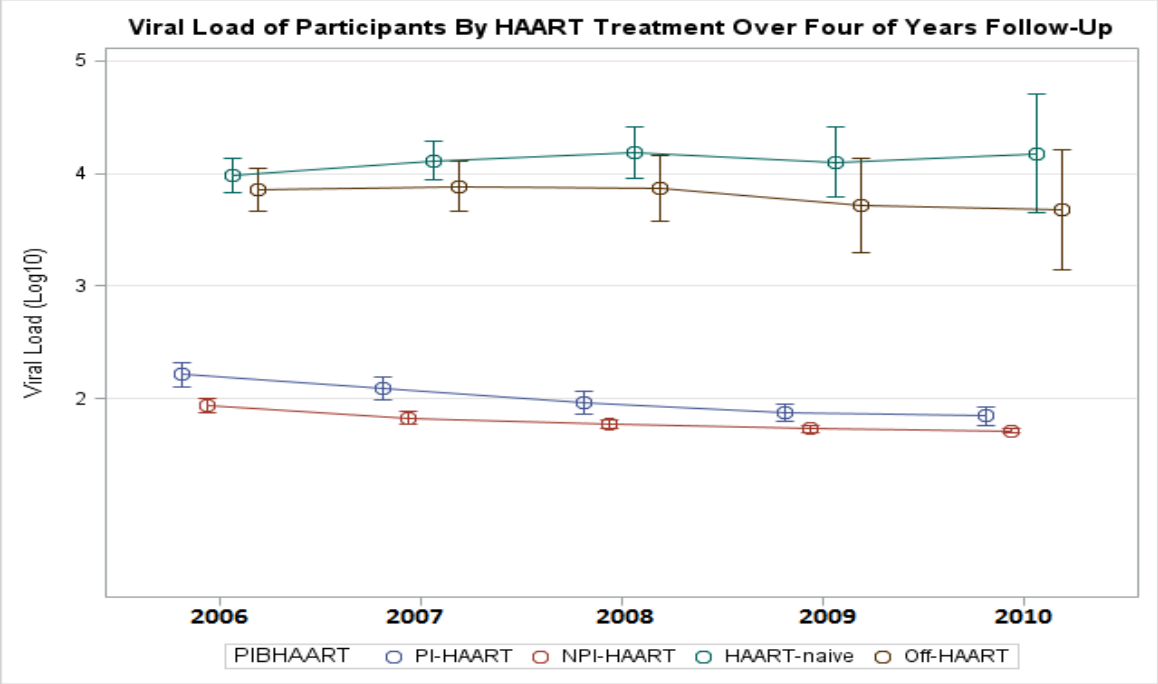


Fig. 3.5: Plasma Viral Load (log_{10}) by Treatment Group Over Four Years of Follow-Up

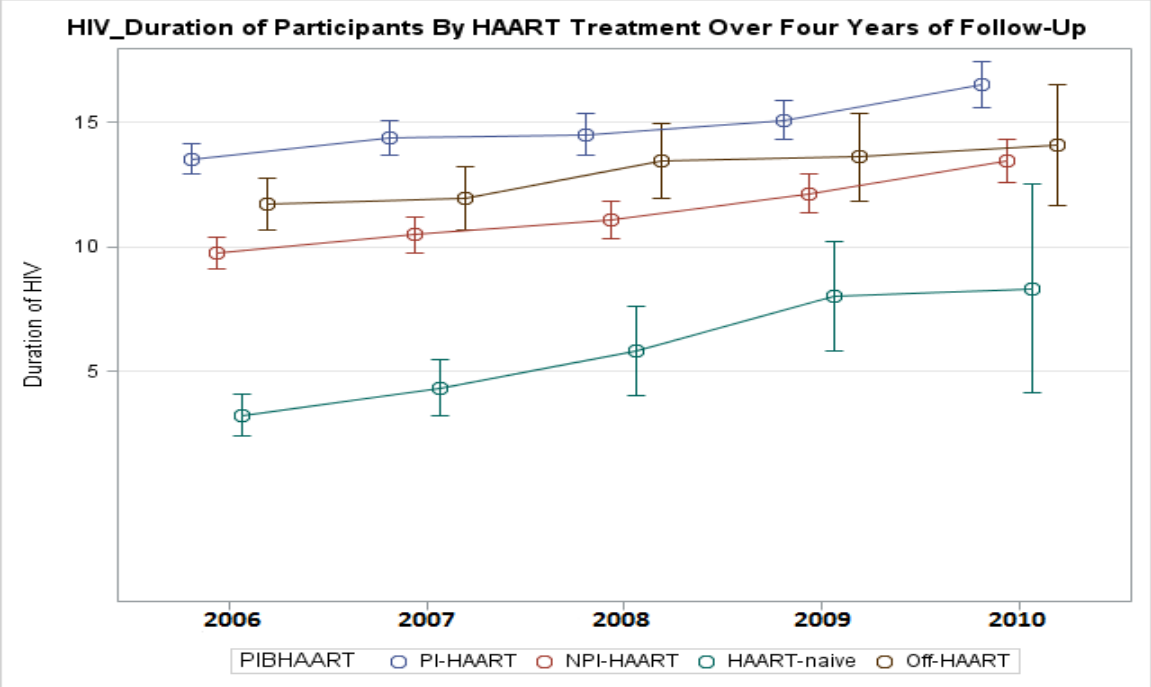


Fig. 3.6: Duration of HIV (Years) by Treatment Group Over Four Years of Follow-Up

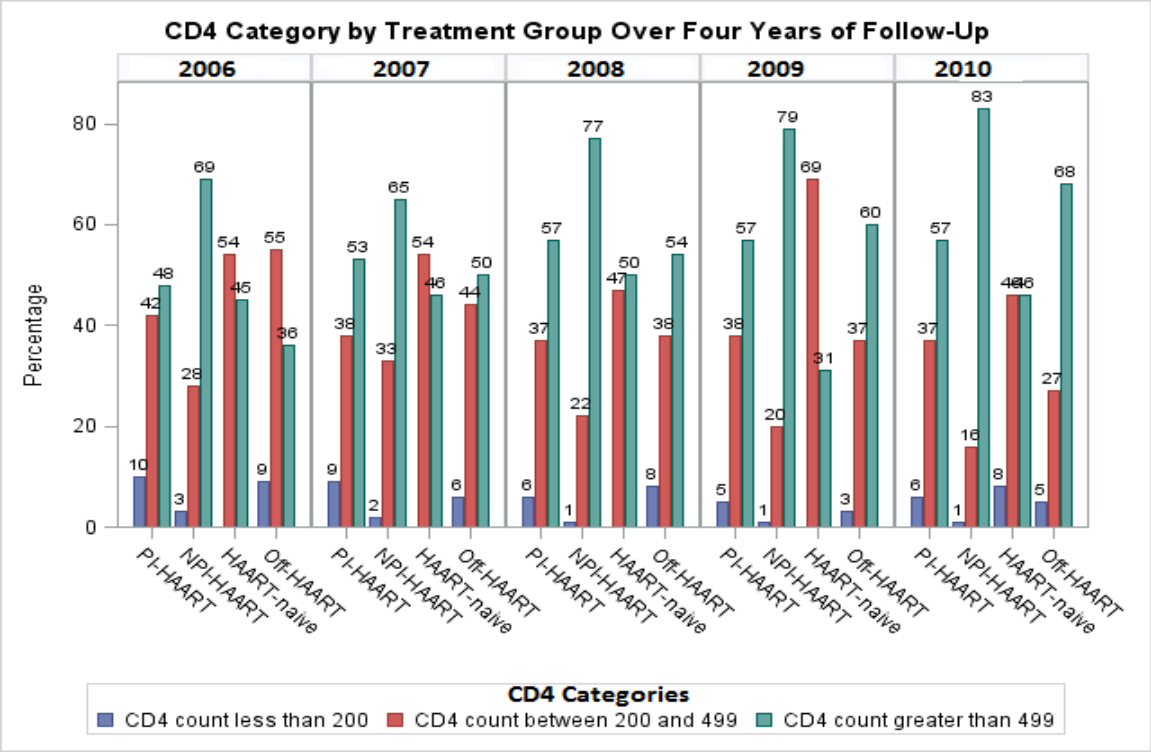


Fig. 3.7: CD4 Categories by Treatment Group Over Four Years of Follow-Up

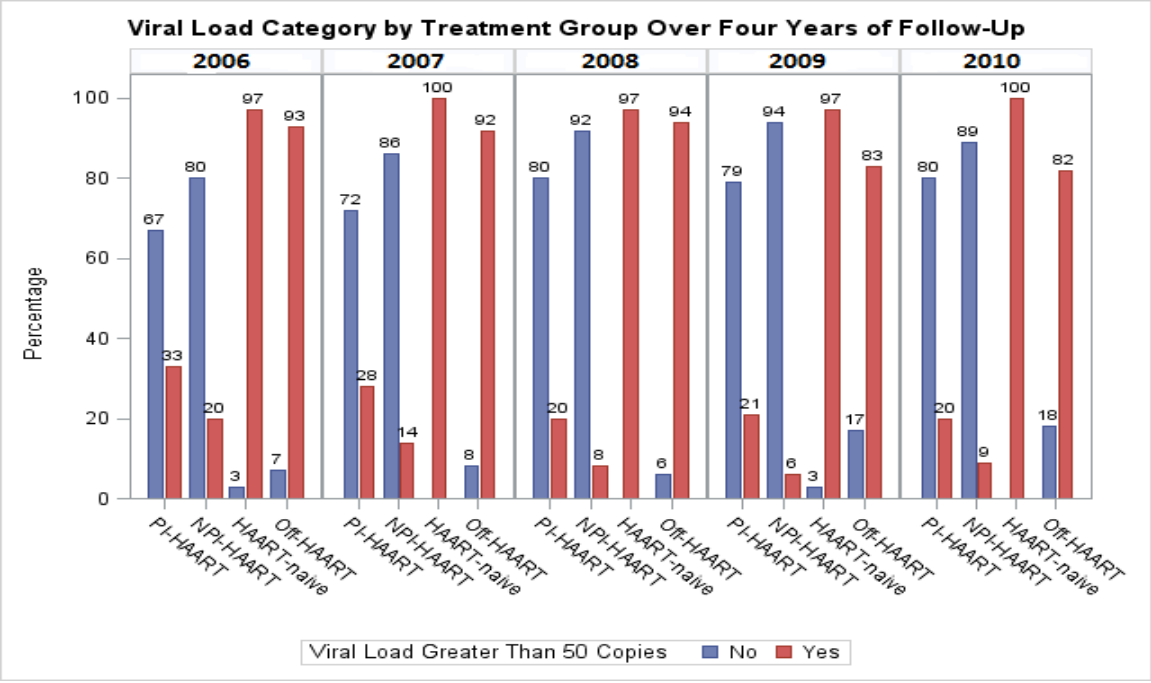


Fig. 3.8: Viral Load Categories by Treatment Group Over Four Years of Follow-Up

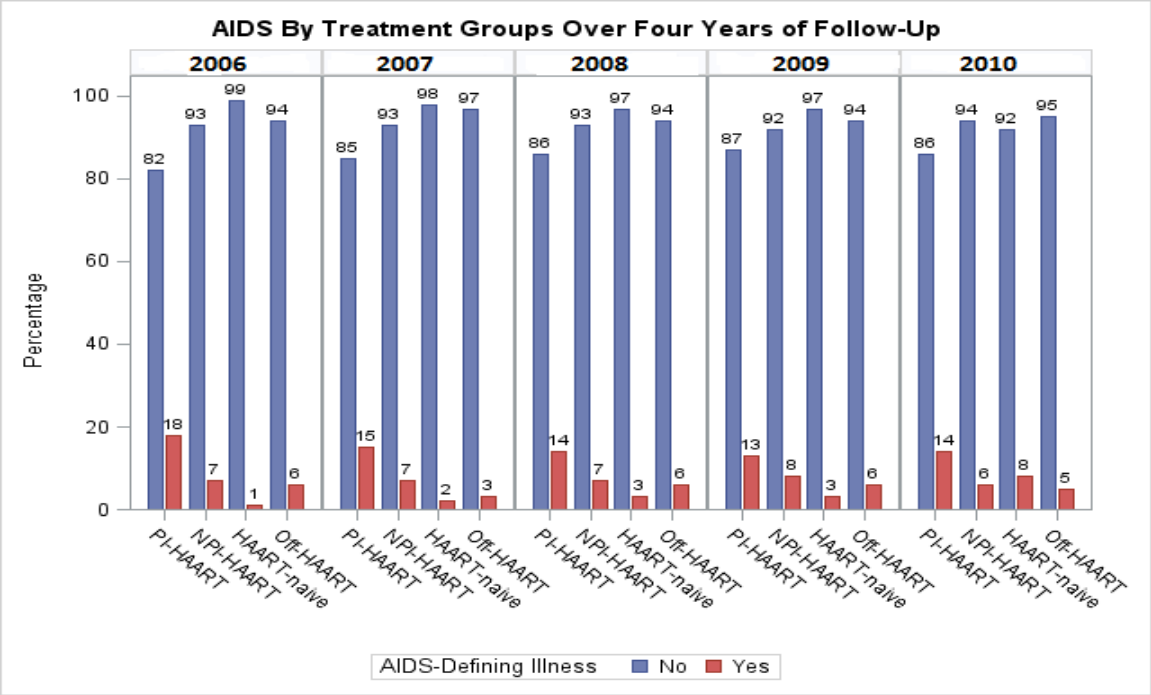


Fig. 3.9: AIDS-Defining Illnesses by Treatment Group Over Four Years of Follow-Up

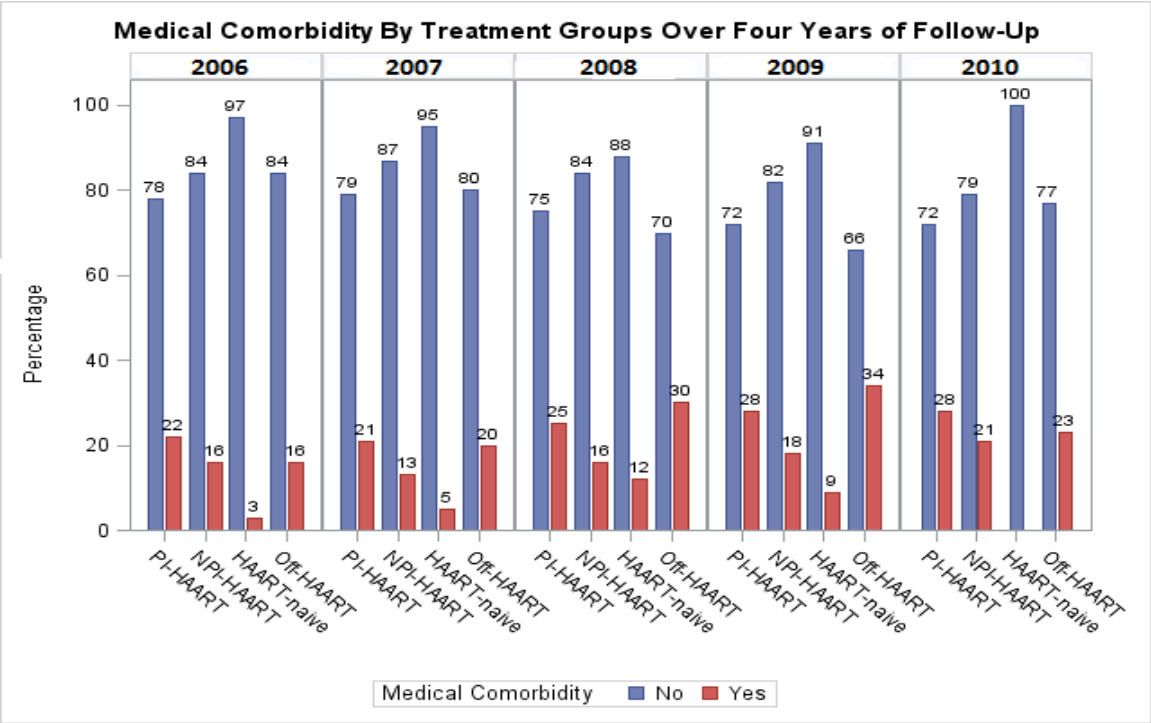


Fig. 3.10: Medical Comorbidity by Treatment Group Over Four Years of Follow-Up

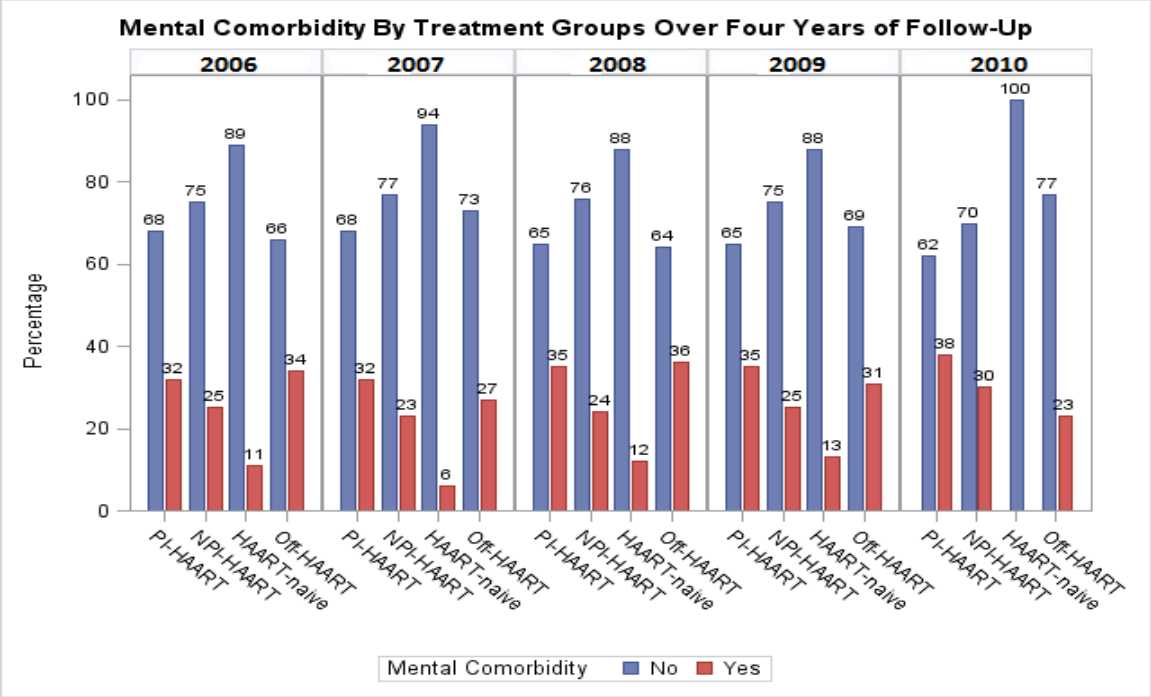


Fig. 3.11: Mental Comorbidity by Treatment Group Over Four Years of Follow-Up

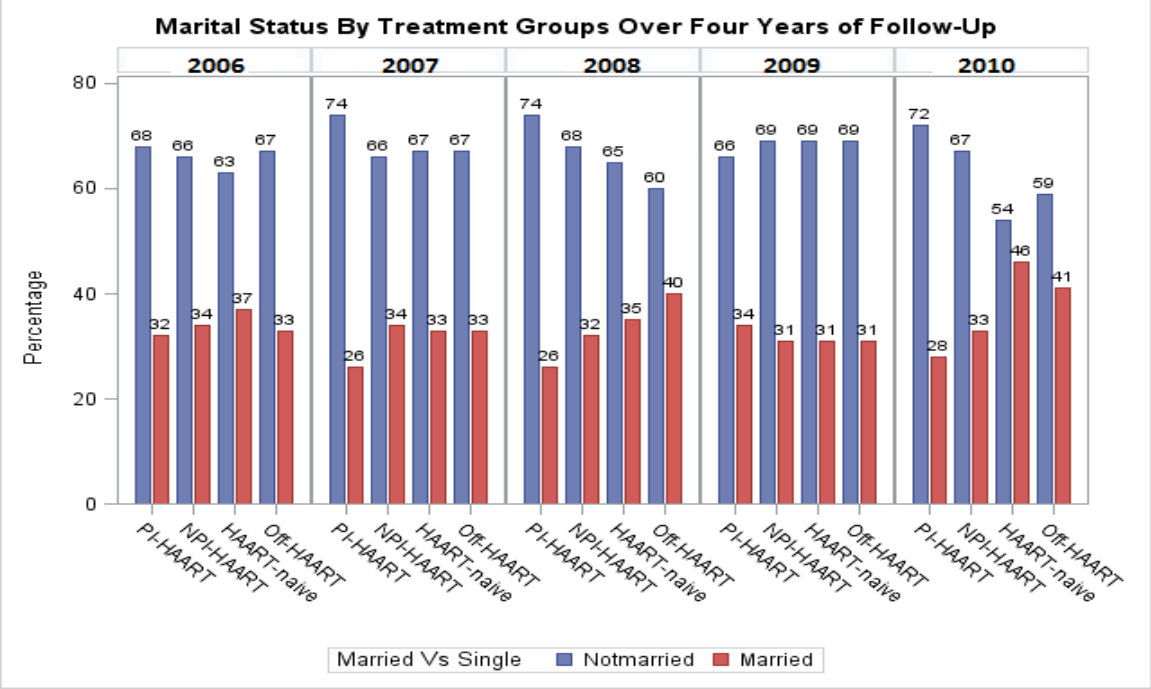


Fig. 3.12: Marital Status by Treatment Group Over Four Years of Follow-Up

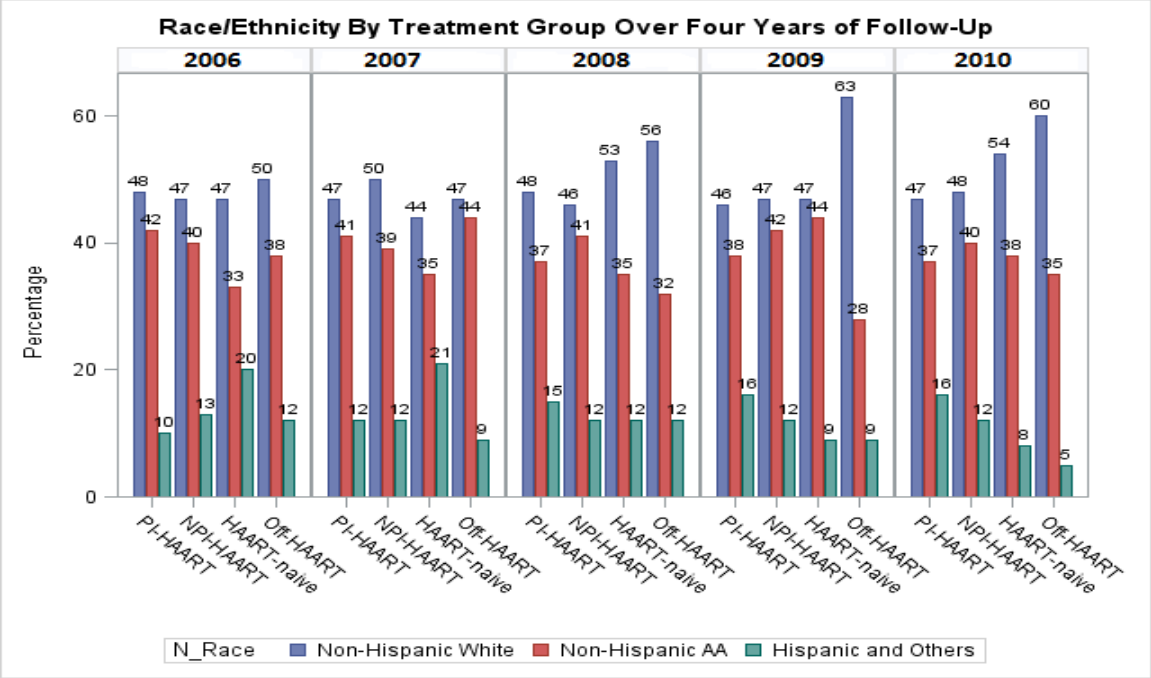


Fig. 3.13: Race/Ethnicity by Treatment Group Over Four Years of Follow-Up

3.8: References

1. Liu C, Ostrow D, Detels R, et al. Impacts of HIV infection and HAART use on quality of life. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2006;15(6):941-949.
2. Chun HM, Fieberg AM, Hullsiek KH, et al. Epidemiology of Hepatitis B virus infection in a US cohort of HIV-infected individuals during the past 20 years. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2010;50(3):426-436.
3. Chun HM, Roediger MP, Hullsiek KH, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. *The Journal of infectious diseases.* 2012;205(2):185-193.
4. Pelak K, Goldstein DB, Walley NM, et al. Host determinants of HIV-1 control in African Americans. *The Journal of infectious diseases.* 2010;201(8):1141-1149.
5. Spaulding AB, Lifson AR, Iverson ER, et al. Gonorrhoea or chlamydia in a U.S. military HIV-positive cohort. *Sexually transmitted infections.* 2012;88(4):266-271.
6. RAND. Scoring instructions for the 36-item short form survey (SF-36). http://www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html. Accessed 05/5/2013.
7. Hays RD. SAS code for scoring 36-item health survey 1.0. http://gim.med.ucla.edu/FacultyPages/Hays/utils/SF36/sf36.sas. Accessed 9/5/2014.
8. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis.* Second ed. New Jersey: Wiley; 2011.
9. Jin Y, Liu Z, Wang X, et al. A systematic review of cohort studies of the quality of life in HIV/AIDS patients after antiretroviral therapy. *International journal of STD & AIDS.* 2014;25(11):771-777.
10. Gakhar H, Kamali A, Holodniy M. Health-related quality of life assessment after antiretroviral therapy: a review of the literature. *Drugs.* 2013;73(7):651-672.
11. Degroote S, Vogelaers D, Vandijck DM. What determines health-related quality of life among people living with HIV: an updated review of the literature. *Archives of public health = Archives belges de sante publique.* 2014;72(1):40.
12. Doyle K, Weber E, Atkinson JH, Grant I, Woods SP. Aging, prospective memory, and health-related quality of life in HIV infection. *AIDS and behavior.* 2012;16(8):2309-2318.
13. Rodriguez-Penney AT, Iudicello JE, Riggs PK, et al. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. *AIDS patient care and STDs.* 2013;27(1):5-16.
14. Effros RB, Fletcher CV, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2008;47(4):542-553.
15. Corless IB, Kirksey KM, Kemppainen J, et al. Lipodystrophy-associated symptoms and medication adherence in HIV/AIDS. *AIDS patient care and STDs.* 2005;19(9):577-586.
16. Nicholas PK, Kirksey KM, Corless IB, Kemppainen J. Lipodystrophy and quality of life in HIV: symptom management issues. *Applied nursing research : ANR.* 2005;18(1):55-58.
17. Burgoyne RW, Tan DH. Prolongation and quality of life for HIV-infected adults treated with highly active antiretroviral therapy (HAART): a balancing act. *The Journal of antimicrobial chemotherapy.* 2008;61(3):469-473.

18. Potard V, Chassany O, Lavignon M, Costagliola D, Spire B. Better health-related quality of life after switching from a virologically effective regimen to a regimen containing efavirenz or nevirapine. *AIDS care.* 2010;22(1):54-61.
19. Protopopescu C, Marcellin F, Spire B, et al. Health-related quality of life in HIV-1-infected patients on HAART: a five-years longitudinal analysis accounting for dropout in the APROCO-COPILOTE cohort (ANRS CO-8). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2007;16(4):577-591.
20. Fumaz CR, Tuldra A, Ferrer MJ, et al. Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens. *Journal of acquired immune deficiency syndromes (1999).* 2002;29(3):244-253.
21. Campo RE, Cohen C, Grimm K, Shangguan T, Maa J, Seekins D. Switch from protease inhibitor- to efavirenz-based antiretroviral therapy improves quality of life, treatment satisfaction and adherence with low rates of virological failure in virologically suppressed patients. *International journal of STD & AIDS.* 2010;21(3):166-171.
22. Crum-Cianflone NF, Grandits G, Echols S, et al. Trends and causes of hospitalizations among HIV-infected persons during the late HAART era: what is the impact of CD4 counts and HAART use? *Journal of acquired immune deficiency syndromes (1999).* 2010;54(3):248-257.
23. Pogany K, van Valkengoed IG, Prins JM, et al. Effects of active treatment discontinuation in patients with a CD4+ T-cell nadir greater than 350 cells/mm3: 48-week Treatment Interruption in Early Starters Netherlands Study (TRIESTAN). *Journal of acquired immune deficiency syndromes (1999).* 2007;44(4):395-400.
24. Joyce VR, Barnett PG, Chow A, et al. Effect of treatment interruption and intensification of antiretroviral therapy on health-related quality of life in patients with advanced HIV: a randomized, controlled trial. *Medical decision making : an international journal of the Society for Medical Decision Making.* 2012;32(1):70-82.
25. Burman WJ, Grund B, Roediger MP, Friedland G, Darbyshire J, Wu AW. The impact of episodic CD4 cell count-guided antiretroviral therapy on quality of life. *Journal of acquired immune deficiency syndromes (1999).* 2008;47(2):185-193.
26. Liu C, Johnson L, Ostrow D, Silvestre A, Visscher B, Jacobson LP. Predictors for lower quality of life in the HAART era among HIV-infected men. *Journal of acquired immune deficiency syndromes (1999).* 2006;42(4):470-477.
27. Anis AH, Nosyk B, Sun H, et al. Quality of life of patients with advanced HIV/AIDS: measuring the impact of both AIDS-defining events and non-AIDS serious adverse events. *Journal of acquired immune deficiency syndromes (1999).* 2009;51(5):631-639.
28. Jia H, Uphold CR, Zheng Y, et al. A further investigation of health-related quality of life over time among men with HIV infection in the HAART era. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2007;16(6):961-968.
29. Jia H, Uphold CR, Wu S, Chen GJ, Duncan PW. Predictors of changes in health-related quality of life among men with HIV infection in the HAART era. *AIDS patient care and STDs.* 2005;19(6):395-405.
30. Walker AM. Confounding by indication. *Epidemiology.* 1996;7(4):335-336.

Chapter 4

Health-Related Quality of Life and Risk of Hospitalization among HIV-infected Individuals

Abstract

Objective: *To determine if HRQOL scores were predictive of all-cause hospitalization in the NHS cohort.*

Methods: *The RAND Short Form 36 (SF-36) was administered between 2006 and 2010 among members of the NHS cohort, and matched with participants' hospitalization records over the same time period. Physical component summary (PCSS) and mental component summary (MCSS) scores were computed based on standard algorithms. We also generated terciles of PCSS and MCSS with the upper terciles as referent groups. Three separate Cox proportional hazard regression models were used to estimate the hazard of hospitalization for PCSS terciles, MCSS terciles, and combined PCSS and MCSS terciles while controlling for same set of demographic and clinical characteristics.*

Results: *21% of participants were hospitalized over the period of follow-up. The median and interquartile ranges (IQR) for terciles of PCSS were 41.8 (35.9-46.1), 54.6 (52.8-55.9), and 58.8 (57.9-59.8) for the lower, middle and upper terciles respectively. The median and IQR for terciles of MCSS were 39.7 (32.0-43.9), 50.7 (49.0-51.8), and 55.3 (54.0-57.3) for the lower, middle and upper terciles respectively. The hazards of hospitalization were 2.12 times (95% CI: 1.59-2.84), 1.59 times (95% CI: 1.19-2.14) higher for the lower and middle terciles of PCSS compared to the upper PCSS tercile. The hazards of hospitalization were 1.33 times (95% CI: 1.02-1.73), 1.20 times (95% CI: 0.91-1.57) higher for the lower and middle terciles of MCSS compared to the upper MCSS tercile. Other predictors of hospitalization we CD4 count < 200 cells/mm^3 (HR= 2.84, 95% CI: 1.96, 4.12), CD4 count 200-349 cells/mm^3 (HR= 1.67, 95% CI: 1.24, 2.26), CD4 count >499 cells/mm^3 (HR= 1.41, 95% CI: 1.09, 1.83), viral load >50 copies/mL (HR= 1.82, 95% CI: 1.46, 2.26), being civilian/retired (HR= 2.04, 95% CI: 1.25, 3.34), and HIV-duration (HR= 0.94, 95% CI: 0.93, 0.96). Mental comorbidity and AIDS diagnosis were also significant predictors of hospitalization in the PCSS and MCSS models but not in the combined model.*

Conclusion: *Our study shows that both PCSS and MCSS were good prognostic tools for estimating the hazard of all-cause hospitalization in an HIV-infected population after controlling for demographic and clinical characteristics.*

Chapter 4

Health-Related Quality of Life and Risk of Hospitalization among HIV-infected Individuals

4.1: Introduction and Background

Although health-related quality of life (HRQOL) is primarily used as a patient-centered outcome measure to assess the individual's overall functional health status and for evaluating therapeutic interventions in human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS)[1,2], few studies have also utilized HRQOL as a prognostic tool for predicting survival in people living with HIV/AIDS (PLWHA)[3-6]. These studies have shown that HRQOL is useful as a risk stratification tool in HIV-infected individuals both in clinical trials and observational studies. But with the declining mortality in PLWHA[7-9], the use of HRQOL measure as a prognostic tool for mortality in HIV-infected individuals may not be very appealing to clinicians given the prolonged survival of PLWHA. The classification of HIV/AIDS as a chronic disease in the era of highly active antiretroviral therapy (HAART) from the fatal disease it used to be in the 1980s and early 1990s may also explain why very few studies have used HRQOL measures to prognosticate mortality in HIV-infected individuals.

With prolonged survival among PLWHA, the lack of cure on currently available treatment, and the steady incidence of HIV in the United States[9] it means the prevalence of the disease and, by extension, the burden of the disease on the healthcare system will continue to rise. In order to mitigate the increasing burden of the disease on the healthcare system, it is important that PLWHA are clinically stable and in optimal functional health, free from medical/mental comorbidities or opportunistic infections, and

have minimal hospitalizations. Poor HRQOL measures have been associated with higher utilization of healthcare resources in other chronic diseases[10-12]. Also, in HIV-infected individuals, HRQOL has been shown to be associated with hospitalization and emergency department utilization[5]. In our cohort, the rate of hospitalization has been previously reported to be as high as 34%[13]. Given the high rate of hospitalization among our cohort, it is important for clinicians to know the factors that may predict hospitalization, especially modifiable risk factors, in the hope that appropriate interventions can be instituted with the ultimate goal of reducing hospitalizations among cohort members.

Both the content and construct validity of the Short Form 36 (SF-36) have been demonstrated in HIV studies of HRQOL in different settings but to the best of our knowledge this instrument has not been used in predictive studies in HIV-infected populations; the medical outcome studies (MOS) for HIV (MOS-HIV) questionnaire was used in two of the four previously cited studies to predict mortality[4,6]. In these studies, the authors concluded that the HRQOL is a useful tool for predicting mortality in HIV-infected individuals. The other HRQOL instruments that have been used to predict survival in HIV-infected populations are the HIV Cost and Services Utilization Study (HCSUS) HRQOL instrument[3] and the EuroQol[5]. This latter instrument was also used to predict hospitalization and emergency department utilization[5]. Previous investigators have argued that HRQOL, especially the physical functional health, may be a better measure of the impact of the disease progression and treatment on the individual than that captured by clinical and laboratory measures including HIV disease indicators such as CD4 count. In this research, we investigate the usefulness of the Research and

Development (RAND) SF-36 in predicting hospitalization in our cohort. Because HRQOL reflects an individual's overall physical and mental functional health status, we hypothesize that participants with lower HRQOL are more likely to be hospitalized compared to participants with higher HRQOL over the period of follow-up. We believe that the ability to predict hospitalization with HRQOL will be important as a risk stratification tool in clinical practice.

4.2: Methods

4.2.1: Study Cohort

The U.S. Military HIV Natural History Study (NHS) is a prospective multicenter continuous enrollment observational cohort of HIV-infected active duty military personnel and other beneficiaries (spouses, adult dependents, and retired military personnel) from the Army, Navy/Marines and Air Force enrolled since 1986[14-17]. Participants are followed at five medical centers in the United States. Demographic data are collected at baseline and updated while medical and medication histories and standard laboratory studies are collected biannually. Blood samples obtained from participants in this cohort from scheduled visits are stored in a repository. Demographic information captured includes race/ethnicity (Caucasian, African American, Hispanic or Puerto Rican, Mexican, Asian, or Pacific Islander, Native American or Alaskan native, or other), age, gender, active duty, retired or dependent, and rank in military. Although not captured in the NHS database, injection drug use (IDU) has been reported to be very rare in this cohort[15,18]. All NHS participants provided informed consent, and approval for this research was obtained from the institutional review board at each participating site.

4.2.2: Study Participants

The RAND Short Form 36 (SF-36) questionnaires were administered annually to the NHS participants from April 2006 to September 2010. However, a few participants had more than one completed questionnaire in a year, and for these participants the last completed questionnaire for that year was used. Baseline was defined as the first ever HRQOL measure irrespective of when the participant was enrolled in the NHS. We used the CD4 count and viral load values closest in time to the HRQOL measure used.

4.2.3: Definitions and Variable Selections

4.2.3.1: Hospitalization and Time from Completed Survey to Hospitalization

Participants' dates of hospitalization, diagnosis at hospitalization, and number of days of hospitalization were retrieved from their hospital records and through participants' interviews. The principal or first-listed diagnosis was considered for purposes of this study. Hospitalization was the outcome variable of interest. Participants hospitalized from April 2006 to September 2010 were considered for inclusion in the analyses. In order to establish a temporal relationship, we ensured that date of completed questionnaire preceded the date of hospitalization. Hospitalization was coded as 'yes' if participant was ever hospitalized after the first completed SF-36 questionnaire and 'no' if participant was never hospitalization after the first completed questionnaire for the duration of the study. We used the initial hospitalization after the baseline HRQOL measure for the purposes of this study. Therefore, if a participant was hospitalized prior to his or her baseline HRQOL measure, but was not hospitalized after being enrolled into the study, that participant was considered not to have been hospitalized; however, if the participant had another

hospitalization after being enrolled in the study, then the participant was considered hospitalized.

4.2.3.2: Health-Related Quality of Life Scores

The norm-based the physical component summary scores (PCSS) and mental component summary scores (MCSS) 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[19,20]. The PCS and MCS scores were categorized into terciles with the upper tercile being the reference group. PCS and MCS scores were the main explanatory variables. We used the PCS and MCS scores immediately prior to hospitalization and if missing the ones before that.

4.2.3.3: Covariates

HAART was defined as a combination of at least three full dose antiretroviral agents similar to previous investigations for this cohort[15]. HAART treatment was divided into four groups: protease inhibitor-based HAART (PI-HAART), for HAART with at least one protease inhibitor in the combined HAART regimen; non-protease-inhibitor-based HAART (NPI-HAART), for HAART with no protease inhibitor in the combined HAART regimen; HAART-naïve group (HAART-N) for those who had never been on HAART, and Off-HAART/Non-HAART ART group, made up of those who were either off treatment or on non-HAART anti-retroviral therapy. Other covariates considered were gender (male/female), age (in increment of 5 years), 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

(≤50 copies/ml, >50 copies/ml), CD4+ count (<350 cells/mm^3, 350 – 499 cells/mm^3 and >499 cells/mm^3), medical comorbidity, mental comorbidity, AIDS-defining illnesses, and HIV duration. AIDS definition was in line with the 1993 Centers for Disease Control and Prevention criteria, with the exception of an isolated CD4 cell count <200 cells/mL as CD4 was analyzed separately. Medical co-morbidity referred to chronic medical conditions, and was classified as having no comorbidity or having one or more comorbidity. Mental comorbidity was classified similarly.

4.2.3.4: Time-Varying and Time-Invariant Covariates

With the exception of gender and race, all other variables were treated as time-varying covariates. For the time-invariant covariates, gender and race/ethnicity, we used the values of these covariates at baseline. For the time-dependent covariates the values of these covariates prior to the date of hospitalization or censorship were used.

4.2.3.5: Follow-up Time

Follow-up began at baseline, which was the time participants were enrolled in the HRQOL study as described in section 4.2.2. Time from baseline to hospitalization was calculated by subtracting the date of admission from the HRQOL date at baseline. Time from baseline to censoring was calculated similarly. The date of administrative censoring was fixed at September 30, 2010.

4.2.3.6: Censoring

There were five HRQOL measures (PCS and MCS scores) over the period of follow-up, and participants who completed the five annual HRQOL measures were censored at September 30, 2010, the date of administrative censorship. For participants who were lost

to follow-up, we censored them 6 months after the date of their last HRQOL measure. For example, if a participant completed only the baseline HRQOL measure, the duration of follow-up for this participant was placed at 6 months. By the same token, participants who had HRQOL measures for the baseline and second year of follow-up but not subsequently, the duration of follow-up was defined as the difference between the second HRQOL date and baseline HRQOL date plus six months. Similarly, censored participants who had HRQOL measures for the first to third year of study but not after, the duration of follow-up was defined as the difference between the third HRQOL date and baseline HRQOL date plus six months, and so forth.

4.2.4: Inclusion and Exclusion Criteria

All participants aged 18 years and above who completed the HRQOL survey questionnaires between 2006 and 2010 were included. 19 participants who had one or more missing values for covariates were excluded from the Cox regression analyses.

4.2.5: Statistical Analyses

We summarized the characteristics of the participants based on their frequency distribution for count variables and the median and interquartile ranges for numeric variables. We conducted further descriptive statistics using the Kaplan-Meier analysis for categorized variables, and used the Tukey-Kramer adjustment for between group differences for the independent variables and covariates with more than two categories. The Cox regression model[21] was used to estimate the hazard of hospitalization for participants. Because separate multivariate models are traditionally used for PCSS and MCSS when these variables are the outcome variables in research settings, we also used

them separately as independent variables in two different models while controlling for the same set of covariates which were significantly predictive of hospitalization in the univariate Cox regression analyses. We also constructed a third model in which both PCSS and MCSS were included in the model. To be eligible for inclusion into the multivariate model, the covariate must achieve a significance level of <0.2 in the univariate Cox regression model. For categorical variables with more than two categories we used the significance level of the global null hypothesis. Accordingly, race/ethnicity, age, gender, marital status, and medical comorbidity did not make it into the final models. In line with the model specifications, we first checked for non-proportionality using a graphical approach[22]. Specifically, we plotted the minus-natural-log-minus-natural-log survival curves of the categorized variables and examined the plots to see if they were 'parallel' over the follow-up period[22,23]. We then conducted formal diagnostics to test for violation of the proportional hazard assumption using both the Schoenfeld residuals[22-24] and covariate-time interaction term as recommended[21,24]. All statistical analyses and graphs were performed using SAS 9.3 [SAS Institute Inc., Cary, NC].

4.3: Results

Out of the 1730 participants eligible for the study there were 370 (21.50%) hospital admissions (table 4.1). 19 participants had one or more missing values for one or more covariates. Our cohort was predominantly male (93%), with about equal representation from non-Hispanic Whites and African American (42% each). About 17% of participants had a medical comorbidity while 29% had mental comorbidity; 12% had a diagnosis of AIDS either in the past or currently. Slightly over 5% of the cohort had CD4 count <200 cells per mm^3 and over 56% had CD4 count >499 cells/mm^3. 35% of participants had

plasma viral load copies greater 50 copies/mL. The lower and upper terciles had 572 participants each while the middle tercile had 573 participants. The median PCS score of the lower PCSS tercile was 41.75 (interquartile range [IQR] 35.88-46.12) compared to 54.55 (IQR, 52.78-55.87) for the middle tercile and 58.81 (IQR, 57.86-59.75) for the upper tercile. The median MCS score of the lower MCSS tercile was 39.71 (IQR, 31.96-43.87) compared to 50.69 (IQR, 49.02-51.82) for the middle tercile and 55.25 (IQR, 54.04-57.29). The Kaplan-Meier product-limit survival estimates for the terciles showed that there were statistically significant differences between all terciles of PCSS and between the lower tercile and other two MCSS terciles but not between the upper and middle terciles of MCSS (figures 4.1 and 4.3). Both terciles of PCSS and MCSS satisfied the proportional hazard assumption based on Schoenfeld residuals (figures 4.2 and 4.4).

In the unadjusted Cox regression model (table 4.2), participants in the lower PCSS tercile were 2.52 times at increased hazard of being hospitalized compared to upper PCSS tercile, and this hazard of hospitalization remained significant at 2.12 for this group even after adjusting for covariates (95% confidence interval [CI] 1.59-2.84). Please see the combined PCSS and MCSS model in table 4.3.a. The hazard of hospitalization among participants in the middle tercile of PCSS was 1.74 times more than for participants in the upper tercile of PCSS in the unadjusted model (95% CI, 1.31-2.33) and in the adjusted model the hazard of hospitalization was still increased by over 59% (95% CI 1.19-2.14). In the unadjusted model, participants in the lower MCSS tercile were 79% at increased hazard of being hospitalized compared to those in the upper MCSS tercile but this hazard fell to 33% in the adjusted combined model (95% CI 1.02-1.73). The hazard of hospitalization among participants was not significantly different between the middle and

upper terciles of MCSS in both the unadjusted (HR: 1.27, 95% CI 0.97-1.67) and adjusted (HR: 1.20, 95% CI 0.91-1.57) models.

The hazards of hospitalization were independently increased in participants with CD4 count <200 cells/mm^3, 200-349 cell/mm^3 and 350-499 cell/mm^3 by 2.84, 1.65, and 1.38 times respectively when compared to those with CD4 count >499 cells/mm^3. Also, having plasma viral load greater than 50 copies/mL, and being retired/civilian were independently associated with an increased hazard of hospitalization. Although the presence of mental comorbidity was not independently associated with an increased hazard of hospitalization in the combined model, it remained predictive of hospitalization in the individual PCSS (HR: 1.31, 95% CI 1.04-1.63) and MCSS models (HR: 1.30, 95% CI 1.04-1.64). While prior AIDS diagnosis was independently predictive of hospitalization in the MCSS model, it was not predictive of not predictive in either the PCSS or combined models. Every one year increment in time from HIV diagnosis led to a 5.6% reduced hazard of hospitalization (95% CI 0.93-0.96). Compared to those on PI-HAART, participants on NPI-HAART had a 30% significantly reduced hazard of hospitalization in the unadjusted model but was no longer significant in the multivariate model. In the univariate model, being in the HAART-naïve or Off-HAART/Non-HAART ART groups were associated with increased hazard of hospitalization by 1.80 and 1.75 times respectively but these were no longer significant in the adjusted models.

4.4: Discussion

Our study shows that both physical and mental functional health status were independently predictive of the risk of hospitalization among HIV-infected individuals in our cohort even after adjusting for HIV disease markers, AIDS diagnosis and duration of

HIV infection. This novel finding supports both the discriminatory and predictive validity of the SF-36 with possible practical implications in both research and clinical settings. Some authors have argued that PCSS is both an inclusive and robust measure of health relevant to the individual's well-being that may not be captured by common clinical and laboratory indicators[3,4]. Our findings support this claim. Furthermore, our study also shows that MCSS is also a useful predictive tool especially when the MCS score is low as was the case with the lower tercile of the cohort. The ability of MCSS to discriminatorily predict hospitalization was, however, much less compared to the PCSS in our study as evidenced by the magnitude of the parameter estimates, the clear dose-response relationship with PCSS and the comparable differences in tercile values for PCSS and MCSS.

It is instructive to note that while mental comorbidity was independently predictive of hospitalization in the individual PCSS and MCSS models, it was no longer predictive in the combined PCSS and MCSS model while MCS score remained predictive of hospitalization in the combined model, clearly showing that between MCS score and mental comorbidity MCS score was a better predictor of hospitalization. While this finding may not counter the view that that mental and psychiatric comorbidity primarily determines mental functional health[25-27], something that is also supported by our research in this cohort (please see chapter 2), it is evident that beyond mental/psychiatric comorbidity, other factors not ordinarily captured clinically may also play a significant role in the mental functioning of the individual, similar to the argument put forward for physical functional health[3,4].

Our study also showed that CD4 count <200 cells/mm^3, CD4 count 200 – 349 cells/mm^3, and CD4 count 350 – 499 cells/mm^3 were respectively associated with increased hazard of hospitalization by 184%, 65% and 38% when compared to CD4 count >499 cells/mm^3. Somewhat similar to our findings, Crum-Ciaflone et al[13], in an earlier work on this cohort, had found that CD4 count >499 cells/mm^3 reduced the risk of hospitalization when compared to CD4 <350 cells/mm^3 but they did not find any difference in the risk of hospitalization between CD4 count >499 cells/mm^3 and CD4 count 350-499 cells/mm^3. Other investigators have also shown that lower CD4 counts is associated with hospitalization, especially when CD4 count falls below 200[28-33]. Viral load greater than 50 copies per ml was also associated with hospitalization in our cohort. Although the levels of dichotomization differed, Fielden et al[33] also found that higher plasma viral load is associated with hospitalization while Mocroft et al[28] demonstrated that in the last of three time points in their study, there was an increased odds of hospitalization for every log unit increase in plasma viral load. Although others had found AIDS diagnosis to be predictive of hospitalization[28,33,34], we found this to be true for only our MCSS model but not in the PCSS or combined models. This shows that in our cohort, after account for physical functional health, prior AIDS diagnosis was no longer predictive of hospitalization.

Interestingly, longer HIV duration was predictive of a reduced hazard of hospitalization in our cohort. One plausible explanation for this finding may be that individuals with longer disease duration may be more experienced with dealing with symptoms (including subtle ones) associated with their infection, and are more likely to seek medical attention early enough before admission is warranted. In the unadjusted

models, those on non-PI based HAART appeared to have a reduced hazard of hospitalization while HAART-naïve and the Off-HAART/Non-HAART ART participants were at increased hazard of hospitalization when compared to those on PI-HAART but these differences were not sustained in the multivariate models. Also, because the Off-HAART/Non-HAART ART group is quite a broad group, we conducted sensitivity analyses in which we excluded non-HAART ART and our results remained essentially the same. The finding that being civilian/retired was associated with over 100% increased hazard of hospitalization in our cohort is not entirely surprising because to remain in active duty one has to be physically fit, and some medical or psychiatric conditions may have contributed to these participants being retired.

One major limitation of our study will be its generalizability within and outside HIV-infected populations. Within HIV-infected populations, the male predominance may limit its generalizability but many HIV studies/cohorts in the United States are predominantly male, and so our findings should apply to similar HIV populations. While HRQOL measure may still be a useful tool for predicting hospitalization in non-HIV-infected populations, our findings may not necessarily be generalizable to them because the factors determining HRQOL differ between HIV-infected and non-HIV-infected populations. Finally, it is possible that some hospital admissions outside the military settings may not have been captured but we believe that the number of non-Military hospital admissions that were not captured will be small as we frequently conducted interviews to capture such admissions.

Our study adds to the nascent literature on the prognostic value of HRQOL, particularly SF-36, as a predictive tool in HIV-infected individuals. To the best of our knowledge,

only one study has looked at the association between HRQOL and hospitalization in HIV-infected individuals, and this study utilized the EuroQol and VAS to assess HRQOL. That findings were similar using different measures of QOL reinforces the validity of HRQOL as a predictor of hospitalization. Important strengths of our study include its large sample size and the heterogeneity of the cohort with regards to HIV disease indicators and other clinical parameters, such as medical and mental comorbidities. The well-established temporal sequence was another major advantage of this study. In sensitivity analyses, we excluded those who were admitted within 7 days of completing their HRQOL questionnaire, and our results were unchanged. Like the disease specific MOS-HIV, our study also showed that the generic SF-36 is a very important predictive tool in HIV-infected population, which should support its use in clinical and research settings. Furthermore, the predictive validity of the MOS-HIV in survival studies in HIV-populations was limited to the physical functional health in previous studies[4,6], unlike ours in which mental functional health remained independently predictive of hospitalization even after controlling for physical functional health.

Although PCS and MCS scores predicted hospitalization in our study this does not imply causation, and the exact mechanism may deserve further elucidation and research. Yet, as others have noted, self-reported functional health status may capture a very broad range of obvious and subtle symptoms and signs that may be more indicative of disease progression beyond what may be clinically obvious. More so, the causes of hospitalization were very diversified, something previously noted in our cohort by other researchers[13]. One advantage HRQOL measures may have over HIV-disease indicators is

that HRQOL is also reflective of perceptions that may affect subsequent health-seeking behaviors and utilization of healthcare resources including preventive services[4,35].

Summary scores of the SF-36 are also known to change with treatment and other important clinical parameters, and some have suggested that score change of 5 may be clinically and socially relevant[36]. As a predictive tool for survival, one group of investigators showed that every unit increase in PCS resulted in a 4% increased chances of survival in a predominantly white male HIV-infected population[6] while another group of investigators showed that every 5 unit increment in PCS led to a 2% reduced hazard of death in a Dutch HIV cohort[4]. When we conducted our analyses using PCS and MCS scores as continuous variables in our models, we found that every unit increase in PCS and MCS scores respectively reduced the hazard of hospitalization by 12% and 6% in the combined model (table 4.3.b). So, for our cohort with wide ranges of PCS (16.66 to 70.67) and MCS (8.56 to 67.60) scores, the SF-36 questionnaire is a very useful tool for predicting hospitalization.

The lifetime cost of HAART treatment continues to rise[37] and this cost is greatly increased by hospitalizations[33,37,38]. The ability to predict hospital admissions beyond HIV disease indicators will be useful to clinicians treating HIV-infected individuals. The simultaneous prediction of hospitalization by HRQOL measures, HIV disease indicators and AIDS diagnosis further supports the concurrent validity of the SF-36[39], an instrument that is self-administered and takes about 10 minutes to complete[40]. Furthermore, the median follow-up time for the non-hospitalized participants was 3.13 years (IQR, 1.53-972) compared to the median follow-up time for hospitalized participants of 1.23 years

(IQR, 0.53-2.38) (table 4.1), which means that a yearly survey or even one survey every other year may suffice for this purpose.

4.5: Conclusion

In summary we found several interesting and important findings. This study shows that both physical and mental function health are good prognostic tools for estimating the hazard of hospitalization in an HIV-infected population even after controlling for HIV disease indicators, and HIV duration. Also, our study supports the content, construct, and criterion-related (predictive and concurrent) validity of the SF-36. Considering the high cost of hospitalization in the United States, measures should be instituted to address the modifiable risk factors that may be associated with lower health related quality of life in HIV-infected individuals.

4.6: Tables

Table 4.1: Characteristics of Participants

Characteristics	N (%)
Hospitalized	
Yes	372 (21.50)
No	1358 (78.50)
Gender	
Male	1610 (93.06)
Female	120 (6.94)
Race	
Non-Hispanic White	723 (41.79)
Non-Hispanic African	736 (42.54)
Hispanic/Others	271 (15.66)
Rank	
Officer/Warrant Officer	126 (7.28)
Enlisted	900 (52.02)
Others (Retired/Civilians)	702 (40.58)
Missing	2 (0.12)
Marriage, Yes	564 (32.60)
Medical Comorbidity, Yes	291 (16.82)
Mental Comorbidity, Yes	501 (28.96)
AIDS, Yes	207 (11.97
HAART	
PI-Based	471 (33.64)
Non-PI-Based	766 (44.28)
HAART-Naïve	243 (14.05)
Off-HAART	121 (6.99)
Non-HAART ART	18 (1.04)
Viral Load >50 copies/mL	
Yes	606 (35.03)
No	1120 (63.67)
Missing	4 (0.23)
CD4 Count Groups	
<200 cells/mm^3	94 (5.43)
200-349 cells/mm^3	246 (14.22)
350-499 cells/mm^3	412 (23.82)
>499 cells/mm^3	975 (56.36)
Missing	3 (0.17)
Age (years) – Median (IQR)	42.00 (34.00 – 49.00)
CD4 Count (x 10^6/L) – Median (IQR)	538.00 (389.00 – 721.00)
Viral Load (Log_{10}) – Median (IQR)	1.70 (1.68 – 2.28)
Time from HIV Diagnosis (years) – Median (IQR)	10.00 (4.00 – 17.08)
Duration of Follow-Up (Years, Overall) – Median (IQR)	2.72 (1.04 – 3.81)
Hospitalized – Median (IQR)	1.23 (0.53 – 2.38)
Not Hospitalized – Median (IQR)	3.13 (1.53 – 3.97)
Physical Component Summary Scores (PCSS)	
Lower Tercile – Median (IQR)	41.75 (35.88-46.12)
Middle Tercile – Median (IQR)	54.55 (52.78-55.87)
Upper Tercile – Median (IQR)	58.81 (57.86-59.75)
Mental Component Summary Scores (MCSS)	
Lower Tercile – Median (IQR)	39.71 (31.96-43.87)
Middle Tercile – Median (IQR)	50.69 (49.02-51.82)
Upper Tercile – Median (IQR)	55.25 (54.04-57.29)

Table 4.2: Univariate Cox Regression Model for Hazard of Hospitalization

Variable	Hazard Ratio	95% CI	P-Value
Physical Component Summary Score (PCSS)			
Lower Tercile of PCSS	**2.52**	**1.92 – 3.32**	**<.0001**
Middle Tercile of PCSS	**1.74**	**1.31 – 2.33**	**0.0002**
Upper Tercile of PCSS	**1.0**	**-**	**-**
Mental Component Summary Score (MCSS)			
Lower Tercile of MCSS	**1.79**	**1.39 – 2.30**	**<.0001**
Middle Tercile of MCSS	1.27	0.97 – 1.67	0.0783
Upper Tercile of MCSS	1.0	-	-
Age (Years, Increment of 5 Years)	0.98	0.94 – 1.03	0.4971
Gender (Male)	1.06	0.70 – 1.62	0.7877
Marital Status (Married)	1.13	0.91 – 1.40	0.2586
Race/Ethnicity			
Non-Hispanic African American	0.96	0.77 – 1.19	0.7077
Hispanic/Others	0.86	0.63 – 1.18	0.3495
Non-Hispanic Caucasian	1.0	-	-
Rank			
Civilian/Retired	1.47	0.93 – 2.35	0.0962
Enlisted	1.22	0.77 – 1.95	0.3922
Officers	1.0	-	-
CD4 Count			
CD4 Count <200 cells/mm^3	**3.89**	**2.78 – 5.44**	**<.0001**
CD4 Count 200-349 cells/mm^3	**2.16**	**1.63 – 2.86**	**<.0001**
CD4 Count 350-499 cells/mm^3	**1.55**	**1.20 – 2.00**	**0.0008**
CD4 Count >499 cells/mm^3	**1.0**	**-**	**-**
Viral Load >50 Copies/mL	**2.36**	**1.92 – 2.89**	**<.0001**
Medical Comorbidity	1.05	0.81 – 1.36	0.7130
Mental Comorbidity	**1.43**	**1.16 – 1.76**	**0.0009**
AIDS	**1.67**	**1.27 – 2.18**	**0.0002**
HIV Duration (Years)	**0.98**	**0.96 – 0.99**	**0.0018**
HAART Treatment			
Non-PI Based HAART	**0.70**	**0.55 – 0.87**	**0.0033**
HAART-Naïve	**1.80**	**1.33 – 2.43**	**0.0002**
Off-HAART/Non-HAART ART	**1.75**	**1.26 – 2.44**	**0.0008**
PI Based HAART	1.0	-	-

Table 4.3.a: Multivariate Cox Regression Model for Hazard of Hospitalization for Terciles of PCSS and MCSS

Variable	PCSS Model			MCSS Model			Combined PCSS and MCSS Model		
	HR	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**
PCSS									
Lower Tercile	**2.18**	**1.64 – 2.90**	**<.0001**				**2.12**	**1.59 – 2.84**	**<.0001**
Middle Tercile	**1.62**	**1.21 – 2.17**	**0.0013**				**1.59**	**1.19 – 2.14**	**0.0018**
Upper Tercile	1.0	-	-				1.0	-	-
MCSS									
Lower Tercile				**1.44**	**1.10 – 1.87**	**0.0077**	**1.33**	**1.02 – 1.73**	**0.0374**
Middle Tercile				1.14	0.87 – 1.49	0.3576	1.20	0.91 – 1.57	0.2010
Upper Tercile				1.0	-	-	1.0	-	-
CD4 Count									
<200 cells/mm^3	**2.84**	**1.96 – 4.12**	**<.0001**	**2.99**	**2.06 – 4.33**	**<.0001**	**2.84**	**1.96 – 4.12**	**<.0001**
200-349 cells/mm^3	**1.69**	**1.25 – 2.27**	**0.0006**	**1.67**	**1.24 – 2.25**	**0.0007**	**1.67**	**1.24 – 2.26**	**0.0007**
350-499 cells/mm^3	**1.41**	**1.09 – 1.82**	**0.0099**	**1.37**	**1.05 – 1.77**	**0.0184**	**1.41**	**1.09 – 1.83**	**0.0094**
>499 cells/mm^3	1.0	-	-	1.0	-	-	1.0	-	-
Viral Load >50 Copies/mL	**1.83**	**1.47 – 2.28**	**<.0001**	**1.88**	**1.51 – 2.34**	**<.0001**	**1.82**	**1.46 – 2.26**	**<.0001**
Mental Comorbidity	**1.31**	**1.04 – 1.63**	**0.0195**	**1.30**	**1.04 – 1.64**	**0.0237**	1.23	0.98 – 1.55	0.0741
AIDS	1.35	1.00 – 1.83	0.0512	**1.47**	**1.09 – 1.99**	**0.0129**	1.34	0.99 – 1.81	0.0608
Rank									
Civilian/Retired	**2.06**	**1.26 – 3.37**	**0.0038**	**2.16**	**1.32 – 3.52**	**0.0022**	**2.04**	**1.25 – 3.34**	**0.0044**
Enlisted	1.18	0.74 – 1.88	0.4864	1.17	0.73 – 1.86	0.5145	1.19	0.74 – 1.89	0.4755
Officer	1.0	-	-	1.0	-	-	-	-	-
HIV Duration (Years)	**0.94**	**0.92 – 0.96**	**<.0001**	**0.94**	**0.93 – 0.96**	**<.0001**	**0.94**	**0.93 – 0.96**	**<.0001**

Table 4.3.b: Multivariate Cox Regression Model for Hazard of Hospitalization (PCSS and MCSS Continuous)

Variable	PCSS Model			MCSS Model			Combined PCSS and MCSS Model		
	HR	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**
PCSS, 5 Unit Increments	**0.87**	**0.83 – 0.92**	**<.0001**				**0.88**	**0.84 – 0.93**	**<.0001**
MCSS, 5 Unit Increments				**0.91**	**0.87 – 0.96**	**0.0007**	**0.94**	**0.89 – 0.99**	**0.0169**
CD4 Count									
<200 cells/mm^3	**2.76**	**1.90 – 4.01**	**<.0001**	**2.96**	**2.04 – 4.29**	**<.0001**	**2.73**	**1.88 – 3.97**	**<.0001**
200-349 cells/mm^3	**1.66**	**1.23 – 2.23**	**0.0009**	**1.67**	**1.24 – 2.25**	**0.0007**	**1.65**	**1.22 – 2.23**	**0.0010**
350-499 cells/mm^3	**1.38**	**1.07 – 1.80**	**0.0133**	**1.37**	**1.05 – 1.77**	**0.0188**	**1.38**	**1.07 – 1.79**	**0.0139**
>499 cells/mm^3	1.0	-	-	1.0	-	-	1.0	-	-
Viral Load >50 Copies/mL	**1.86**	**1.49 – 2.32**	**<.0001**	**1.89**	**1.52 – 2.36**	**<.0001**	**1.86**	**1.49 – 2.31**	**<.0001**
Mental Comorbidity	**1.31**	**1.05 – 1.64**	**0.0185**	**1.28**	**1.02 – 1.61**	**0.0360**	1.23	0.97 – 1.54	0.0867
AIDS	1.34	0.99 – 1.82	0.0624	**1.48**	**1.09 – 2.00**	**0.0120**	1.34	0.99 – 1.82	0.0596
Rank									
Civilian/Retired	**2.21**	**1.35 – 3.61**	**0.0016**	**2.14**	**1.31 – 3.49**	**0.0024**	**2.15**	**1.32 – 3.52**	**0.0023**
Enlisted	1.28	0.80 – 2.04	0.3087	1.16	0.73 – 1.85	0.5240	1.27	0.79 – 2.02	0.3244
Officer	1.0	-	-	1.0	-	-	-	-	-
HIV Duration (Years)	**0.94**	**0.92 – 0.96**	**<.0001**	**0.95**	**0.93 – 0.96**	**<.0001**	**0.94**	**0.93 – 0.96**	**<.0001**

4.7: Figures

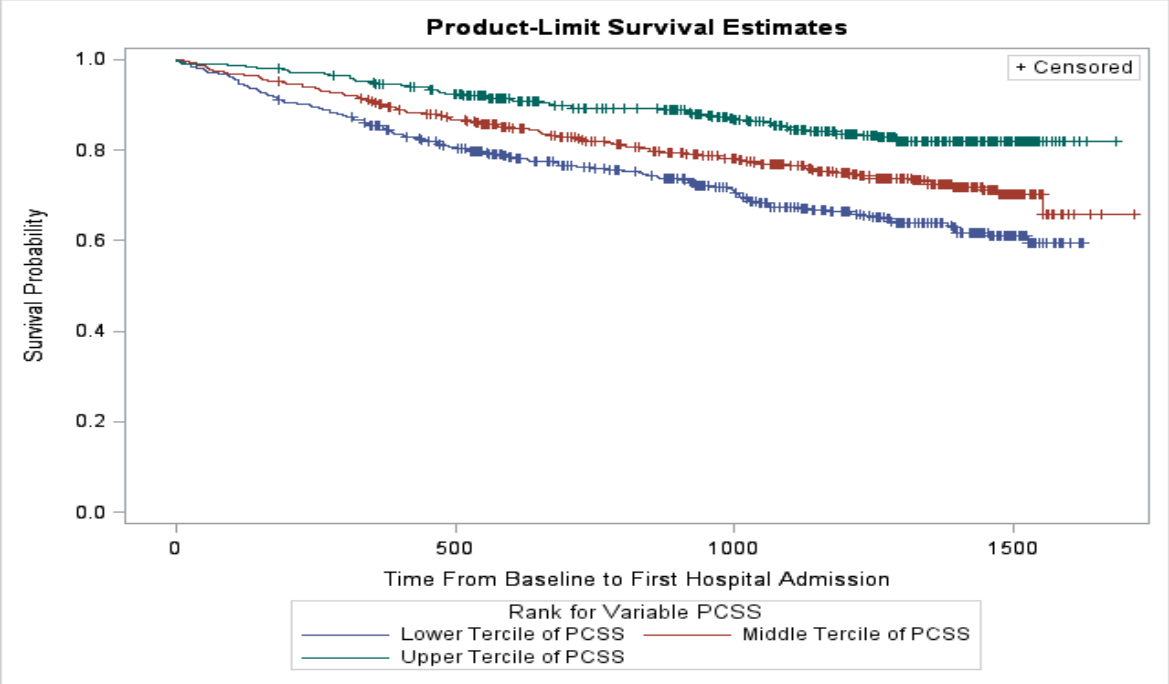


Fig. 4.1: Kaplan-Meier Survival Curve for Physical Component Summary Score (PCSS)

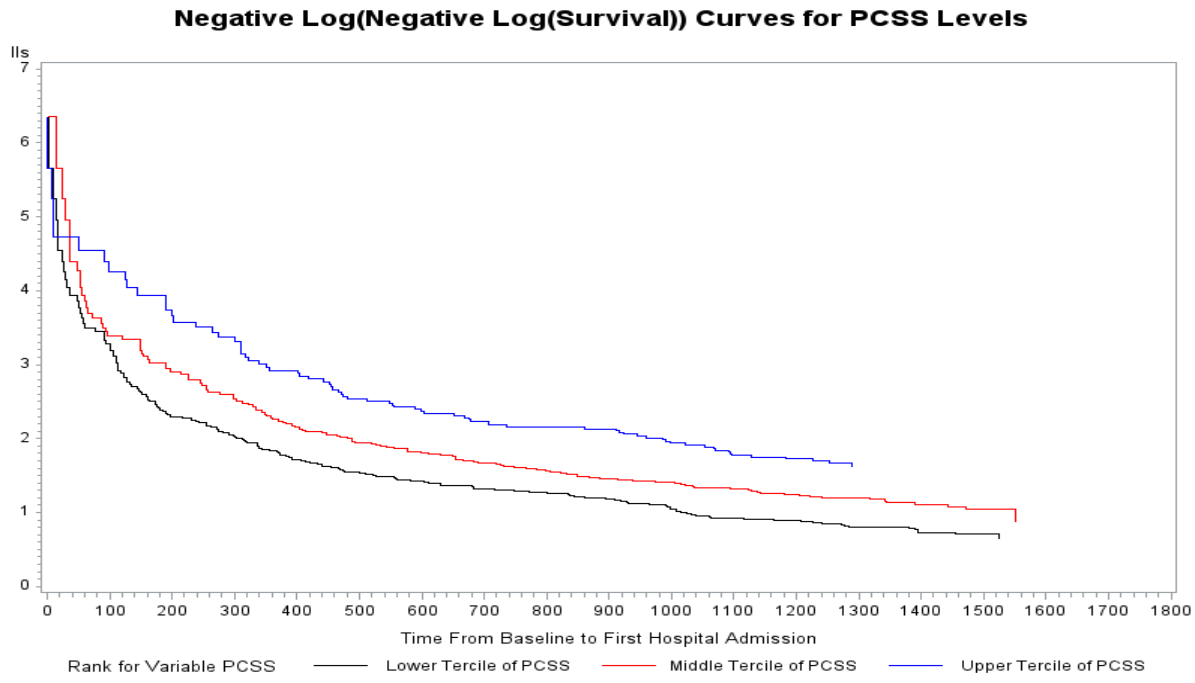


Fig. 4.2: Minus-Log-Minus-Log Survival Curve for Physical Component Summary Score (PCSS)

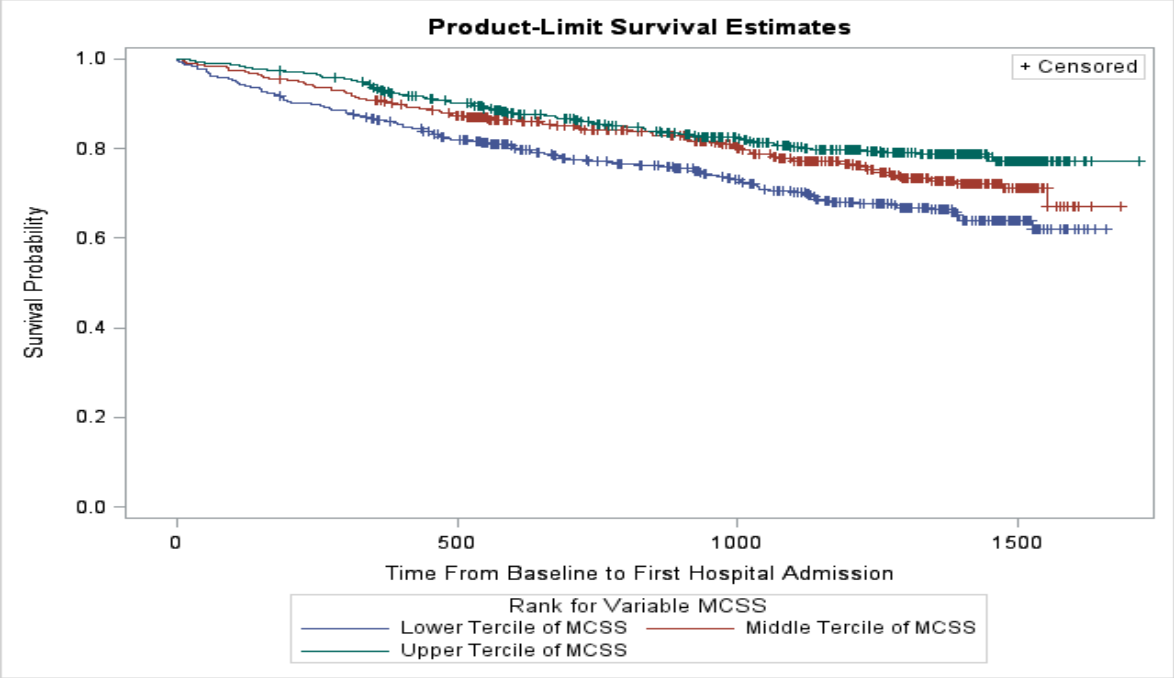


Fig. 4.3: Kaplan-Meier Survival Curve for Mental Component Summary Score (MCSS)

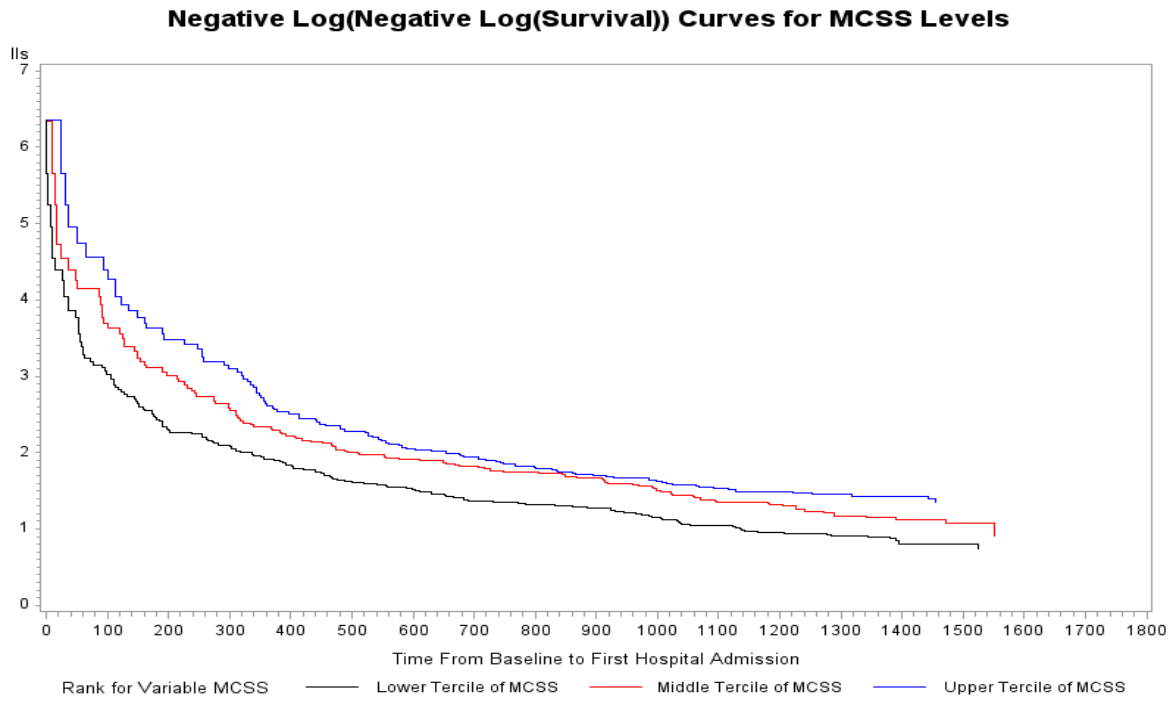


Fig. 4.4: Minus-Log-Minus-Log Survival Curve for Mental Component Summary Score (MCSS)

4.8: References

1. Gakhar H, Kamali A, Holodniy M. Health-related quality of life assessment after antiretroviral therapy: a review of the literature. *Drugs.* 2013;73(7):651-672.
2. Degroote S, Vogelaers D, Vandijck DM. What determines health-related quality of life among people living with HIV: an updated review of the literature. *Archives of public health = Archives belges de sante publique.* 2014;72(1):40.
3. Cunningham WE, Crystal S, Bozzette S, Hays RD. The association of health-related quality of life with survival among persons with HIV infection in the United States. *Journal of general internal medicine.* 2005;20(1):21-27.
4. de Boer-van der Kolk IM, Sprangers MA, Prins JM, Smit C, de Wolf F, Nieuwkerk PT. Health-related quality of life and survival among HIV-infected patients receiving highly active antiretroviral therapy: a study of patients in the AIDS Therapy Evaluation in the Netherlands (ATHENA) Cohort. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2010;50(2):255-263.
5. Mathews WC, May S. EuroQol (EQ-5D) measure of quality of life predicts mortality, emergency department utilization, and hospital discharge rates in HIV-infected adults under care. *Health and quality of life outcomes.* 2007;5:5.
6. Jacobson DL, Wu AW, Feinberg J. Health-related quality of life predicts survival, cytomegalovirus disease, and study retention in clinical trial participants with advanced HIV disease. *Journal of clinical epidemiology.* 2003;56(9):874-879.
7. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet.* 1998;352(9142):1725-1730.
8. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *The New England journal of medicine.* 1998;338(13):853-860.
9. Centers for Disease Control and Prevention (CDC). Rates of diagnoses of HIV infection among adults and adolescents, by area of residence, 2011—United States and 6 dependent areas. 2011; http://www.cdc.gov/hiv/pdf/statistics_2011_HIV_Surveillance_Report_vol_23.pdf. Accessed 01/26/2015.
10. Singh JA, Borowsky SJ, Nugent S, et al. Health-related quality of life, functional impairment, and healthcare utilization by veterans: veterans' quality of life study. *Journal of the American Geriatrics Society.* 2005;53(1):108-113.
11. Singh JA, Nelson DB, Fink HA, Nichol KL. Health-related quality of life predicts future health care utilization and mortality in veterans with self-reported physician-diagnosed arthritis: the veterans arthritis quality of life study. *Seminars in arthritis and rheumatism.* 2005;34(5):755-765.
12. Centers for Disease Control and Prevention. *Measuring Healthy Days.* Atlanta, Georgia: CDC.2000.
13. Crum-Cianflone NF, Grandits G, Echols S, et al. Trends and causes of hospitalizations among HIV-infected persons during the late HAART era: what is the impact of CD4 counts and HAART use? *Journal of acquired immune deficiency syndromes (1999).* 2010;54(3):248-257.
14. Chun HM, Fieberg AM, Hullsiek KH, et al. Epidemiology of Hepatitis B virus infection in a US cohort of HIV-infected individuals during the past 20 years. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2010;50(3):426-436.

15. Chun HM, Roediger MP, Hullsiek KH, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. *The Journal of infectious diseases.* 2012;205(2):185-193.
16. Pelak K, Goldstein DB, Walley NM, et al. Host determinants of HIV-1 control in African Americans. *The Journal of infectious diseases.* 2010;201(8):1141-1149.
17. Spaulding AB, Lifson AR, Iverson ER, et al. Gonorrhoea or chlamydia in a U.S. military HIV-positive cohort. *Sexually transmitted infections.* 2012;88(4):266-271.
18. Brodine SK, Starkey MJ, Shaffer RA, et al. Diverse HIV-1 subtypes and clinical, laboratory and behavioral factors in a recently infected US military cohort. *AIDS (London, England).* 2003;17(17):2521-2527.
19. RAND. Scoring instructions for the 36-item short form survey (SF-36). http://www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html. Accessed 05/5/2013.
20. Hays RD. SAS code for scoring 36-item health survey 1.0. http://gim.med.ucla.edu/FacultyPages/Hays/utils/SF36/sf36.sas. Accessed 9/5/2014.
21. Cox D.R. Regression Models and Life Tables. *Journal of the Royal Statistical Society.* 1972;Series B34(2):34.
22. Kleinbaum DG, Klein M. Evaluating the proportional hazards assumption. *Survival Analysis: A Self-Learning Text*. Third ed. New York: Springer; 2012:161-200.
23. Bellera CA, MacGrogan G, Debled M, de Lara CT, Brouste V, Mathoulin-Pelissier S. Variables with time-varying effects and the Cox model: some statistical concepts illustrated with a prognostic factor study in breast cancer. *BMC medical research methodology.* 2010;10:20.
24. Allison PD. Estimating Cox Regression Models with PROC PHREG. *Survival Analysis Using SAS: A Paricticall Guide*. Cary, NC: SAS Institute Inc.; 2010:125-201.
25. Briongos Figuero LS, Bachiller Luque P, Palacios Martin T, Gonzalez Sagrado M, Eiros Bouza JM. Assessment of factors influencing health-related quality of life in HIV-infected patients. *HIV medicine.* 2011;12(1):22-30.
26. Liu C, Johnson L, Ostrow D, Silvestre A, Visscher B, Jacobson LP. Predictors for lower quality of life in the HAART era among HIV-infected men. *Journal of acquired immune deficiency syndromes (1999).* 2006;42(4):470-477.
27. Preau M, Marcellin F, Carrieri MP, Lert F, Obadia Y, Spire B. Health-related quality of life in French people living with HIV in 2003: results from the national ANRS-EN12-VESPA Study. *AIDS (London, England).* 2007;21 Suppl 1:S19-27.
28. Mocroft A, Monforte A, Kirk O, et al. Changes in hospital admissions across Europe: 1995-2003. Results from the EuroSIDA study. *HIV medicine.* 2004;5(6):437-447.
29. Paul S, Gilbert HM, Lande L, et al. Impact of antiretroviral therapy on decreasing hospitalization rates of HIV-infected patients in 2001. *AIDS research and human retroviruses.* 2002;18(7):501-506.
30. Buchacz K, Baker RK, Moorman AC, et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994-2005. *AIDS (London, England).* 2008;22(11):1345-1354.
31. Krentz HB, Dean S, Gill MJ. Longitudinal assessment (1995-2003) of hospitalizations of HIV-infected patients within a geographical population in Canada. *HIV medicine.* 2006;7(7):457-466.
32. Gebo KA, Fleishman JA, Moore RD. Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states. *Journal of acquired immune deficiency syndromes (1999).* 2005;40(5):609-616.

33. Fielden SJ, Rusch ML, Levy AR, et al. Predicting hospitalization among HIV-infected antiretroviral naive patients starting HAART: determining clinical markers and exploring social pathways. *AIDS care.* 2008;20(3):297-303.
34. Weber AE, Yip B, O'Shaughnessy MV, Montaner JS, Hogg RS. Determinants of hospital admission among HIV-positive people in British Columbia. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2000;162(6):783-786.
35. Idler EL, Kasl SV. Self-ratings of health: do they also predict change in functional ability? *The journals of gerontology. Series B, Psychological sciences and social sciences.* 1995;50(6):S344-353.
36. Hopman WM, Berger C, Joseph L, et al. Health-related quality of life in Canadian adolescents and young adults: normative data using the SF-36. *Canadian journal of public health = Revue canadienne de sante publique.* 2009;100(6):449-452.
37. Farnham PG. Do reduced inpatient costs associated with highly active antiretroviral therapy (HAART) balance the overall cost for HIV treatment? *Applied health economics and health policy.* 2010;8(2):75-88.
38. Barbour KE, Fabio A, Pearlman DN. Inpatient charges among HIV/AIDS patients in Rhode Island from 2000-2004. *BMC health services research.* 2009;9:3.
39. A dictionary of epidemiology. In: Last JM, ed. Fourth ed. New York: Oxford University Press; 2001.
40. Grossman HA, Sullivan PS, Wu AW. Quality of life and HIV: current assessment tools and future directions for clinical practice. *The AIDS reader.* 2003;13(12):583-590, 595-587.

Chapter 5

Conclusions and Recommendations

5.1: Conclusions

With the introduction of highly active anti-retroviral therapy (HAART), infection with human immunodeficiency virus (HIV) has evolved from being a progressive fatal illness to a manageable chronic disease. However, the improved control of HIV with HAART is associated with adverse drug effects. Also, as people living with HIV (PLWH) grow older they are faced with greater burden of age-associated diseases, such as diabetes, cardiovascular and renal diseases all of which may affect the quality of life of PLWH. Health-related quality of life (HRQOL) is a patient-centered outcome measure that has the potential to improve care by assessing and monitoring treatment effects, enhancing communication between patient and provider, and tracking changes in functional status over time[1]. Furthermore, HRQOL provides valuable information to policy makers and administrators on the efficiency, effectiveness and cost-benefit ratios of healthcare programs[2,3]. The pharmaceutical industry and regulatory agencies also rely on HRQOL to evaluate the effectiveness and treatment benefit of new drugs[2-5].

The importance of HRQOL in HIV is underscored by its relationship to biologic markers of HIV disease progression[6-9], disease burden[10], survival[11-14], and health care utilization[13,15,16]. It is not surprising therefore that research on HRQOL has dramatically increased over the last 3 to 4 decades[17], and particularly so for HRQOL in the HIV-infected population for the past 2 decades[18]. Yet, comparison of HRQOL studies is difficult because of varying instruments used, period under study (pre-HAART versus HAART era), HRQOL dimensions studied (health domain scores vs. summary scores vs.

overall HRQOL), whether or not the instrument is disease specific or generic, the research setting (clinical trial vs. non-clinical trial) and the population studied (men, women, high or low income countries). Often, the research questions addressed by different investigators make it impossible to provide an overview and assess the status of HRQOL research in HIV[18]. Of the 825 articles Drewes et al selected in their descriptive study of HRQOL in HIV-infected persons they found 122 of these to be instrument studies, 265 interventional studies and the remaining 465 correlational studies[18]. However, Gakhar et al included only 26 studies in their 2003 review of articles on HRQOL, HIV and anti-retroviral therapy (ART). Degroote et al reviewing journal articles published in high-income countries prior to July 2013 included 49 studies[3]. To be included in their review, the study should have included either the overall HRQOL measure or the two summary measures (physical/mental health summary scores)[3]. Cohort studies on HRQOL are even fewer. For example, Jin et al in a systematic review of cohort studies on HRQOL in HIV-infected patients on anti-retroviral therapy included only 8 studies published prior to December 2012 out of 1,675 potentially relevant citations[19]. To be included in this study, four criteria had to be met, viz: (i) be a cohort study; (ii) the patients initiated combination anti-retroviral therapy at baseline; (iii) presented QOL data at baseline; and (iv) follow-up for more than 12 weeks.

In the light of the aforementioned, our work comes as a useful addition to HRQOL studies in HIV-infected individuals in the HAART era. We have not only corroborated current knowledge but have extended it. Furthermore, our work clearly shows the need to have an expanded explanatory model on the relationship between HRQOL, HIV and HAART especially on the long term. Before we delve further into conceptual models on

HIV, HAART and HRQOL, we will highlight some pertinent findings in our studies and use those as reference points in our discussion as we find suitable.

We found that the physical functional health of our cohort was slightly better than that of the United States' general population while the mental functional health of our cohort was slightly worse than that of the US general population. Both our cohort's physical and mental functional health were worse than that of the United States Military Millennium Cohort but the difference mental functional health was much wider (>5 points). Our study further confirmed the SF-36 as a reliable instrument for measuring the eight domain scores as evident by the high Cronbach's alpha (see chapter 1). Important factors that were negatively associated with physical HRQOL at baseline were CD4 count <200 cells/mm^3, medical and mental comorbidities, increasing age, and AIDS. Other factors that were negatively associated with physical functional health were being enlisted or civilians/retired, and being married. Factors that were negatively associated with mental functional health were CD4 count <200 cells/mm^3 and mental comorbidity while being African American and increasing age were positively associated with mental functional health.

In our longitudinal study, we found that being on a non-protease inhibitor HAART (NPI-HAART) did not provide any treatment benefit over being on a protease inhibitor HAART (PI-HAART). Although participants who were HAART naïve or Off-HAART could freely move into either the NPI-HAART or PI-HAART groups based on their disease progression, we did not find being on PI-HAART to have treatment benefit over being HAART-naïve or Off-HAART. Furthermore, we found that being on any HAART group (PI-HAART, NPI-HAART, HAART-Naïve, and Off-HAART) did not result in

significant HRQOL changes over the period of follow-up in our multivariate models. However, being HAART-Naïve or on NPI-HAART were positively predictive of physical functional health. We believe this group differences may be due to residual confounding, the lack of randomization or confounding by indication[20]. The other factors independently predictive of physical functional health were all negative predictors and they include CD4 count of <200 cells/mm^3, CD4 count 200-499 cells/mm^3, medical and mental comorbidities, AIDS diagnosis, increasing age and being married. Over the period of follow-up, having a medical comorbidity led to improvement in physical functional health. Factors independently predictive of mental functional health were CD4 count <200 cells/mm^3 or mental comorbidity while being African American was positively predictive of mental functional health. There were no differences in mental functional health by HAART groups.

As a predictive tool we also found that both physical (PCS) and mental (MCS) component summary scores were predictive of hospitalization in our cohort even after adjusting for demographic and HIV-disease indicators with a clear dose-response relationship for PCS groups. Similar to PCS groups, there was a dose-response relationship between CD4 count and the hazard of hospitalization, with CD4 count <200 cells/mm^3 being most predictive of this risk. Other factors in our model that were predictive of hospitalization were plasma viral load (>50 copies/mL), AIDS diagnosis, and mental comorbidity. Duration of HIV infection was associated with reduced hazard of hospitalization. It was interesting to note that while pVL was predictive of hospitalization it was neither independently associated with HRQOL in the baseline study nor predictive of HRQOL in the longitudinal study. While the study by Call et al[7] found

pVL to be independently associated with PCS, it is difficult to compare that study with ours because of the difference in categorizing pVL. For example, the lowest pVL category in their study was ≤5,000 copies/mL compared to ours of <50 copies/mL. Another study that clearly showed a relationship between pVL and HRQOL was that by Gill et al[6] but this study, beyond the difference in categorization of pVL, did not provide summary scores making comparison difficult. While the work by Preau et al used summary scores, their pVL cut-point was ≤400 copies/mL[9]. This difficulty in comparing plasma viral load in HRQOL/HIV research cuts across the literature as technological advancement led to fever viral copies being detected per mL of plasma. We avoided the use of the term 'detectable' for even within our cohort that term had applied to varying cut points over the years (<400copies/mL, <50 copies/mL and 48 copies/mL). That being said, and as we noted earlier in chapter 2, several studies in the late HAART era did not find an association between pVL and HRQOL[2,21-24].

The relationship between CD4 count and physical functional health is better established both in cross-sectional and longitudinal studies[7,9,10,21,23,25-27]. Yet, as others have noted the impact of ART on CD4 count is more evident in those with CD4 count <200 cells per cubic millimeter[28]. In our cohort we did not find differences between CD4 count 200-499 cells/mm^3 and CD4 count >499 cells/mm^3 at baseline but found the CD4 count 200-499 cells/mm^3 group had a slightly lower PCS scores over the period of follow-up similar to the findings by others[21]. Current recommendations on HAART initiation by the Department of Health and Human Services (DHHS) is for all HIV-infected individuals to start HAART irrespective of the level of CD4 count although the strength of the recommendation varies by CD4 groups[29]. While the recommendation for HAART

initiation for those with CD4 count >499 cells/mm^3 is based on expert opinion, the recommendation for HAART initiation in the those with CD4 count 350-500 cells/mm^3 is based on evidence from observational studies[29]. On the other hand, the World Health Organization[30] recommends starting ART at CD4 count <500 cells/mm^3. Unfortunately, these recommendations for HAART initiation were anchored solely on evidence that early ART initiation delayed progression to AIDS and reduced mortality[29,30] without taking into consideration the impact of HAART on HRQOL[31], which may actually affect HAART use on the long term. Burgoyne and Tran in their review of HRQOL in HIV-infected individuals in the HAART era cautioned on the need to balance prolonging life with the quality of life of the infected individual[31]. Perhaps the Strategic Timing of Anti-Retroviral Treatment (START) trial, which recently published its baseline HRQOL findings, may help determine the optimum time to initiate HAART in the antiretroviral-naïve HIV-infected persons[32]. The relationship between CD4 count and mental functional health is less defined with many studies finding no association while a few, like ours, found lower CD4 count to be associated with mental functional health[9,26,33].

A fundamental question that begs for answer in HRQOL research is: what is the clinical implication of HRQOL scores? When should the clinician pay particular attention to a patient based on his HRQOL scores? To answer this question some researchers have used the recommended using change in effect size[34-36] in describing changes in HRQOL scores in their longitudinal studies[37]. One approach in calculating effect size is to divide the differences in mean of the of the HRQOL scores at the different time points by pooled standard deviation of the means[37]. Others suggest using the baseline standard deviation instead[36]. Cohen suggested the use certain thresholds to determine the clinically

important differences with 0.2, 0.5 and 0.7 considered small (SCID), moderate (MCID), and large (SCID) clinically important differences (CID)[34]. Apart from the paucity of literature on the subject, its application in HRQOL research is limited[36]. In our current work for example, while covariates (with the exception of medical comorbidity) did not result in changes in HRQOL measures over time they still remained significant long-term predictors of the individual's perceived health. We will therefore take a look at another approach used by other investigators[6,10].

In their work, Gill et al[6] calibrated effect sizes by substituting known clinical conditions (acute diarrhea and clinical depression) for estimating effect sizes of these conditions on the HRQOL domain score. We note here that the use of the term 'effect size' is different from how Cohen used it, and refers to the magnitude of the beta coefficient (β) in the regression model in line with the use of the term by Ellis in his book, Essential Guide to Effect Sizes[38]. Substituting acute diarrhea and clinical depression in their multivariate models led to a score difference in physical functioning (PF) score by -4.6 (p = .03) and -6.5 (p = .003) respectively. On the other hand, the score differences in PF for CD4 count <200 cells/mm^3, pVL ($\log_{10}$), and HAART use were respectively -8.8, -7.7, and -5.4[6]. For their participants, having a CD4 count <200 cells/mm^3 was worse than having clinical depression or being on HAART was worse than having acute diarrhea! Similar arguments were put forward by Lorenz et al[10]. Hopman et al have suggested that HRQOL domain scores of 5 and above or summary scores (PCS and MCS) of 2 to 3 may be clinically and socially relevant[39]. This suggestion is in fact corroborated in our multivariate analyses (chapters 2 and 3). It may also be important to consider the baseline score for the cohort as reflected by the intercept for the model since a difference in score of 3 from 42 to 39

may be more useful clinically than a difference in score of 5 from 63 to 58. While score differences of 2 - 3 and above from covariates that are modifiable risk factors may warrant intervention, attention should also be placed on non-modifiable risk factors with summary score differences in that range as they may constitute a special risk group. In our baseline study for example, being civilian/retired was associated with a 3.3 point decrement in perceived physical health making them a possible risk group. In chapter 4, we see that being civilian/retired increased the hazard of hospitalization by over 100% even after adjusting for the other covariates including PCS and MCS.

But beyond the clinician, policy makers and administrators may also be interested in risk stratification in order to identify areas for possible intervention, and the cost-benefit analyses of which intervention to choose based on limited budget. Information sort by the health care administrator or a policy maker may not be very different from that sort by the clinician although the goal for such an inquiry may be different. Let us assume that a retired military personnel (PCS score = -2.5) with post-traumatic disorder (PCS score = -3.5) also has problems with housing but after seeing his PCP he is placed on therapy, referred to a psychiatrist, and his housing issues are resolved through the help of administrators. Suppose also that based on these measures his PCS score improves by 3, then we may have reduced his chances of hospitalization by 7.2% (please see chapter 4, table 4.3.b). If a 7.2% reduction in hospitalization across board leads to lessening of the clinicians workload with better quality services then this will be considered clinically significant[40]. From the economic point of view, if providing ancillary services to retired military personnel on the one hand leads to a significant reduction in hospitalization

resulting in a net budgetary gain, then the administrator and policy makers should have benefitted from the investment.

HRQOL measures should be seen as a predictor and not a cause of hospitalization. Attempts to provide explanatory models should be directed at fully understanding the factors contributing to HRQOL including those not well established. The conceptual model put forward by Wilson and Cleary was an important effort in that direction[41]. These authors expounded a conceptual model linking clinical variables to HRQOL. The model basically traces the cause to the biologic or physiologic process that results in a symptom status which could in turn affect functional status. Functional status then results in certain general health perceptions that affect the HRQOL of the individual. They also conceptualized the interplay between environmental factors and the individual's characteristics on the one hand and the clinical variables and HRQOL variables on the other (please see figure 5.1). The conceptual model expounded by Vidrine et al[42] is also appealing as it takes into account the role latent variables may play in HRQOL. Variables that are more likely to be affected by concerns on social desirability, such as alcohol use and smoking, may be better analyzed using structural equation modeling[42]. More recently the link between inflammatory markers and HRQOL seem to gaining attention in certain quarters, especially with psychiatric conditions such as depression[43] and post-traumatic stress disorder[44], and end stage renal disease[45]. While there appears to be a correlation between inflammatory markers and depression/PTSD[44], the evidence of such a relationship with end stage renal disease is lacking[45]. For inflammatory markers to be fully accepted as an explanatory model for HRQOL measures, first there has to be consistent association between common inflammatory markers (C-reactive protein

[CRP], tumor necrosis factor [TNF], and the interleukins [IL-1, IL-6]) and HRQOL, and two, a temporal sequence clearly showing that the inflammatory markers preceded the HRQOL outcome. Even then, the inflammatory markers would have to directly influence functional status well before routinely observed or measured symptoms appear. This is akin to having HRQOL serving as a screening test, pointing to the disease before it is obvious.

The impact of age and age-associated comorbidities on HIV-infected persons further complicates the relationship between HIV, HAART and HRQOL. It is estimated that by 2015, the number of older adults (defined as ≥50 years) would have reached 50%[46]. Although only 17% of our cohort fall into the older age group, age showed a positive linear relationship with physical functional health both in the baseline and longitudinal studies and an inverse relationship with mental functional health at baseline. Age is associated with increased vulnerability towards more rapidly advancing disease, including AIDS-defining illness, HIV-associated neuro-cognitive disorders, and mortality due to immune senescence and differential response to HAART[47-50]. Common comorbidities affecting HRQOL in HIV-infected persons include diabetes, cardiovascular and renal diseases, and cancers[47] (also see chapter 1). While there is increased comorbidity burden associated with age[47], the relationship could be more complex. For example, we noticed an improvement in PCS scores over the period of follow-up in those with medical comorbidity (chapter 3). How much of this positive impact is a reflection of the healthcare system is unknown. In our cohort by far the most important psychiatric comorbidity is depression.

Finally, one would expect significant variations in scores over time given the dynamic and subjective nature of HRQOL measures but that was not the case with our longitudinal study (chapter 3). Others have reported similar stability in HRQOL scores with long-term follow-up[33,51]. For our cohort, possible reasons for this would be the free movement of participants across groups especially the HAART-naïve and the Off-HAART groups to the PI-HAART and NPI-HAART groups, but even the PI-HAART and NPI-HAART groups crossed over. Descriptive analyses showed that between the first and second year there were 72 such cross overs, 41 between the second and third year and 31 for both the $3^{rd}/4^{th}$ and $4^{th}/5^{th}$ years. These cross-overs were basically influenced by HIV-disease markers (CD4 count and plasma viral load) but factors such as drug toxicities, and HIV-resistance strains may have played a role. As time passes, the perception of the individual may change and his or her priorities (values/goals) may also change, and these have the potential to keep scores stable or fluctuate only slightly over time as they may allocate higher scores to health domains they had previously scored low and low scores to domains they previously scored high. This adaptation of the individual to his changing health situation is what has been described as response shift[52-54]. Rapkin[53] defines response shift in QOL as a 'deviation of an observed score from some expected value, associated with a change in the way that the individual appraises QOL'. For response shift to occur, three criteria must be fulfilled: (i) a change in the respondent's internal standards of measurement resulting in *scale recalibration*; (ii) a change in the respondents values or the importance of the component domains constituting the target construct; and (iii) a redefinition of the target construct or *reconceptualization*[52,54]. Although response shift offers an attractive model to explain stability in HRQOL scores

over time, its evaluation often requires qualitative research[53,54]. One clue to possible presence of response shift in a multivariate regression model may be the degree of variances in the model and the presence of significant interaction term affecting the HRQOL score[53]. In our longitudinal models, the relative smallness of the error terms in the treatment groups (PI/NPI) compared to the non-treatment groups (Naïve/Off), and the significant effect of comorbidity*time interaction term are perhaps the best clue of the presence of response shift (figures 3.1.a-d and 3.2.a-d; tables 3.2.a, 3.2.b, 3.3.a). In concluding we will note that while some domain measures in the HRQOL assessment, such as general health perception, are affected by response shift, others, such as physical functioning, which ask questions about accomplishment of specific tasks, are not affected by response shift.

5.2: Recommendations

A few instruments have been recommended for use in clinical settings including clinical trials[1,55]. Grossman et al[1] recommended two generic instruments, the linear analogue self-assessment questionnaire (LASA), the SF-12 for their brevity, or the MOS-HIV in clinical setting. On the other hand Clayson et al[55] recommended the EQ-5D, the SF-36, health utilities index (HUI), functional assessment of HIV infection (FAHI) and MOS-HIV. Clayson et al based their recommendation on (1) content validity for physical function, social/role function and mental health/emotional well-being, (2) practicality (self-administered, taking $\leq$ 15 minutes with $\leq$ 50 items), (3) psychometric properties (dimensionality, reliability, validity, and responsiveness), and (4) the availability of normative data and/or population-based preference weights[13]. Based on the results of our studies (chapters 1, 2, 3, and 4), in which we used the summary scores both as outcome

as well as explanatory variables, our findings strongly support the use of SF-36 in clinical practice. The predictive, discriminative and concurrent validity makes it very suitable for use in risk stratification in clinical and research settings. We have clearly seen from our study the need to address the mental health needs of HIV-infected military personnel. To do so will need a commitment on the part of both administrators and clinicians. Furthermore, a multi-disciplinary approach may be more beneficial. Because completing the SF-36 questionnaire may take some valuable time during office visits, we encourage its completion well prior to patients clinical encounters with their primary care physicians/providers. Following this reasoning, we encourage the use of secured patients' portal in the electronic health records (EHR) system, which should be readily incorporated into their health records. With the passage of the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009[56] and the other incentives programs by the Centers for Medicare and Medicaid (CMS), such as Meaningful Use of the EHR[57], we believe it will be much easier to incorporate these measures now than it was in the past. Taking the HRQOL survey ahead of their annual comprehensive physical examination may make it more acceptable to patients. On the part of developers of the instrument, we encourage the development of SF-36 application that is user friendly. This app should allow for both domain and summary scores to be calculated, at least for the provider specific SF-36 app. In that case, the information in the patient-specific app should be transferable to the clinician-specific app. We believe such measures are likely to make incorporating HRQOL measurement in clinical practice more acceptable to practitioners.

We recommend future research using the SF-36 or other instruments to separately report both the physical component summary scores (PCSS) and mental component summary scores (MCSS), rather than the global or overall HRQOL scores. This is because the summary scores (PCSS and MCSS) capture different attributes in the individual or participants[32] (chapters 2, 3, and 4). Also, it facilitates comparisons of results across different HIV-infected populations, and across groups with different medical conditions but even more importantly with general US population, therefore enabling us to gauge the burden of HIV on the individual. Reporting of only the eight health domain scores without inclusion of the summary scores should be discouraged. That being said, we encourage further subscale (or domain) analyses in order to fully understand which domains are primarily affected in the summary scores, which might be important in respect to specific interventions. This could still be done for our cohort.

Further support for the use of the SF-36 is based on the increasing burden of medical and psychiatric comorbidities among HIV-infected persons. We believe its use may provide more advantages than the use of HIV-disease specific instruments under these circumstances. With HAART being increasingly started at higher CD4 counts, it is unlikely that routine clinical assessment of the infected individual based on HIV-disease indicators (CD4 count and viral loads) will provide the needed information on patient satisfaction with treatment, and assessment of HRQOL may offer that opportunity. While HIV-infection can now be classified as a chronic disease, such as hypertension, diabetes and coronary artery disease, we must not fail to lose sight of the fact that HIV is still an infectious disease, and that the infected individual may engage in risk taking behaviors over time. Efforts should therefore be made to always assess the individual's overall

well-being and motivational level, and we believe measurement of HRQOL provides that opportunity.

5.3: Figures

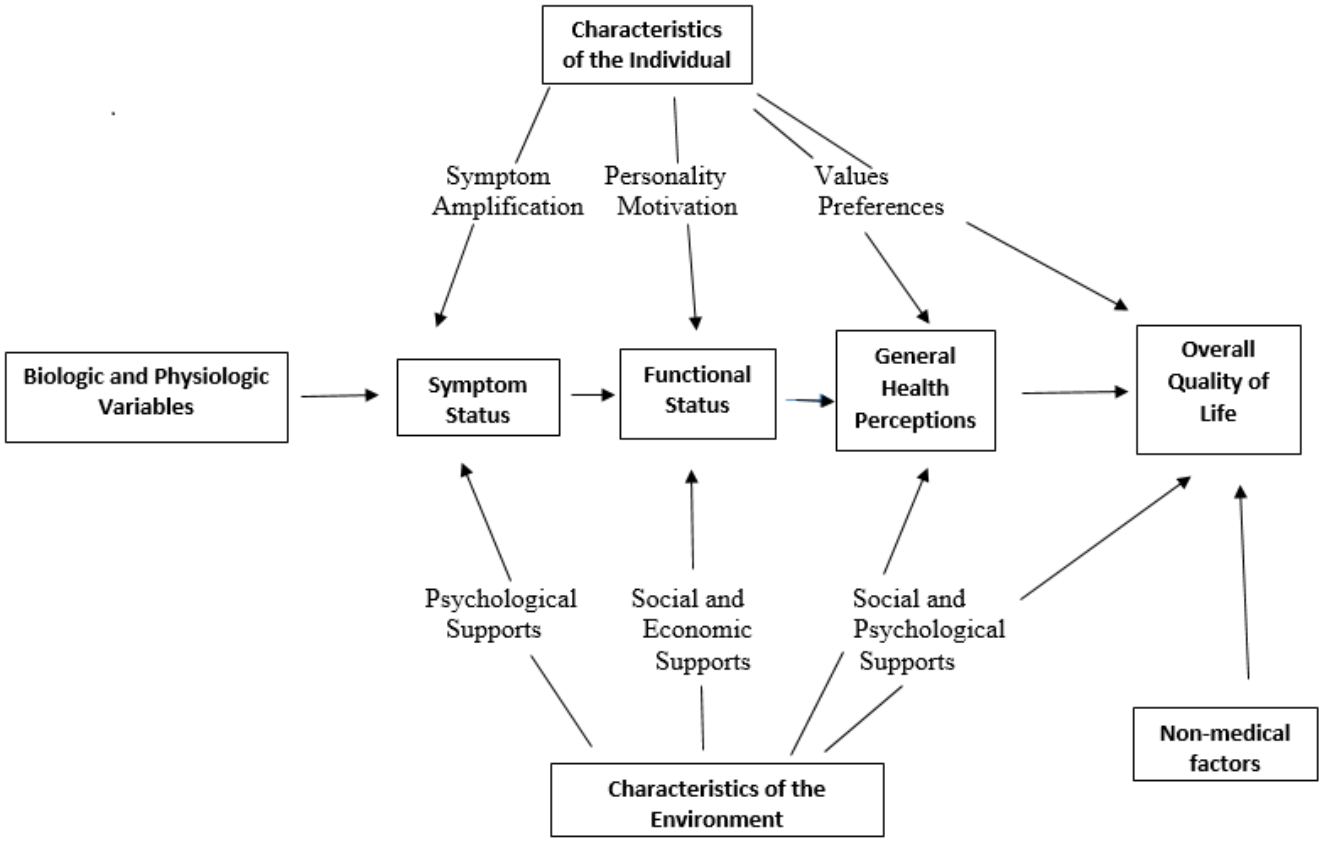


Figure 5.1: Relationship among measures of patient outcome in HRQOL conceptual model. From Linking Clinical Variables with HRQOL: Aconceptual Model of Patient Outcomes - I.B. Wilson and P.D. Cleary

5.4: References

1. Grossman HA, Sullivan PS, Wu AW. Quality of life and HIV: current assessment tools and future directions for clinical practice. *The AIDS reader.* 2003;13(12):583-590, 595-587.
2. Briongos Figuero LS, Bachiller Luque P, Palacios Martin T, Gonzalez Sagrado M, Eiros Bouza JM. Assessment of factors influencing health-related quality of life in HIV-infected patients. *HIV medicine.* 2011;12(1):22-30.
3. Degroote S, Vogelaers D, Vandijck DM. What determines health-related quality of life among people living with HIV: an updated review of the literature. *Archives of public health = Archives belges de sante publique.* 2014;72(1):40.
4. Gnecco C, Lachenbruch PA. Regulatory Aspects of Quality of Life. In: Mesbah M, Cole BF, Lee TM, eds. *Statistical Methods for Quality of Life Studies: Design, Measurements and Analysis*. Dordrecht/Boston/London: Kluwer Academic Publishers; 2000.
5. Gakhar H, Kamali A, Holodniy M. Health-related quality of life assessment after antiretroviral therapy: a review of the literature. *Drugs.* 2013;73(7):651-672.
6. Gill CJ, Griffith JL, Jacobson D, Skinner S, Gorbach SL, Wilson IB. Relationship of HIV viral loads, CD4 counts, and HAART use to health-related quality of life. *Journal of acquired immune deficiency syndromes (1999).* 2002;30(5):485-492.
7. Call SA, Klapow JC, Stewart KE, et al. Health-related quality of life and virologic outcomes in an HIV clinic. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2000;9(9):977-985.
8. Campsmith ML, Nakashima AK, Davidson AJ. Self-reported health-related quality of life in persons with HIV infection: results from a multi-site interview project. *Health and quality of life outcomes.* 2003;1:12.
9. Preau M, Marcellin F, Carrieri MP, Lert F, Obadia Y, Spire B. Health-related quality of life in French people living with HIV in 2003: results from the national ANRS-EN12-VESPA Study. *AIDS (London, England).* 2007;21 Suppl 1:S19-27.
10. Lorenz KA, Cunningham WE, Spritzer KL, Hays RD. Changes in symptoms and health-related quality of life in a nationally representative sample of adults in treatment for HIV. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2006;15(6):951-958.
11. Jacobson DL, Wu AW, Feinberg J. Health-related quality of life predicts survival, cytomegalovirus disease, and study retention in clinical trial participants with advanced HIV disease. *Journal of clinical epidemiology.* 2003;56(9):874-879.
12. Cunningham WE, Crystal S, Bozzette S, Hays RD. The association of health-related quality of life with survival among persons with HIV infection in the United States. *Journal of general internal medicine.* 2005;20(1):21-27.
13. Mathews WC, May S. EuroQol (EQ-5D) measure of quality of life predicts mortality, emergency department utilization, and hospital discharge rates in HIV-infected adults under care. *Health and quality of life outcomes.* 2007;5:5.
14. de Boer-van der Kolk IM, Sprangers MA, Prins JM, Smit C, de Wolf F, Nieuwkerk PT. Health-related quality of life and survival among HIV-infected patients receiving highly active antiretroviral therapy: a study of patients in the AIDS Therapy Evaluation in the Netherlands (ATHENA) Cohort. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2010;50(2):255-263.

15. O'Cleirigh C, Skeer M, Mayer KH, Safren SA. Functional impairment and health care utilization among HIV-infected men who have sex with men: the relationship with depression and post-traumatic stress. *Journal of behavioral medicine.* 2009;32(5):466-477.
16. Cook JA, Cohen MH, Burke J, et al. Effects of depressive symptoms and mental health quality of life on use of highly active antiretroviral therapy among HIV-seropositive women. *Journal of acquired immune deficiency syndromes (1999).* 2002;30(4):401-409.
17. Schwartz CE, Sprangers MAG. Introduction. In: Schwartz CE, Sprangers MAG, eds. *Adaptation to Changing Health: Response Shift in Quality-of-Life Research*. Washington, DC: American Psychological Association; 2000.
18. Drewes J, Gusy B, Ruden U. More than 20 years of research into the quality of life of people with HIV and AIDS--a descriptive review of study characteristics and methodological approaches of published empirical studies. *Journal of the International Association of Providers of AIDS Care.* 2013;12(1):18-22.
19. Jin Y, Liu Z, Wang X, et al. A systematic review of cohort studies of the quality of life in HIV/AIDS patients after antiretroviral therapy. *International journal of STD & AIDS.* 2014;25(11):771-777.
20. Walker AM. Confounding by indication. *Epidemiology.* 1996;7(4):335-336.
21. Liu C, Johnson L, Ostrow D, Silvestre A, Visscher B, Jacobson LP. Predictors for lower quality of life in the HAART era among HIV-infected men. *Journal of acquired immune deficiency syndromes (1999).* 2006;42(4):470-477.
22. Ruiz Perez I, Rodriguez Bano J, Lopez Ruz MA, et al. Health-related quality of life of patients with HIV: impact of sociodemographic, clinical and psychosocial factors. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2005;14(5):1301-1310.
23. Murri R, Fantoni M, Del Borgo C, et al. Determinants of health-related quality of life in HIV-infected patients. *AIDS care.* 2003;15(4):581-590.
24. Worthington C, Krentz HB. Socio-economic factors and health-related quality of life in adults living with HIV. *International journal of STD & AIDS.* 2005;16(9):608-614.
25. Kowal J, Overduin LY, Balfour L, Tasca GA, Corace K, Cameron DW. The role of psychological and behavioral variables in quality of life and the experience of bodily pain among persons living with HIV. *Journal of pain and symptom management.* 2008;36(3):247-258.
26. Armon C, Lichtenstein K. The associations among coping, nadir CD4+ T-cell count, and non-HIV-related variables with health-related quality of life among an ambulatory HIV-positive patient population. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2012;21(6):993-1003.
27. Jia H, Uphold CR, Wu S, Chen GJ, Duncan PW. Predictors of changes in health-related quality of life among men with HIV infection in the HAART era. *AIDS patient care and STDs.* 2005;19(6):395-405.
28. Nieuwkerk PT, Hillebrand-Haverkort ME, Vriesendorp R, Frissen PH, de Wolf F, Sprangers MA. Quality of life after starting highly active antiretroviral therapy for chronic HIV-1 infection at different CD4 cell counts. *Journal of acquired immune deficiency syndromes (1999).* 2007;45(5):600-601.
29. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. .

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed May 22, 2015.

30. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2013; http://www.who.int/hiv/pub/guidelines/arv2013/download/en/. Accessed May 22, 2015.
31. Burgoyne RW, Tan DH. Prolongation and quality of life for HIV-infected adults treated with highly active antiretroviral therapy (HAART): a balancing act. *The Journal of antimicrobial chemotherapy.* 2008;61(3):469-473.
32. Lifson AR, Grandits GA, Gardner EM, et al. Quality of life assessment among HIV-positive persons entering the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. *HIV medicine.* 2015;16 Suppl 1:88-96.
33. Protopopescu C, Marcellin F, Spire B, et al. Health-related quality of life in HIV-1-infected patients on HAART: a five-years longitudinal analysis accounting for dropout in the APROCO-COPILOTE cohort (ANRS CO-8). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2007;16(4):577-591.
34. Cohen J. *Statistical power analysis for the behavioral sciences.* 2nd ed. Hillsday, New Jersey.: Lawrence Erlbaum Associates; 1988.
35. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Medical care.* 1989;27(3 Suppl):S178-189.
36. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *PharmacoEconomics.* 1999;15(2):141-155.
37. Burgoyne RW, Rourke SB, Behrens DM, Salit IE. Long-term quality-of-life outcomes among adults living with HIV in the HAART era: the interplay of changes in clinical factors and symptom profile. *AIDS and behavior.* 2004;8(2):151-163.
38. Ellis E. *The Essential Guide to Effect Sizes: Statistical Power, Meta-Analysis, and the Interpretation of Research Results.* Cambridge, United Kingdom: Cambridge University Press; 2010.
39. Hopman WM, Berger C, Joseph L, et al. Health-related quality of life in Canadian adolescents and young adults: normative data using the SF-36. *Canadian journal of public health = Revue canadienne de sante publique.* 2009;100(6):449-452.
40. Wittes J. The Use of Soft Endpoints in Clinical Trials: The Search for Clinical Signifiance. In: Mesbah M, Cole BF, Lee M-LT, eds. *Statistical Methods for Quality of Life Studies: Design, Measurements and Analysis*. Boston, USA: Kluwer Academic Publishers; 2002:129-140.
41. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA.* 1995;273(1):59-65.
42. Vidrine DJ, Amick BC, 3rd, Gritz ER, Arduino RC. Assessing a conceptual framework of health-related quality of life in a HIV/AIDS population. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2005;14(4):923-933.
43. Bonaccorso S, Marino V, Puzella A, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J Clin Psychopharmacol.* 2002;22(1):86-90.

44. Gill JM, Saligan L, Lee H, Rotolo S, Szanton S. Women in recovery from PTSD have similar inflammation and quality of life as non-traumatized controls. *J Psychosom Res.* 2013;74(4):301-306.
45. Spiegel BM, Melmed G, Robbins S, Esrailian E. Biomarkers and health-related quality of life in end-stage renal disease: a systematic review. *Clin J Am Soc Nephrol.* 2008;3(6):1759-1768.
46. Doyle K, Weber E, Atkinson JH, Grant I, Woods SP. Aging, prospective memory, and health-related quality of life in HIV infection. *AIDS and behavior.* 2012;16(8):2309-2318.
47. Rodriguez-Penney AT, Iudicello JE, Riggs PK, et al. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. *AIDS patient care and STDs.* 2013;27(1):5-16.
48. Gardner ID. The effect of aging on susceptibility to infection. *Rev Infect Dis.* 1980;2(5):801-810.
49. Bamford LP, Ehrenkranz PD, Eberhart MG, Shpaner M, Brady KA. Factors associated with delayed entry into primary HIV medical care after HIV diagnosis. *AIDS (London, England).* 2010;24(6):928-930.
50. Effros RB, Fletcher CV, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2008;47(4):542-553.
51. Holodniy M, Brown ST, Cameron DW, et al. Results of antiretroviral treatment interruption and intensification in advanced multi-drug resistant HIV infection from the OPTIMA trial. *PloS one.* 2011;6(3):e14764.
52. Sprangers MA, Schwartz CE. Integrating Response Shift Into Health-Related Quality of Life Research: A Theoretical Model. In: Schwartz CE, Sprangers MA, eds. *Adaptation to Chaning Health: Response Shift in Quality-of-Life Research*. Washington DC: American Psychological Association; 2000:11-23.
53. Rapkin BD. Personal Goals and Response Shifts: Understanding the Impact of Illness and Events on Quality of Life of People Living With AIDS. In: Schwartz CE, Sprangers MA, eds. *Adaptation to Chaning Health: Response Shift in Quality-of-Life Research*. American Psychological Association: Washington DC; 2000:53-71.
54. Wilson IB. Clinical Understnading and Clinical Implications of Response Shift. In: Schwartz CE, Sprangers MA, eds. *Adaptation to Chaning Health: Response Shift in Quality-of-Life Research*. Washington DC: American Psychological Association; 2000:159-173.
55. Clayson DJ, Wild DJ, Quarterman P, Duprat-Lomon I, Kubin M, Coons SJ. A comparative review of health-related quality-of-life measures for use in HIV/AIDS clinical trials. *PharmacoEconomics.* 2006;24(8):751-765.
56. Buntin MB, Burke MF, Hoaglin MC, Blumenthal D. The benefits of health information technology: a review of the recent literature shows predominantly positive results. *Health Aff (Millwood).* 2011;30(3):464-471.
57. Centers for Medicare and Medicaid Services (CMS). EHR Incentive Programs. 2011; http://www.cms.gov/EHRIncentiveprograms. Accessed May 23, 2015.

VITA

Leonard Emuren obtained his Bachelor of Medicine, Bachelor of Surgery (MBBS) degree from the University of Ibadan, Nigeria. He completed his internship at the University of Port-Harcourt Teaching Hospital, Nigeria, after which he practiced in various clinical settings before relocating to the United States of America.

Leonard obtained his master of public health (MPH) degree with concentration in Epidemiology from the Eastern Virginia Medical School/Old Dominion University, Norfolk. His master's degree research collaboration with the Hampton (City) Health Department led to the publication of "Epidemiology of infant death among black and white non-Hispanic populations in Hampton Roads, Virginia".

Certified by the Educational Commission for Foreign Medical Graduates (ECFMG), Leonard has a strong interest in infectious diseases, clinical medicine, and public health research.