BONES, FRACTURES, ANTIRETROVIRAL THERAPY AND HIV

by

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A thesis submitted to the Faculty and the Board of Trustees of the Colorado School of Mines in partial fulfillment for the degree of Doctor of Philosophy (Environmental Science and Engineering).

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ABSTRACT

Although low bone mineral density (BMD) and bone fractures are increased among HIV-infected adults compared with the general population, no studies have yet characterized their causal association or probability of fracture in the context of HIV infection. Using dual energy X-ray absorptiometry (DEXA) BMD values of the left femoral neck, clinical data collected from two US Centers for Disease Control and Prevention-sponsored HIV cohort studies, factors associated with low BMD, and association of low BMD with subsequent incident fracture were analyzed. Using the FRAX® algorithm, rates of any new bone fracture and major osteoporotic fracture per 100 person-years of follow-up, stratified by initial FRAX® score intervals were assessed. Clinical and demographic risk factors for any new fracture were identified.

Among 1008 patients contributing 5,032 person-years of follow-up, 36.3% had osteopenia and 2.9% had osteoporosis. Ninety-five incident fractures were observed, predominantly rib/sternum, hand, foot and wrist. Low BMD was significantly associated with age, lower nadir CD4, history of fracture, and male-male sex HIV transmission risk. In multivariable analyses, only osteoporosis and increasing age remained associated with incident fracture. In a separate analysis, FRAX® score of >3% was also independently predictive of new fracture.

In this cohort, median FRAX® scores were higher for those who had any subsequent new fracture vs. those who did not. Of the new fractures, 7.1% occurred among persons with FRAX® score <3% (1.39 per 100py) and 15.3% among persons with FRAX® score ≥3% (3.27 per 100py). New major osteoporotic fractures were
observed among 1.5% of persons with FRAX® score <3% (0.30 per 100py), and among 4.9% (1.04 per 100py) of persons with FRAX® score ≥3%.

In this large convenience sample of relatively young HIV-infected U.S. adults, low baseline BMD and increasing age were strongly associated with elevated risk of incident fracture, highlighting the potential value of DEXA screening in this population. A FRAX® score ≥3%, low baseline BMD, history of prior fracture, and increasing age were significantly associated with elevated risk of new fracture.
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<tr>
<td>ACTG</td>
<td>AIDS Clinical Trials Group</td>
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<tr>
<td>aHR</td>
<td>Adjusted hazard ratio</td>
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<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<tr>
<td>ANI</td>
<td>Asymptomatic neurocognitive impairment</td>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>AVN</td>
<td>Avascular necrosis</td>
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<td>AZT</td>
<td>Azidothymidine</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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<td>BMI</td>
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<tr>
<td>cART</td>
<td>Combined antiretroviral therapy</td>
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<td>CHARTER</td>
<td>Central Nervous System HIV Antiretroviral Therapy Effects Research</td>
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<tr>
<td>CI</td>
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<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>CSM</td>
<td>Colorado School of Mines</td>
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<tr>
<td>CTL</td>
<td>Cytotoxic T-lymphocytes</td>
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<tr>
<td>DEXA</td>
<td>Dual energy x-ray absorptiometry</td>
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<td>DIDC</td>
<td>Denver Infectious Disease Clinic</td>
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<td>Diagnosis</td>
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<td>EIA</td>
<td>Enzyme immunoassay</td>
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<td>EACS</td>
<td>European AIDS Clinical Society</td>
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<td>EOS</td>
<td>Endocrine Society</td>
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<td>ETOH</td>
<td>Alcohol</td>
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<tr>
<td>FRAT</td>
<td>Fall risk assessment tool</td>
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<td>FRAX</td>
<td>Fracture risk assessment tool</td>
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<td>HAND</td>
<td>HIV-associated neurocognitive disorder</td>
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<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
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<td>HCV</td>
<td>Hepatitis-C virus</td>
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<td>HIV</td>
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<tr>
<td>HIV+</td>
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<td>HIV-</td>
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<td>HOPS</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>HSE</td>
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<td>HSSE-SR</td>
<td>Health Safety Security Environment and Social Responsibility</td>
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<td>IDSA</td>
<td>Infectious Disease Society of America</td>
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<td>IDU</td>
<td>Intravenous drug use</td>
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<tr>
<td>IFA</td>
<td>Immunofluorescent assay</td>
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<tr>
<td>INSTI</td>
<td>Integrase strand transfer inhibitor</td>
<td></td>
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<tr>
<td>IOF</td>
<td>International Osteoporosis Foundation</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>IRB</td>
<td>Internal Review Board</td>
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<tr>
<td>ISCD</td>
<td>International Society for Clinical Densitometry</td>
<td></td>
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<tr>
<td>IU</td>
<td>International unit</td>
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<tr>
<td>MSM</td>
<td>Men having sex with men</td>
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NHAMCS-OPD  National Hospital Ambulatory Medical Care Survey Outpatient Departments
NHANES III  National Health and Nutrition Examination Survey III
NOF  National Osteoporosis Foundation
NRTI  Nucleoside reverse transcriptase inhibitor
NNRTI  Nucleoside analog reverse transcriptase inhibitor
PCR  Polymerase chain reaction
PI  Protease inhibitor
PLWH  People living with HIV
RANKL  Receptor activator of nuclear factor kappa-B ligand
RAL  Raltegravir
SD  Standard deviation
SI  Syncytia-inducing
SUN  Study to Understand the Natural History of HIV in the Era of Effective Therapy
TDF  Tenofovir difumarate
VACS  Veterans Aging Cohort Study
VACS-VC  Veterans Aging Cohort Study Virtual Cohort
VHA CCR  Veterans Health Administration Clinical Case Registry
WIHS  Women’s Interagency HIV Study
ACKNOWLEDGMENTS

I would like to thank my advisors, Dr. John R. Spear and Dr. Benjamin Young, Dr. Carl Armon, Biostatistician with Cerner Corporation, the SUN and HOPS Investigators and most of all, the SUN and HOPS patients without whose participation this work would not have been created.

I would also like to thank my committee: Dr. Ramona M. Graves, Dr. Junko M. Marr, Dr. Mark G. Miller, and Dr. Daniel T. Teitelbaum.
CHAPTER 1
GENERAL INTRODUCTION

1.1 Background

Health, safety, security, environment and social responsibility (HSSE-SR) are critical elements of sound project investment and development. A comprehensive development program must include analysis of HSSE-SR considerations and challenges to mitigate risks and to achieve development goals. The challenge is to identify new sources of risks and new approaches to manage these risks. Newer and evolving in the oil and gas industry is the element of social responsibility (SR). Managing SR is now an operational budget item as it drives innovation, attracts business opportunities, and builds reputational capital, at a minimum.

The prevention and management of infectious diseases, including human immunodeficiency virus (HIV) infection, has been an area of increasing focus of the oil and gas industry. HIV infection is highly prevalent in many of the regions where oil and gas production occurs. With the introduction of antiretroviral therapy, people living with HIV are living longer and able to participate in the work force. Recent epidemiological studies indicate that age-related illnesses are more common in HIV-infected individuals than in age-matched uninfected individuals. Together with the typical age-related illnesses of older people, challenging workplace issues are foreseeable.

Among long-term survivors of HIV infection, increased risk of bone, heart, cognitive diseases and certain malignancies have been described. Associations exist between bone health in HIV-infected persons and increased risk of fragility fractures. Additionally, cardiovascular disease and neurocognitive deficits are recognized as
occurring prematurely in HIV-infected individuals. Further, it is suggested that long-term antiretroviral therapy may result in medication toxicity. Such degenerative illnesses have wide impact on health and the working environment during exploration and production operations including reduced productivity, reduction in labor pool experience, and increased safety risks in transporting, lifting, and equipment operation. Outcomes like these result in additional project and health costs that are ultimately paid by the operator, contractor, stakeholder and the community.

My dissertation research falls squarely within the intersection of environmental science and engineering. No engineering project is devoid of the human workforce. The health of that workforce is a risk issue and a project management issue. Understanding recent epidemiological findings and their application to project environments is essential to maintaining a healthy workforce and a timely, cost effective engineering project.

1.2 Motivation for Research

As a petroleum engineer and attorney, I frequently traveled to resource-limited countries to discuss hydrocarbon project development with government officials, engineers and stakeholders. During my travels, I became interested in the health of persons in these countries who were stricken by infectious diseases, namely, tuberculosis, malaria and human immunodeficiency virus – 1 (HIV). My interest in HIV and public health led me to seek a research project working with Benjamin Young, MD, PhD, who studies bone health among other topics in HIV-infected individuals. Under the guidance of Dr. John R. Spear, Department of Civil and Environmental Engineering, at Colorado School of Mines (CSM), this ongoing project studying bone health in HIV-
infected adults, in collaboration with the United States (US) Centers for Disease Control and Prevention (CDC), has emerged as the focus of my PhD dissertation.

For several years, the CDC-funded HIV Outpatient Study (HOPS) has been involved in research on bone health in the HIV population. HOPS reported the first nation-wide survey on bone fracture rates, finding that age- and gender-adjusted fracture rates were 2- to 3-times higher among HIV-infected adults than the general population (Young et al. 2011). Additional analyses explored the relationship between bone mineral density (BMD) and fracture risk and showed that even among a population of relatively young, HIV-infected adults, low bone mineral density was associated with increased fracture risk. This research is presented in Chapter 5 of this dissertation. Further analyses explored new fractures and the FRAX® 10-year probability of fracture in HIV-infected adults and revealed that a FRAX score ≥ 3%, low baseline BMD, history of prior fracture, and increased age were significantly associate with elevated risk of new fracture. This research is presented in Chapter 6 of this dissertation.

HOPS bone analyses have been featured at the 2013 European AIDS Clinical Society Conference in Brussels, Belgium and the 2014 Conference on Retroviruses and Opportunistic Infections in Boston, Massachusetts.

1.2 Thesis Organization

This thesis comprises presented, published, and intended to be published work in the field of human immunodeficiency virus – 1 (HIV), HIV and aging, and bone health and fracture risk of HIV-infected adults. In Chapter 1, the motivation and organization of this thesis is described. Chapter 2 includes a published conference proceedings paper, presented internationally in poster format, describing comorbidities in people living with
HIV (PLWH) in an engineering project workplace context. I am the primary researcher, author and corresponding author. Dr. John R. Spear, Colorado School of Mines and Dr. Benjamin Young, International Association of Providers in AIDS Care and APEX Family Medicine and Research, are co-authors.


Chapter 4 is a literature review modified from a peer-reviewed journal article in World Journal of AIDS describing changes in bone mineral density (BMD) through 96 weeks in antiretroviral-naïve HIV-1 infected patients receiving Abacavir/Lamivudine and Raltegravir in the SHIELD Trial. I am the primary author, Amy Thomas, Brian Wine, Belinda Ha are co-authors. Dr. Benjamin Young is the corresponding author.

In collaboration with the United States (US) Centers for Disease Control and Prevention (CDC), Chapter 5 focuses on bone mineral density (BMD) and its association with incident fracture risk in HIV-infected adults participating in two CDC-funded study populations, the HIV Outpatient Study (HOPS) and the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN). This material was presented both orally and in poster format at international and domestic conferences and will be submitted to the peer-reviewed journal, Clinical
Infectious Diseases. I am the primary researcher and author. Co-authors include Kate Buchacz, Centers for Disease Control and Prevention, Carl Armon, Cerner Corporation, Edgar T. Overton, University of Alabama School of Medicine, John Hammer, Denver Infectious Disease Consultants, Pragna Patel, Centers for Disease Control and Prevention, Joan Chmiel, Feinberg School of Medicine, Northwestern University, Tim Bush, Centers for Disease Control and Prevention, John T. Brooks, Centers for Disease Control and Prevention and Benjamin Young, corresponding author, APEX Family Medicine and Research, International Association of Providers in AIDS Care.

Chapter 6 is a continued analysis of data from the SUN and HOPS describing new fracture risk and FRAX® 10-year probability of fracture in HIV-infected adults. This material was presented domestically in poster format, is accepted for upcoming international presentation and will be submitted to the peer-reviewed journal, Clinical Infectious Diseases. I am the primary researcher and author. Co-authors include Kate Buchacz, Centers for Disease Control and Prevention, Carl Armon, Cerner Corporation, Edgar T. Overton, University of Alabama School of Medicine, John Hammer, Denver Infectious Disease Consultants, Joan Chmiel, Feinberg School of Medicine, Northwestern University, Pragna Patel, Centers for Disease Control and Prevention, Tim Bush, Centers for Disease Control and Prevention, John Brooks, Centers for Disease Control and Prevention, and Benjamin Young, corresponding author, APEX Family Medicine and Research, International Association of Providers in AIDS Care.

Chapter 7 is a peer-reviewed, invited review article in Current Infectious Diseases Reports (epublished ahead of print, March 2014) describing the state-of-the-science of bones, fractures, antiretroviral therapy and HIV. I am the primary author.
Co-authors include Dr. Benjamin Young, APEX Family Medicine and Research, International Association of Providers in AIDS Care, and Dr. Edgar Turner Overton, corresponding author, University of Alabama School of Medicine. Chapter 8 provides a general discussion and recommendations for future research.

Appendix A is a discussion of HIV, immune system components and antiretroviral therapy (ART). Appendix B describes statistical analyses used in the thesis and includes the curriculum vitae of CDC contracted Cerner Corporation biostatistician, Dr. Carl Armon, who performed the statistical analyses in Chapters 5 and 6. Appendix C includes the SUN and HOPS Study Patient Consents. Appendix D includes the permissions to include my publications in the thesis.
CHAPTER 2
HIV AND AGING: AN EVOLVING CHALLENGE FOR THE OIL AND GAS INDUSTRY

A paper published in the proceedings of the Society of Petroleum Engineers (SPE)/Australian Petroleum Production & Exploration Association (APPEA) International Conference on Health, Safety, and Environment in Oil and Gas Exploration and Production held in Perth, Australia 11 – 13 September 2012, SPE-158121-PP and presented in poster format at the conference.

Linda A. Battalora, John R. Spear, Benjamin Young

2.1 Abstract

The prevention and management of infectious diseases, including human immunodeficiency virus (HIV) infection, has been an area of increasing focus of the oil and gas industry. HIV infection is highly prevalent in many of the regions where oil and gas production occurs. With the introduction of antiretroviral therapy, people living with HIV are living longer and able to participate in the work force. Recent epidemiological studies indicate that age-related illnesses are more common in HIV-positive (HIV+) individuals than in age-matched HIV-negative (HIV-) individuals. Together with the typical age-related illnesses of older people, challenging workplace issues are foreseeable.

Among long-term survivors of HIV infection, increased risk of bone, heart, cognitive diseases and certain malignancies have been described. Correlations exist between bone health in HIV-infected persons and increased risk of fragility fractures. Additionally, cardiovascular disease and neurocognitive deficits are recognized as occurring prematurely in HIV+ individuals. Further, it is suggested that long-term antiretroviral therapy may result in medication toxicity. Such degenerative illnesses
have wide impact on health and the working environment during exploration and production operations including reduced productivity, reduction in labor pool experience, and increased safety risks in transporting, lifting, and equipment operation. Outcomes like these result in additional project and health costs that are ultimately paid by the operator, contractor, stakeholder and the community.

This paper highlights recent epidemiological findings based on cohort studies, translates their relevance to the oil and gas industry, discusses their direct impact on health and the working environment, personal safety, health safety and environment (HSE) management, and suggests timely industry preparation for workplace issues resulting from HIV and aging, both premature and chronological aging.

2.2 Introduction

HIV and aging, both premature and chronological, is an evolving challenge that the oil and gas industry, similar to other global employers, will need to address. Recent epidemiological findings should raise industry awareness of the increase in premature age-related illnesses of the HIV+ work force and increased potential for employee work cessation as a result of these illnesses. Obvious areas for discussion include the need for internal corporate modifications concerning occupational health, assessment, job placement and health care programs. What remains for consideration is the impact of HIV and aging “in the field.”

Bone, cardiovascular, and renal disease, certain malignancies, and neurocognitive deficits, i.e., comorbidities, are increasingly more common among long-term survivors of HIV infection. As the work force ages, both prematurely and chronologically, employers must be proactive in mitigating the potential for reduced
productivity resulting from increased employee work cessation and a reduction in labor pool experience. Other concerns arise directly from the oil and gas fields.

How to mitigate personal safety, well site safety, and health safety and environment (HSE) management risks with an HIV+ work force population burdened with comorbidities and performing typical exploration and production operations, including transporting, lifting, and equipment operation, is worthy of consideration at this time. The goal of this paper is to increase recognition of HIV associated comorbidities that may negatively impact the performance of the work force resulting in unwanted economic consequences for the oil and gas operator, contractor, stakeholder and community.

2.3 Discussion

In the following section, HIV and aging, both premature and chronological aging, will be described. This is followed by a discussion of comorbidities including bone diseases and risk of fracture in the HIV-infected population, cardiovascular disease, liver and renal diseases, certain malignancies, neurocognitive diseases, and medication toxicity.

2.3.1 HIV and Aging, Both Premature and Chronological Aging

With the introduction of antiretroviral therapy (ART), people living with HIV/AIDS (PLWHA) are living longer. Consequently, there is a shift in the HIV population from younger to older individuals (Mack and Ory 2003; Ofotokun and Weitzmann 2010). As much as 35 years of additional life expectancy is now predicted at the time of HIV diagnosis (Lohse et al. 2007). It is suggested that by 2015, 50% of people living with HIV infection in the United States will be ≥50 years of age (High et al. 2012). Similar
trends are emerging in resource-limited regions (Negin et al. 2010a; Negin and Cumming 2010b).

Diseases unrelated to HIV but found in aging individuals are now commonly diagnosed in PLWHA at younger ages than their non-infected counterparts (Slavin et al. 2011). Low bone mineral density (BMD) resulting in osteopenia and osteoporosis, diabetes mellitus, renal disease, cardiovascular disease (CVD), liver disease, neurocognitive impairment, and some cancers (Hasse et al. 2011) are among these diseases. It is suggested too that HIV/AIDS may hasten the aging process in HIV-infected persons (Ofotokun 2011; Deeks and Phillips 2009).

Age-related illnesses typically manifest in decline of physical function often leading to the inability to earn a living and decreased social interaction. Further, these changes in socio-economic conditions can affect the mental health of the patient resulting in depression and limitations in cognitive functional areas (Fumaz et al. 2012).

The economic impact of aging rests not with the patient alone. Often the patient becomes disabled, requiring rehabilitation or a long-term care facility. The cost of this care is largely the responsibility of the afflicted individual, but without ability to earn a living, or increased illness severity, resources can become quickly exhausted. Thus, the monetary burden is shared with society as a whole through lost productivity, unemployment, increased health care costs and greater demand on health care providers.

Aging, apart from an infectious disease such as HIV, is a natural, sequential part of life, and the fact that it is occurring prematurely in PLWHA is the subject of considerable study and some debate (Fisher and Cooper 2012). The epidemiological
findings from these studies are instructive not only to the medical community, but to insurers, stakeholders, and employers.

2.3.2 HIV and Comorbidities

While extensive studies and findings exist in the literature regarding HIV, aging and comorbidities, this paper is limited to a brief presentation of common comorbidities associated with PLWHA. Multiple large cohort studies reveal the changing distribution of medical conditions.

In the observational Swiss HIV Cohort study (SHCS), Hasse and colleagues investigated morbidity and aging in 8,444 HIV-seropositive cohort participants in three age groups, <50 years (68.2% of the participants), 50-64 years (26.4% of the participants), and ≥65 years (5.3% of the participants), from January 2008 to December 2010 (Hasse et al. 2011). Baseline participant characteristics included 7184 (85%) participants taking ART, 15.4 years median duration of HIV-infection, median age of 45 years, 29% female, and 23% having prior clinical AIDS. From January 2008 to December 2010, 994 incident non-AIDS events were observed including 201 cases of bacterial pneumonia, 55 myocardial infarctions, 39 strokes, 70 cases of diabetes mellitus, 123 trauma-related fractures, 37 non-trauma related fractures, and 115 non-AIDS related malignancies. There were 1812 hospitalizations, 127 deaths (caused by malignancies, infectious diseases and cardiovascular events), 95 new cases of AIDS-defining illness, and 100 new Centers for Disease Control And Prevention (CDC) category B events (Hasse et al. 2011).
2.3.3 Bone Diseases and Risk of Fracture in HIV+ populations

Bone mineralization abnormalities are increasingly apparent among people living with HIV (PLWHIV) (Amorosa and Tebas 2006; Walker Harris and Brown 2012a,b). The World Health Organization (WHO) defines two categories of bone abnormalities, osteoporosis and osteopenia, based on comparison with the mean bone mineral density (BMD) of young healthy women (T-score). Osteoporosis is defined as low bone mass and micro-architectural deterioration of bone tissue with BMD value more than 2.5 standard deviations below the mean BMD of young adult women (bone mineral density T-score <-2.5). Osteopenia is defined as low bone mass with BMD value between 1 and 2.5 standard deviations below the mean BMD of young healthy women (Woolf et al. 2003). In the general population, BMD peaks at about 22 to 35 years of age (Orwoll and Klein 1995). BMD appears to decrease by 2-6% during the first one to two years of antiretroviral therapy (ART). Thereafter, in men and women, BMD levels stabilize or improve.

Prevalence of low bone mineral density has been found in populations of adults living with HIV (Brown and Qaqish 2006). Several cohort studies investigated this topic in diverse populations of HIV+ individuals, including ART naïve participants and those undergoing ART therapy (Bedimo et al. 2012; Looker et al. 1998; Tebas et al. 2000; McComsey et al. 2011).

2.3.4 Bone Fractures

Multiple studies show a correlation in HIV+ populations between low bone mass and greater risk of bone fractures. Incident fractures rates among HIV-infected persons in the HIV Outpatient Study (HOPS) were increased nearly 3-fold when compared with
the U.S. general population between the years of 2000 to 2006 (Young et al. 2011). Rates of first fractures at any anatomic site were analyzed on 5,826 participants (median baseline age of 40 years, 79% male, 52% white, 73% ART). Rates of fracture were indirectly standardized to the general population by age and sex, using data from outpatients in the National Hospital Ambulatory Medical Care Survey (NHAMCS-OPD). Greater proportions of fractures were located at the hip, wrist or spine in HIV+ subjects; fractures were associated with lower CD4 count nadir, duration of HIV diagnosis and hepatitis C infection. The study suggested that younger HIV-infected adults, particularly those between the ages of 25-54 years of age, are at an increased risk of bone fracture compared with the general population.

In the Danish HIV Cohort Study, a comparative, sex- and age-matched study involving 5,306 HIV+ participants and a general population cohort of 26,530 HIV- participants, Hansen and colleagues studied the incidence of fragility fractures in HIV+ individuals not undergoing treatment with ART and HIV+ individuals undergoing treatment with highly active antiretroviral therapy (HAART) (Hansen et al. 2011). HIV+ participants were observed to have an increased overall rate of fractures, increased risk of low-energy fractures but not high-energy fractures in HIV+ participants without hepatitis C virus (HCV) coinfection, and moderate risk of low-energy fracture in HIV+ participants undergoing HAART when controlled for traditional osteoporosis risk factors of age, comorbidity and smoking.

McComsey and colleagues determined that fracture rates increased in 269 HIV+ patients during the first two years of ART initiation as compared to additional years of therapy in the AIDS Clinical Trials Group (ACTG) A5224s, a substudy of ACTG A5202.
Differences in BMD change were observed between patients who initiated different ART regimens, but no significant differences in fracture rate were reported (McComsey et al. 2011; Yin et al. 2012).

These cohort studies suggest that in addition to traditional risk factors such as older age, smoking and HCV, HIV disease-associated factors (duration of infection, CD4 count nadir) and ART factors are important predictive indicators of fracture risk in HIV\(^+\) individuals. Data is currently limited on the association between BMD and fracture risk in HIV-infected persons.

### 2.3.5 Cardiovascular Disease

HIV-infected patients are developing cardiovascular disease (CVD) earlier than the general population (Bhatia et al. 2012). Traditional risk factors common in HIV\(^+\) individuals such as dyslipidemia, diabetes, smoking and hypertension do not appear to tell the whole story (Bhatia et al. 2012). The risk of CVD is higher in ART naïve HIV patients than experienced patients, suggestive of an important role for disease factors in CVD pathogenesis. HIV disease itself is linked with higher risk of CVD as low CD4\(^+\) T cell count, proximal CD4\(^+\) T cell count and biomarkers of inflammation cultivate a proatherogenic environment (Deeks 2011). Additionally some studies show that certain antiretroviral drugs (e.g. protease inhibitors and nucleoside analogues) may increase the risk of CVD (Deeks and Phillips 2009). Other studies have shown a link between uncontrolled HIV replication and CVD and that ART may be cardioprotective (Ghandi et al. 2012; Thompson et. al 2010).
2.3.6 Liver and Renal Diseases

Higher rates of liver and kidney (renal) disease have been observed in HIV-infected persons than age-matched uninfected persons (Deeks 2011). Risk factors include hypertension, diabetes, hepatitis C virus (HCV) and certain antiretroviral therapy (Scherzer et al. 2012). Many antiretroviral medications have the potential to cause liver or kidney injury; the long-term safety of ART in an aging HIV population is an area of increasing concern (Deeks 2011).

Decreased liver volume, blood flow, hepatocyte numbers, drug metabolism and hepatoregenerative capacity are common causes of decreased liver function (Effros et al. 2008). Increased alcohol misuse and higher rates of chronic viral hepatitis exacerbate liver condition in HIV+ individuals (Deeks and Phillips 2009). Interrupted or delayed ART has been shown to increase the likelihood of liver failure in HIV+ individuals (El-Sadr et. al 2006), although ART does not appear to reverse existing manifestations of liver disease (Weber et al. 2006).

Chronic kidney disease (CKD) and acute renal failure are both linked to HIV-HCV co-infection (Effros et al. 2008). Both of these diseases are linked to low proximal CD4+ T cell count (Deeks 2011). Similar to decreased liver function, chronological aging is a factor in decreased kidney function. However, CKD is more common in PLWHA over 50 years of age, especially in ethnically Black HIV+ populations (Naftalin et al. 2011; Slavin et al. 2011).

2.3.7 Certain Malignancies

HIV+ individuals are at a higher risk for non-AIDS defining cancers including anal cancer, Hodgkin’s disease, liver cancer, lung cancer, colorectal cancer, and melanoma
than their age-matched counterparts (Patel et al. 2008; Deeks 2011). Traditional cancer risks in HIV\(^+\) individuals include smoking, alcohol use, and oncogenic virus co-infection (Silverberg et al. 2011). Evidence suggests a direct link between lower CD4\(^+\) T cell count and higher risk for Kaposi Sarcoma (KS) and non-Hodgkin lymphoma (NHL) (Silverberg et al. 2011; Clifford and Franceschi 2009; Franceschi et al. 2008; Polesl et al. 2008).

In a Kaiser Permanente Northern California (KPNC) study involving 22,081 HIV\(^+\) participants and 230,069 HIV\(^-\) participants, comparative age at cancer diagnosis, stage at diagnosis and survival were studied for five non-AIDS cancers, Hodgkin lymphoma, prostate, anal, lung and colorectal cancer (Silverberg et al., CROI 2012). Notably lower average ages at diagnosis were determined in the HIV\(^+\) participants for anal, lung and colorectal cancer. Nearly equivalent age at diagnosis was determined for both participant groups for prostate cancer and Hodgkin lymphoma as well as cancer stage at diagnosis for all five non-AIDS cancers with the exception of trends for more frequent diagnosis at stage 4 for lung cancer and Hodgkin lymphoma. Lower five-year survival rates were observed in the HIV\(^+\) participants for Hodgkin lymphoma, prostate cancer and lung cancer.

### 2.3.8 Neurocognitive Diseases

HIV and aging affect the brain independently and regardless of whether the HIV\(^+\) individual is undergoing HAART (Ances et al. 2012). Neurocognitive impairment, ranging from mild deficits to severe dementia, is found in approximately 50% of HIV\(^+\) individuals (McCutchan et al. 2012; Cysique et al. 2004; McCutchan et al. 2007; Tozzi et al. 2005)
In a Central Nervous System (CNS) HIV Antiretroviral Therapy Effects Research (CHARTER) longitudinal study of 387 HIV+ patients with and without HIV-associated neurocognitive disorders (HAND), Heaton and colleagues studied neurocognitive decline over 18 to 42 months finding that asymptomatic neurocognitive impairment (ANI), the most common HAND diagnosis (33% of 1555 CHARTER cases (Heaton et al. 2010)), and mild neurocognitive disorder (MND) are significant indicators of future symptomatic decline (Heaton et al., CROI 2012). Compared at last follow up, the ANI and MND participants showed greater neurocognitive decline from baseline than the neuropsychologically normal (NP-N) participants (23%, 30% vs. 13%; \( p=0.004 \)) and the ANI participants showed less likelihood to improve than the NP-N participants (7% vs. 21%, \( p=0.008 \)).

HIV and aging also impact emotional status. Reported mental health issues include depression, anxiety, bipolar disorder, schizophrenia and substance abuse resulting in functional limitations (High et al. 2012). Perceptions of premature aging, feeling older than HIV-negative persons, in addition to limitations in daily life functioning, interpersonal relationships and work activity are factors that contributed to depression in HIV+ persons (Fumaz et al. 2012). Insufficient social interaction and lack of social network contributes to incidences of incarceration and use of tobacco, alcohol and psychoactive drugs (High et al. 2012). Strengthened community engagement is a recommended response to HIV as successfully demonstrated in Australia (Slavin et al. 2011).
2.3.9 Medication Toxicity

With the introduction of antiretroviral therapy, PLWH are living longer and able to participate in the work force. Antiretroviral medications are generally well tolerated and have limited risk for toxicity. However, recent studies suggest that long-term antiretroviral therapy may result in medication toxicity. The possibility of neurotoxic risks is a concern with long-term administration of HAART (Cysique and Brew 2009; White et al. 2010). Neuronal function loss has been observed after introduction of HAART (Guinta et al. 2011; Liner et al. 2010; Ernst et al. 2010). A higher prevalence of HAND has been found in HIV+ individuals taking efavirenz (Ciccarelli et al. 2011). Neuropsychological improvement was observed in HIV+ individuals after discontinuing HAART (Marra et al. 2009) or after drug treatment interruption (Robertson et al. 2010). Switching of single-agents in ART regimens may decrease toxicity, prevent drug interactions, and result in lower pill burden (Thompson et. al 2010).

2.4 Impact on Health and the Working Environment

Comorbidities, apart from HIV infection, significantly affect the risk of work cessation (Dray-Spira et al. 2012). In the French ANRS-C09-COPANA multicenter cohort study comprising 622 adult participants (29.9% women and 40.5% migrants (58.4% from sub-Saharan Africa)) < 60 years old (legal retirement age in France), recently diagnosed with HIV-1, and antiretroviral naïve at baseline, Dray-Spira and colleagues investigated from 2004 to 2010 the risk of work cessation following HIV diagnosis in a subset of 376 participants (60.4%) who were employed at baseline. The median age of this subset was 36 years. The participants’ varied socio-demographic and occupational characteristics were acknowledged throughout the multivariate study.
Results of the study showed an increase in work cessation due to comorbidities such as diabetes, hypertension and depression rather than HIV disease severity (i.e. diagnosis of stage B or C-defining illness in the preceding 6 months; or CD4 cell count < 350 cells/μl or viral load ≥5 log_{10} copies/ml). Other factors identified in the study, including HIV-related discrimination, combined antiretroviral therapy (cART) and hepatitis co-infection were non-influential to this finding.

The ANRS-C09-COPANA Study raises awareness that age-related illnesses and their progression in HIV+ individuals can impact the stability of the workforce in larger dimension than the HIV disease itself.

2.5 HIV and Aging, and the Oil and Gas Industry

The prevention and management of infectious diseases, including HIV infection, has been an area of increasing focus of the oil and gas industry. Progress has been made to prioritize, strategize and respond to HIV/AIDS within the corporate context (Donnelly and Arvanitidis 2010; Fakunle et al. 2008; Melville et al. 2011; McCashin 2008). Meanwhile, advancement in ART has increased the longevity of HIV+ individuals including HIV+ employees and sub-contractors. New epidemiological findings alert us to another variable in the equation – age-related HIV-associated comorbidities, whether premature or chronologically induced. Based on the socio-economic ramifications of these findings, no longer should we attempt to approach the management of HIV in our business solely from the corporate context. The need exists to redefine the issue of HIV in our work place to include “HIV and aging and comorbidities” in our workplace and to explore it using a multidisciplinary integrative approach.
2.6 Multidisciplinary Integrative Approach to HIV and Aging in the Oil and Gas Industry

At the Colorado School of Mines (CSM) and in particular, the Petroleum Engineering Department, we teach multidisciplinary integration and implementation skills in our senior design course (Battalora et al. 2011). Challenged with an open-ended problem statement, students work in multidisciplinary teams to solve the problem and make recommendations to management at the conclusion of the course. The authors posit that through translational learning, the multidisciplinary integrative methods developed and implemented in this course are applicable to begin exploring the evolving challenge of HIV and Aging in the oil and gas industry.

2.6.1 A Model Multidisciplinary Integrative Approach to Explore HIV and Aging in the Oil and Gas Industry

A model for exploring HIV and aging through multidisciplinary integration and implementation is set forth below. Given the open-ended “problem statement” of HIV and aging in the oil and gas industry work place and a hypothetical exploration and production project to be implemented in a remote region where HIV is prevalent the following steps may be followed.

Step 1. Develop the Multidisciplinary Team.

The team requires representatives from the following fields, at a minimum:

- Healthcare (including, but not limited to governmental ministries and medical universities; to provide medical expertise and interpret epidemiological findings)
- Engineering (provide information as to specific job details in the field including labor, project task sequences, environmental issues)
- Contractors (provide information as to specific job details in the field including labor pool and sub-contractor labor pool)
• Sub-contractors (provide information as to specific job details in the field and demographics and health status of labor pool)

• Legal (provide expertise regarding risk management, occupational health, insurance, employment, environmental, business and other areas of the law)

• Accounting (provide expertise as to project costs, budgets, taxes)

• Human Resources (provide expertise as to sick leave, health care plans, retirement benefits, long-term and disability plans)

• Specialists based on geographic project location (ex: scientists, local legal counsel)

• Local government (provide tools to implement changes in local vicinity).

• Community organizations (including, but not limited to PLWH, to provide knowledge and support).

Step 2. Analyze the Preliminary Data

The team meets to review preliminary data relevant to the project and to identify additional data that is needed, for example:

- Project objective, plan and risks

- Geographic location: health risks, political stability, access to health care facilities, potable drinking water

- Labor pool: demographics and health status of company employees, contracted employees and sub-contracted employees; review of previously obtained health assessment data; status of on-going health assessment programs

- Status of Company, Contractor and Sub-contractor health programs and viability of health facilities

Step 3. Determine Tasks of Project and Role of Team Members: Responsible, Accountable, Consulted and Informed (RACI)

Team members assess the tasks to be performed during the project and assign roles to each team member: responsible, accountable, consulted, and informed (RACI), for each task of the project relating to HIV and Aging. The tasks and assignments are
compiled in a diagram or spreadsheet that is continuously updated as actions are planned, implemented and closed out. A dynamic process, additional tasks and roles may be assigned throughout the course of the project.

**Step 4. Identify Risks from HIV and Aging to the project:**

The team meets to identify risks specific to the project:

- Geographic location: political stability, access to health care facilities, potable drinking water
- Health status of prospective employees and in particular, sub-contracted nationals; HIV-infection rate, number of HIV+ prospective employees, demographics of these employees
- Status of agreement between Contractor and Sub-contractor to provide health care to sub-contracted nationals (Melville et al. 2008)
- Status of agreement between stakeholders to provide health care to HIV+ employees
- Risks in the field from transporting, lifting and equipment operation as a result of potential falls, fractures and neurocognitive impairments
- Risk of reduced productivity (McCashin 2008)
- Risk of work cessation (Dray-Spira et al. 2012)
- Risk of inadequate supply of skilled workers due to health-induced work cessation (McCashin 2008)
- Risk of increased project and health costs that are ultimately paid by the operator, contractor, stakeholder and community

**Step 5. Identify Preliminary Risk Mitigation Strategies**

The Team meets to discuss preliminary risk mitigation strategies prior to project implementation. A RISK matrix is prepared wherein each identified risk (including upside and downside risks) is assigned a frequency and probability of occurrence during the project and is coupled to an action or manageability “owned” by a team
member according to categories and tasks assigned in the RACI spreadsheet.

Strategy priority may change during the course of the project and additional risk mitigation strategies may be added as additional risks are identified during the course of the project. Some example risk mitigation strategies for HIV and Aging are listed below:

- Awareness of global epidemiological findings and trends in HIV and aging
- Strengthened efforts to improve HIV testing, entry into and retention in HIV medical care (Thompson et al. 2012)
- Earlier screening, diagnosis and treatment of HIV comorbidities (Guaraldi et al. 2011) to maintain the health and safety of the work force and to mitigate negative downstream economic consequences (e.g. increased health care costs, lost productivity, long-term care or disability costs)
- Identification of HIV-infected employees at risk for certain non-AIDS related illnesses and implementing appropriate intervention
- Continuous evaluation of appropriate screening methods and support for more effective diagnostic tools.
- Recognition of the link between employment status and psychological and physiological effects, standard of living, access to basic necessities, including antiretroviral therapy, counseling, prevention and maintenance (Fumaz et al. 2012)
- Timely preparation for workplace issues resulting from HIV and aging, both premature and chronological aging
- Regular assessment of HIV-infected persons for fracture risk and in particular, those with low nadir CD4+ cell counts and other established fracture risk factors (Young et al. 2011)
- Treatment of depression and other mental health issues to be given a greater priority (Thompson et al. 2012)
- Community engagement (Slavin et al. 2011)
- Lifestyle modifications, including reduction of smoking and alcohol consumption (High et al. 2012)
Step 6. Preparation of a Statement of Requirements (SOR)

The Team prepares a spreadsheet of project requirements for management review based on the unique needs of each multidisciplinary team member category as selected in Step 1. This document serves as a directive of the detailed, actionable requirements of the multidisciplinary project. A detailed listing of services, equipment, tools and deliverables is included in the SOR for each team member category, for example, for healthcare, engineering, legal, human resources, etc. Upon submission of the SOR to management for approval, the SOR cannot easily be changed, thus allowing the project to move from planning stage to implementation stage.

Step 7. A Preliminary Plan is Presented to Management

Upon acceptance of the SOR by management, the Team meets to discuss each Team member’s research and deliverables based on tasks assigned and completed in Steps 2 - 6. The Team prepares and presents the Preliminary Plan to Management for approval.

Step 8. Preliminary Management Review

Management reviews the Preliminary Plan with the Team present to identify strengths, weaknesses and knowledge gaps of the plan. The Team reconvenes to begin preparation of the Final Project Plan based on Management’s comments during the Preliminary Management Review.

Step 9. Final Project Plan is Presented to Management for Approval

After further research and analysis, the Team prepares and presents the Final Project Plan to Management for approval, highlighting economics and risk management.
Step 10. Project Plan Implementation

With Management approval, the project moves forward to implementation. Management and Team members acknowledge that risk assessment and mitigation strategies may continue to be addressed as work and health issues change in the field.

Step 11. Project Assessment

Project assessment is ongoing as issues not within the direct control of the Team members may arise (e.g., force majeure).

2.6.2 Application of Model

The skills presented in this model are applicable to addressing the larger issue of HIV and aging in the oil and gas workplace and may be applied to subset issues that are of particular concern to a region. For example, Nigeria, a significant region in oil and gas development, has the second largest population of PLWHA in sub-Saharan Africa (WHO et al. 2011). A multidisciplinary, integrative plan is required to address issues such as retention in HIV medical care, adherence to ART and expansion of existing healthcare facility infrastructure to accommodate the screening, diagnosis and treatment of HIV comorbidities in the growing number of people chronologically aging with HIV.

2.7 Conclusion

HIV and aging, both premature and chronological, is an evolving challenge that the oil and gas industry will need to address. With the introduction of ART, people living with HIV are living longer and able to participate in the work force. Bone, cardiovascular, and renal disease, certain malignancies, and neurocognitive deficits, i.e., comorbidities, are increasingly more common among long-term survivors of HIV.
infection. As the work force ages, both prematurely and chronologically, employers must be proactive in mitigating the potential for reduced productivity resulting from increased employee work cessation and a reduction in labor pool experience. A model multidisciplinary integrative approach to explore HIV and aging in the oil and gas industry is presented.

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2.9 References Cited


CHAPTER 3
HIV AND BONE HEALTH


Linda A. Battalora and Benjamin Young

3.1 Introduction

With improved long-term survival among populations of people living with Human Immunodeficiency Virus – 1 (HIV) and acquired immunodeficiency virus (AIDS) (see Appendix A for a summary of HIV, AIDS and antiretroviral therapy (ART)), it has been suggested that HIV/AIDS may hasten the aging process (Ofotokun, 2011; Deeks, 2009). There is increasing evidence that cardiovascular, renal and bone disease, and neurocognitive deficits may be more common among long-term survivors of HIV infection. Recent revelations from cohort and prospective randomized studies suggest that people living with HIV (PLWH) are at increased risk of abnormal bone mineral density and related fractures (Battalora 2013, Young 2011, Womack 2011).

3.2 Bone Mineralization Abnormalities

The World Health Organization (WHO) defines two categories of bone abnormalities based on comparison with the mean bone mineral density (BMD) of young healthy women (T-score): (1) osteoporosis, low bone mass and micro-architectural deterioration of bone tissue, BMD value more than 2.5 standard deviations below the mean BMD of young adult women (bone mineral density T-score <-2.5); and (2) osteopenia, low bone mass, BMD value between 1 and 2.5 standard deviations
below the mean BMD of young adult women (-2.5 < bone mineral density T-score <-1) (Woolf et al. 2003). Osteomalacia is a third type of bone mineralization abnormality referring to softening of bones due to impaired bone mineralization, typically resulting from severe Vitamin D deficiency (McComsey 2010; WHO Technical Report of Prevention and Management of Osteoporosis, 2003). Osteonecrosis or avascular necrosis (AVN) is yet another bone mineralization abnormality resulting from interrupted blood supply to a bone or part of a bone, commonly occurring as a complication of a fracture, typically located at the articular end of a bone (WHO Manual of Diagnostic Imaging, 2002).

In the general population, BMD peaks at about 22 to 35 years of age (Orwoll et al. 1995). BMD appears to decrease by 2-6% during the first one to two years of antiretroviral therapy. Thereafter, in men and women, BMD levels stabilize or improve.

Bone strength is a function of bone density and bone quality. Bone quality refers to rate of remodeling, microarchitecture, size, shape, amount of mineralization in the bone, and matrix quality (Yin, CROI 2012). Rate of remodeling is measured from serum levels of bone turnover markers, OCN (formation marker) and NTX (resorption marker). Microarchitecture is observed with CT imaging. Mineralization quantity and matrix quality are determined by biopsy (Yin, CROI 2012).

3.3 Prevalence of Low BMD in the HIV Population

Multiple cohort studies have found a higher than expected prevalence of low bone mineral density in populations of adults living with HIV (Brown, et al., 2006). Notably, these studies represent diverse populations of HIV+ individuals, including ART
naïve and experienced people (Bedimo et al. 2012; Looker et al. 1998; Tebas et al. 2000; McComsey et al., 2011).

Postmenopausal women HIV+ women demonstrate a greater decline in BMD. In a longitudinal study of bone loss in post-menopausal HIV-infected women (Yin et al. 2011), higher rates of bone loss at the spine and forearm were observed in postmenopausal HIV+ than HIV- minority women. Thus, higher rates of bone loss at the spine and forearm of post-menopausal HIV+ women described in this study coupled with increased fracture prevalence among HIV-infected individuals (Triant et al. 2008) suggest that an increased rate of fractures in post-menopausal HIV+ women is a concern (Yin et al. 2011). Similarly, higher rates of bone loss were observed in HIV+ men over age 50 (Orwoll, et al. 1995). There is very little data on bone loss for HIV+ women and men over age 65 years, the period in which fractures are prevalent in the general population. (Yin, CROI 2012).

3.4 Higher Prevalence and Incidence of Fractures in HIV Population

Several recent studies have concluded that HIV+ populations are at greater risk of bone fractures. Triant and colleagues presented findings that fracture prevalence is greater in HIV+ women and men as compared to the general population. (Triant et al. 2008). Analyzing over 11 years of data from a large U.S. single healthcare database, it was determined that HIV+ participants had a larger number of vertebral, hip, wrist and combined fractures compared with non-HIV+ participants. These findings were consistent across age, race and sex categories but no correlations were made as to specific risk factors due to lack of data.
Subsequently, four large observational cohort studies published findings correlating fracture incidence in HIV\(^+\) individuals as compared to control groups. Differences in population, controls and fracture definitions, i.e., fracture and fragility fracture definitions, were unique to each study.

In the Women’s Interagency HIV Study (WIHS), Yin et al. studied fracture incidence in 1728 HIV\(^+\) and 663 HIV\(^-\) predominantly premenopausal women and reported on all fractures (Yin et al. 2010). Rates of fracture were not increased in HIV\(^+\) patients as compared to HIV\(^-\) patients and in the HIV\(^+\) patients; the history of AIDS-defining illness (ADI) was a more predictive indicator of fracture than ART.

Incident fractures rates among HIV-infected persons in the HIV Outpatient Study (HOPS) were increased nearly 3-fold when compared with the U.S. general population between the years of 2000 to 2006 (Young et al. 2011). Rates of first fractures at any anatomic site were analyzed on 5,826 participants (median baseline age of 40 years, 79% male, 52% white, 73% ART). Rates of fracture were indirectly standardized to the general population by age and sex, using data from outpatients in the National Hospital Ambulatory Medical Care Survey (NHAMCS-OPD). Greater proportions of fractures were located at the hip, wrist or spine in HIV\(^+\) subjects; fractures were associated with lower CD4 count nadir, duration of HIV diagnosis and hepatitis C infection. The study suggested that younger HIV-infected adults, particularly those between the ages of 25-54 years of age, are at an increased risk of bone fracture compared with the general population. The authors recommend regular assessment of HIV-infected persons for fracture risk and in particular, those with low nadir CD4+ cell counts and other established fracture risk factors.
In the all-male Veterans Aging Cohort Study Virtual Cohort (VACS-VC), Womack and colleagues reported that HIV\(^+\) men were at greater risk for fragility fracture than HIV\(^-\) counterparts (Womack et al. 2011). In this study of 119,318 men, of whom 33\% were HIV\(^+\) and 34\% of this group were 50 years or older at baseline and 55\% were black or Hispanic, fracture risk factors included age, race, alcohol dependency, liver disease, tobacco smoking, or current use of corticosteroids or proton pump inhibitors.

Hansen and colleagues studied the incidence of fragility fractures in HIV\(^+\) individuals not undergoing treatment with ART and HIV\(^+\) individuals undergoing treatment with HAART in the Danish HIV Cohort Study (Hansen et al. 2011). In this comparative, sex- and age-matched study involving 5,306 HIV\(^+\) participants and a general population cohort of 26,530 HIV\(^-\) participants, the HIV\(^+\) participants were observed to have an increased overall rate of fractures, increased risk of low-energy fractures but not high-energy fractures in HIV\(^+\) participants without HCV co-infection, and moderate risk of low-energy fracture in HIV\(^+\) participants undergoing HAART when controlled for traditional osteoporosis risk factors of age, comorbidity and smoking.

In the AIDS Clinical Trials Group (ACTG) A5224s, a substudy of ACTG A5202, McComsey and colleagues concluded that fracture rates increased in 269 HIV\(^+\) patients during the first two years of ART initiated during the clinical trial as compared to additional years of therapy. While differences in BMD change were observed between patients who initiated different ART regimens, no significant differences in fracture rate were reported (Yin et al. 2011; McComsey et al. 2011).

Osteoporotic fractures were associated with cumulative exposure to tenofovir difumarate (TDF) and ART in a large retrospective cohort study (56,600 patients) with a
mean age of 45 years (Bedimo et al. 2012). Ninety five percent of this cohort was male, limiting the ability to generalize the conclusion to females.

In summary, the cohort studies suggest that in addition to traditional risk factors such as older age, smoking and HCV, HIV-associated factors (CD4 count nadir) and ART factors are important predictive indicators of fracture risk in HIV+ individuals (Yin, CROI 2012). Data is currently lacking on the association between BMD and fracture risk in HIV-infected persons.

3.5 Pathophysiology and Risk Factors

Bone loss in people living with HIV is likely multifactorial involving three common elements: the host, the virus and ART. Lower bone density in HIV+ persons is often attributable to host risks including smoking, alcohol consumption, exposure to glucocorticoids, decreased activity, lipodystrophy, hepatitis C virus infection, vitamin D deficiency, weight loss, hypogonadism, and CKD. HIV may directly affect bone cells by viral protein induction of osteoclastogenesis or by causing osteoblast apoptosis. Moreover, T cell and B cell activation during HIV infection results in increased circulating cytokines, including TNFα, IL6, and RANKL, which appear to induce osteoclast bone resorption. Similar increases in cytokine levels have been reported in other chronic inflammatory diseases for example, rheumatoid arthritis.

ART initiation is associated with BMD decrease of 2-6% with the largest decrease occurring in the first 6 to 12 months of treatment and then stabilizing. Greater BMD losses occur with initiation of zidovudine (van Vonderen et al. 2009), tenofovir (McComsey et al. 2011, Yin et al. 2011) and certain protease inhibitors (Duvivier et al. 2009 and McComsey et al. 2011). Younger HIV+ men and women on established ART
demonstrate stable BMD. (Yin, CROI 2012). Among post-menopausal women, higher rates of loss of BMD were observed among the recipients of tenofovir-containing ART (Yin et al. 2011). Fracture rates, both fragility and non-fragility, are higher in HIV+ individuals and associated with HCV infection and possibly ART use. (Young et al. 2011; Bedimo et al., 2012; Yin, CROI 2012). Presently, the fracture incidence is estimated to be approximately 3 to 5 per 1000 person years but will likely increase as the population of HIV+ individuals chronologically age.

3.6 Screening for Bone Disease

There are limited HIV-specific evidence-based recommendations regarding screening for bone disease, though extrapolation of screening recommendations from the general population is, at a minimum, reasonable.

The National Osteoporosis Foundation (NOF) published recommendations to clinicians for postmenopausal women and men age 50 and older (NOF, 2013). Below is a listing of the major recommendations:

- “Counsel patient on risk of osteoporosis and related fractures.

- Check for secondary causes.

- Advise patient on adequate amounts of calcium (at least 1,200 mg/day) and vitamin D (800-1,000 IU per day) including supplements if necessary for individuals age 50 and older.

- Recommend regular weight-bearing and muscle-strengthening exercise to reduce risk of falls and fractures.

- Advise against tobacco smoking and excessive alcohol consumption.

- Recommend bone mineral density (BMD) testing in women age 65 and older and men age 70 and older.
• In postmenopausal women and men age 50-69, recommend BMD testing based on risk factor profile.

• Recommend BMD testing to patients that have had a fracture, to determine degree of disease severity.

• Initiate treatment in patients with hip or vertebral (clinical or morphometric) fractures.

• Initiate therapy in patients with BMD T-scores ≤ -2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry (DXA), after appropriate evaluation.

• Initiate treatment in postmenopausal women and men age 50 and older with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck or spine and a 10-year hip fracture probability ≥ 3% or a 10-year major osteoporosis-related fracture probability ≥ 20% based on the US-adapted WHO absolute fracture risk model FRAX® (http://www.shef.ac.uk/FRAX).

• Current FDA-approved pharmacologic options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate, alendronate plus D, ibandronate, risendronate and zoledronic acid), calcitonin, estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene), tissue specific estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone [PTH (1-34), teriparatide] and the RANKL inhibitor denosumab.

• BMD testing performed in DXA centers using accepted quality assurance measures is appropriate for monitoring bone loss. For patients on pharmacotherapy, it is typically performed two years after initiating therapy and every two years thereafter; however, more frequent testing may be warranted in certain clinical situations.” (NOF 2013).

3.7 Screening for Vitamin D Insufficiency

Three institutions provided guidance for vitamin D deficiency. The Institute of Medicine (IOM) published dietary reference intakes for calcium and vitamin D but it did not provide screening recommendations or specifically reference intakes for HIV+ individuals (IOM, November 2010). The Endocrine Society (EOS) 2011 and the European AIDS Clinical Society (EACS) 2013 recommended screening at-risk patients and those on ART and having risk factors for low vitamin D or fracture risks (EOS 2011;
EACS 2013). There are limited data on vitamin D supplementation in HIV+ patients but some beneficial effects on parathyroid hormone (PTH) have been determined while no effects on BMD have been reported (Childs et al. 2012).

3.8 Screening for Fall risk

Fall risk assessment tools (FRAT) are used to determine the probability of future falls. Typical categories of the assessment tool include fall risk factors (e.g., recent falls, medications, psychological, cognitive status, vision, mobility, transfer, behaviors, activities of daily living (ADL), environment, nutrition, continence and other risk factors).

3.9 Screening for Fracture Risk with FRAX®

The fracture risk assessment tool, FRAX® (FRAX), was developed by the World Health Organization Metabolic Bone Disease Group (2008) to assess fractures with more optimal predictors of fracture risk than T-scores (van den Bergh et al. 2010); FRAX tool, http://www.shef.ac.uk/FRAX). This assessment tool is not HIV specific. FRAX provides the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (hip, spine, shoulder, forearm) probability is estimated based on clinical risk factors (CRF) and BMD values from the femoral neck (WHO Metabolic Bone Disease Group, FRAX tool, 2008: http://www.shef.ac.uk/FRAX). Models have been developed based on location, i.e., Asia, Europe, Middle East and Africa, North America, Latin America and Oceania and ethnicity. CRFs included in the calculation tool are: age, sex, weight (kg), height (cm), previous fracture (yes/no), parent fractured hip (yes/no), current tobacco smoking (yes/no), exposure to glucocorticoids (yes/no), rheumatoid arthritis (yes/no), secondary osteoporosis (yes/no), alcohol intake of 3 or more units/day (yes/no) and BMD (g/cm²) or alternatively, T-score based on the

The International Osteoporosis Foundation (IOF), the NOF, the American Society for Bone and Mineral Research, and the International Society for Clinical Densitometry endorse the use of FRAX (van den Bergh et al. 2010). NOF recommends using FRAX for postmenopausal women and men ≥50 years of age who are not on treatment, who have not had spine or hip fractures and who have T-scores between -1.0 SD and -2.5 SD (NOF, 2008; van den Bergh 2010). If the FRAX 10-year probability exceeds 20% for major osteoporotic fractures or 3% risk for hip fracture, NOF guidelines recommend drug treatment (NOF, 2013).

Though FRAX may underestimate fracture risk in HIV+ persons, EACS recommends FRAX screening in all persons age greater than 40 years (EACS 2013).

3.10 Dual Energy X-Ray Absorptiometry (DEXA)

BMD measurements are widely obtained using Dual Energy X-ray absorptiometry (DEXA). Relevant measurement locations include the hip, spine and forearm. DEXA is a two-dimensional system wherein size of the specimen is directly proportional to the estimate of area density. Overestimation of BMD values obtained from larger patients is a concern (Amorosa et al. 2006). Of greater concern is that DEXA has not been validated for fractures among people living with HIV (PLWH). Further, less data exists on younger adults. Additional concerns are the application of WHO definitions for osteoporosis and osteopenia to populations and skeletal sites other
than those serving as the basis for the DEXA correlations upon which these bone abnormality definitions are described (Amorosa et al. 2006).

DEXA is non-invasive and convenient, but does not assess bone condition, bone structure or quality, a factor directly linked to load bearing strength (Ofotukun et al. 2011). It is suggested that DEXA may underestimate fracture risk (Ofotokun et al. 2011). Nguyen and colleagues in 2007 demonstrated that 50% of postmenopausal women experiencing a fracture do not meet the clinical definition of osteoporosis based on DEXA values (Ofotukun et al. 2011).

Other BMD measurement tools exist and assist in the prediction of fragility fracture risk but have inherent limitations. Quantitative CT scanning (QCT) detects volumetric density and in some clinical studies has shown to detect a higher occurrence of osteoporosis and osteopenia (Pitukcheewanot et al. 2005). However, it costs more than DEXA, requires a higher radiation dose and is mainly used in research settings (Amorosa et al., 2006). Other tools including quantitative ultrasound and analysis of biochemical and hormonal markers may prove increasingly useful in the future (Amorosa et al. 2006).

The NOF recommends DEXA screening for osteoporosis in the general population of women ≥ 65 years of age and men ≥ 70 years regardless of clinical risk factors (NOF 2013). Postmenopausal women < 65 years, women in menopausal transition, and men age 50 to 69 with clinical risk factors for fracture should also be screened. Men and women ≥ 50 years who have suffered a fracture after age 50 and if other risk factors including rheumatoid arthritis or glucocorticoid use are observed should be screened (NOF 2013). NOF does not provide HIV-specific guidelines for
DEXA screening.

The Infectious Diseases Society of America (IDSA) recommends baseline DEXA screening in HIV-infected postmenopausal women and men aged ≥ 50 years. Periodic monitoring of risk factors for premature bone loss is recommended thereafter (Aberg et al. 2014). Risk factors include white race, small body habitus, sedentary lifestyle, cigarette smoking, alcoholism, phenytoin therapy, corticosteroid therapy, hyperparathyroidism, vitamin D deficiency, thyroid disease and hypogonadism (Aberg et al. 2013).

McComsey and colleagues recommend DEXA screening in HIV+ men and women age ≥ 50 years since the majority of HIV patients have an additional risk factor and fracture data suggesting that HIV and ART are linked to increased fracture risk (McComsey et al. 2010).

The European AIDS Clinical Society (EACS) recommends DEXA screening for any patient with one or more of the following conditions, preferably prior to initiation of ART:

- “Postmenopausal women
- Men ≥ 50 years of age
- History of low impact fracture or high risk for falls
- Clinical hypogonadism
- Oral glucocorticoid use.” (EACS 2013)

3.11 Treatment

Treatment is dependent on multiple factors including the patient profile, risk factor reduction and drug regimen adherence.
3.11.1 Behavioral and Lifestyle Advice

Several lifestyle factors are associated with low BMD and/or fractures in the general population. Modification of diet to optimize calcium and vitamin D intake, increasing weight-bearing exercise and smoking cessation would be prudent in general, but especially among persons at increased risk of low BMD or fractures. Additionally, since excess alcohol consumption (>3 units/daily) and substance dependency are associated with fracture risk, strategies to reduce consumption is reasonable.

3.11.2 Identify and Treat Secondary Causes of Low BMD

Among persons with fragility fractures or T-scores less than ≤ 1, clinicians should evaluate and address secondary causes of osteoporosis and particularly in cases where vitamin D deficiency or phosphate wasting are observed. These conditions can cause osteomalacia or bone mineralization deficiency and are difficult to differentiate from osteoporosis based on DEXA scans (Yin, CRIO 2012).

3.11.3 Vitamin D and Calcium Replacement

Vitamin D deficiency is common among persons living with HIV and may contribute to low BMD and/or fractures. Though there are no standardized guidelines for vitamin D and calcium replacement, the Institute of Medicine (IOM) published a Report Brief in November 2010, revised March 2011, providing suggested Dietary Reference Intakes (DRIs) for Calcium and Vitamin D. (IOM 2011). It suggests 1,000 milligrams of calcium daily for most adults ranging in ages 19 through 50 years and for men up to 71 years. No more than 1,200 milligrams of calcium per day are suggested for women over 50 years and both men and women 71 years and older (IOM 2011).
Assuming minimal sun exposure in geographic regions consisting of the United States and Canada, the IOM suggests 600 International units (IUs) of vitamin D per day for most persons of ages 1 through 70 years and 800 IUs for persons of ages 71 years and older (IOM 2011).

These recommendations are not specific to HIV-infected persons. However, it appears reasonable to monitor 25-hydroxyvitaminD (25-OHD) levels in HIV+ individuals and provide supplementation in situations of ART initiation and continued therapy (Yin, CROI 2012).

3.11.4 Testosterone Replacement

Testosterone deficiency is common among men living with HIV and is associated with increased risk of low BMD in the general population. Clinicians should assess the risks and benefits of testosterone replacement in persons with low BMD and low testosterone levels.

3.11.5 Pharmacologic Interventions

Currently, there are no specific guidelines for the treatment of BMD disorders among persons living with HIV. Rather the management of bone disease among the HIV population follows guidance from the general population. The National Osteoporosis Foundation recommends pharmacologic treatment of postmenopausal women and men age 50 and older with hip or vertebral fractures or a T-score ≤ -2.5 at the femoral neck or spine after evaluation to exclude secondary causes (NOF, 2013). Additionally, patients with a T-score between -1.0 and -2.5 at the femoral neck or spine and 10-year probability fracture by FRAX® ≥ 3% at the hip and ≥ 20% for any osteoporosis-related fracture should be considered for treatment (NOF 2013).
Bisphosphonates are indicated for prevention and treatment of osteoporosis and other bone diseases including Paget's disease (FDA 2013). Bisphosphonates inhibit osteoclast resorption and have shown to reduce vertebral and non-vertebral fractures by 25-50% in HIV-negative individuals.

The effectiveness of antiresorptive therapy in HIV patients has been evaluated in six placebo-controlled randomized clinical trials. Five studies evaluated patients with T-scores not within the osteoporotic range (Guaraldi et al. 2004; Mondy et al. 2005; McComsey et al. 2007; Bolland et al. 2007, Huang et al. 2009), one trial (Rozenberg et al. 2012) studied patients with T-scores <-2.5. Resulting data showed significant increases in BMD at the lumbar spine in all six studies and large increase at the hip in three (McComsey et al. 2007; Bolland et al.2007; Huang et al. 2009). The two-year treatment trials (Rozenberg et al. 2012 and Bolland et al. 2007) demonstrated the greatest change in BMD. Notably, an increase in BMD was detected in the placebo groups that were also given calcium and vitamin D.

Adverse effects of bisphosphonates include osteonecrosis of the jaw (<1 case per 100,000 py of exposure) and subtrochanteric fractures or atypical femoral shaft fractures (uncommon in patients with <5 years of treatment) (Yin, CROI 2012). Thus, only patients with a strong indication for treatment should be administered bisphosphonates and the FDA expert panel recommends treatment up to five years (Yin, CROI 2012).

Other treatments for osteoporosis include teriparatide, a recombinant form of parathyroid hormone, that stimulates osteoblasts and is used in patients that do not respond to bisphosphonates. However, no data exists on teriparatide’s efficacy in HIV+ patients.
individuals (Yin, CROI 2012). Denosumab, a monoclonal RANKL antibody, blocks the RANKL/RANKL interaction but may increase the likelihood of infection (Yin, CROI 2012). For this reasons, more data is needed to determine the safety of denosumab in HIV+ patients (NOF 2013; Yin, CROI 2012). Hormone replacement including estrogen and raloxifene for women may be appropriate in some cases, however risk of cardiovascular side effects exist (Yin, CROI 2012).

3.12 Role of ART Switch

There are limited data on the efficacy of ART switch strategies. HIV clinicians may consider avoidance of tenofovir or HIV protease inhibitors in high-risk patients. Two short term studies have shown that switching virologically suppressed patients from tenofovir to abacavir or raltegravir has resulted in improvement in BMD (Martin et al. 2009; Yin, CROI 2012).

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Ofotokun I, Weitzmann MN. HIV-1 infection and antiretroviral therapies: risk factors for osteoporosis and bone fracture. *Current opinion in endocrinology, diabetes, and


Yin M. Bone loss in HIV: Virus, Host or ART. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 5-8, 2012; Seattle, WA.

4.1 Abstract

Decreased bone mineral density (BMD) and osteoporotic fractures are areas of increasing concern among HIV-infected persons. Particular concern is the rapid decline in BMD after initiation of antiretroviral treatment (ART). This report describes DEXA-assessed changes in BMD and body fat in a study of fifteen antiretroviral-naïve adults initiating abacavir/lamivudine and raltegravir for 96 weeks. Median percent changes from baseline at weeks 48 and 96 in BMD were 0.29% and -0.11% (spine); -1.25% and -1.75% (left hip). Median percent changes from baseline in fat from baseline were -0.82% and -3.04% (trunk); 2.12% and 2.01% (limb). In this pilot study, ABC/3TC + RAL treatment had limited impact on BMD and body fat.

4.2 Introduction

There is a growing concern about the risks of decreased bone mineral density (Brown et al. 2007) and osteoporotic fractures (Triant et al. 2008; Young et al. 2011c) among HIV-infected persons. Among multiple risk factors, some antiretroviral medications have been implicated in reduction in bone mineral density (BMD) (McComsey et al. 2011; Yin et al. 2010) or bone fracture (Yin et al. 2012; Bedimo et al.
2012). Of note, a rapid decline in BMD has been observed after the initiation of antiretroviral treatments (Brown et al. 2009).

4.3 Review

Previously in this journal, we reported the 48- and 96-week results of an open-label, prospective, pilot trial of abacavir/lamivudine (ABC/3TC) and the integrase strand transfer inhibitor (INSTI) raltegravir (RAL) in HIV-1-infected, antiretroviral (ART)-naïve adults (COL111429, the SHIELD Study) (Young et al. 2010; Young et al. 2011a). In the SHIELD study, ABC/3TC + RAL demonstrated durable virologic suppression through week 96 in those patients who remained on treatment and was generally well tolerated with little toxicity reported. RAL is a preferred antiretroviral agent in current US Department of Health and Human Services guidelines for the initial treatment of HIV-1 infected adults and ABC + 3TC + RAL has been added to the list of alternate regimens (McComsey et al. 2011). While a growing body of literature has reported on the impact of nucleoside reverse transcriptase inhibitors, including impact of ABC/3TC and TDF/FTC on BMD, there is a paucity of data on the effects of raltegravir on BMD and none with the ABC/3TC + RAL combination. This publication reports the changes in bone mineral density in a subset of SHIELD subjects.

SHIELD included HIV-1-infected individuals who were ≥ 18 years of age, ART-naïve, HLA-B * 5701-negative, and had screening HIV-1 RNA > 1000 copies/mL within 21 days prior to study enrollment. Inclusion and exclusion criteria are detailed in the 48-week report (Young et al. 2010) and all patients provided written informed consent. Enrolled patients were given coformulated ABC/3TC 600 mg/300 mg (Epzicom® GlaxoSmithKline, Research Triangle Park, NC) dosed 1 tablet once daily and RAL 400
mg (Isentress®, Merck & Co., Inc., Whitehouse Station, NJ) dosed 1 tablet twice daily. Subjects from a single site underwent BMD and body composition measurement by DEXA (GE Lunar Podigy 1RDF + 15700) at baseline and weeks 48 and 96. All laboratory tests were performed at a central laboratory by Quest Diagnostics (Van Nuys, California, USA).

The majority of the 15 patients enrolled in this sub-study were white (87%) and male (93%). Their mean age (SD) was 39.5 (9.8) years and mean weight was 85.5 (14.9) kg. Mean height was 180.5 (8.9) cm and mean BMI was 26.4 (5.6). The baseline demographics and patient characteristics of this group are shown in Table 4.1 and are similar to the entire SHIELD cohort, as previously reported (Young et al. 2010).

Fourteen of 15 subjects completed week 96 of the study. At week 96, HIV-1 RNA was <50 copies/mL in 93% (14/15) of patients using an MD = F analysis. One patient experienced confirmed virologic failure and discontinued from the study at week 48. This individual was later found to have been infected with virus resistant to four drug classes and has been reported in detail elsewhere (Young et al. 2011b). As was seen in the entire SHIELD cohort, immunologic results were robust, with a median change from baseline in CD4 cell count of +207 cells/mm³ at week 48 (n = 15) and +291 cells/mm³ at week 96 (n = 14).

In this study, limited changes in the median bone mineral density at the spine (total) and left hip, and trunk and limb total body fat were observed (Figure 4.1, Table 4.2). Median percent change from baseline in spine BMD increased by 0.29% at week 48 and decreased by -0.11% at week 96. Median percent change from baseline in left hip BMD decreased by -1.25% at week 48 and decreased by -1.75% at week 96.
Median changes from baseline in T-score at 48 and 96 weeks were 0.0 and 0.0 for the spine and -0.10 and -0.15 for the left hip. Trunk fat median percent changes from baseline were -0.82% at week 48 and -3.04% at week 96. Limb total fat median percent changes from baseline were 2.12% at week 48 and 2.01% at week 96.

One fracture reported among the fifteen subjects. This subject had fractured ribs, associated with trauma unrelated to study medications.

A number of prospective clinical trials have evaluated changes in bone mineral density among individuals initiating antiretroviral therapy. Greater decreases in spine and hip BMD through 96 weeks in participants randomized to receive TDF-FTC compared to ABC-3TC in the A5224s study (substudy of ACTG A5202) [4] in which 269 HIV-infected, treatment naïve participants were randomized to receive ABC/3TC or TDF-FTC with efavirenz (EFV) or atazanavir plus ritonavir (ATV/r). A greater bone loss predicted by lower bone formation and lower fat mass was reported in patients receiving TDF-FTC than those receiving ABC-3TC through 96 weeks in the STEAL study (Haskelberg et al. 2012). In another study, switching from zidovudine/lamivudine (ZDV/3TC) to TDF/ FTC regimen resulted in increased bone turnover markers and decreased BMD through 48 weeks compared to ABC-3TC switch (Rasmussen et al. 2012). In the ASSERT study, ART-naïve, immunodeficient, young (mean age 37 years old), ethnically diverse participants treated with TDF-FTC compared with ABC-3TC experienced greater increases in bone turnover and decreases in BMD at 48 weeks (Stellbrink et al. 2010).

Other studies report changes in BMD of participants randomized to receive RAL in antiretroviral combinations. In the PROGRESS study, ART-naive participants
randomized to receive lopinavir/ritonavir (LPV/r) plus TDF/FTC demonstrated at 96 weeks a -2.48% mean percent decrease in BMD from baseline (p < 0.001) compared with a 0.68% decrease in BMD in ART-naive participants randomized to receive LPV/r plus RAL (Reynes et al. 2013). Increases in peripheral fat, but not trunk fat were observed in the LPV/r plus RAL patients. In the KITE study, virologically suppressed HIV-infected patients who were switched from standard highly active ART to a nucleoside reverse transcriptase inhibitor (NRTI) sparing combination of LPV/r and RAL showed no differences between the regimens in BMD, total body fat composition, creatinine clearance or CD4 T-cell counts at week 48 (Ofotokun et al. 2011).

4.4 Conclusions

The conclusions of this study are limited by the non-comparative nature and small sample size inherent to pilot studies. Subjects in this analysis were largely healthy men with normal baseline BMI, perhaps minimizing their non-HIV risk factors for loss of BMD notwithstanding these limitations. This study provides an exploratory look at changes in bone mineral density in antiretroviral-naïve HIV-1 infected patients taking ABC/3TC + RAL.

In this pilot study of therapy naïve individuals, ABC/3TC+RAL treatment appears to have limited impact on BMD and body fat through 96 weeks. ABC/3TC + RAL demonstrated durable virologic suppression and was generally well tolerated in those patients who remained on treatment through week 96. The results of this study, though limited by a small sample size and single-arm design, suggest the effectiveness and safety of ABC/3TC with an INSTI. This combination should be tested in a larger, randomized trial.
4.5 Acknowledgements

The SHIELD Study investigators were: Edwin Dejesus, Orlando, Florida; Trevor Hawkins, Santa Fe, New Mexico; Thanes Vanig, Phoenix, Arizona; Benjamin Young, Denver, Colorado.

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4.6 Previous Publications

This study was presented in part at the 11th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV, 26-28 October, 2009, Philadelphia, PA; the 12th European AIDS Conference, 11-14 November 2009, Cologne, Germany; the XVIII International AIDS Conference, 18-23 July 2010, Vienna, Austria, and the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 17-20 July 2011, Rome, Italy.

4.7 Disclosures

Benjamin Young has received consulting fees from Bristol-Myers Squibb Company, Cerner Corporation, Gilead Sciences, GlaxoSmithKline, Merck & Co., Tibotec, and ViiV Healthcare. He has served on speakers’ bureaus for Merck & Co., and ViiV Healthcare. In addition, he has received research funding from Bristol-Myers Squibb Company.
Squibb Company, Cerner Corporation, Gilead Sciences, GlaxoSmithKline, and Merck & Co.

Belinda Ha is an employee of GlaxoSmithKline. Brian Wine is a contractor for GlaxoSmithKline. Linda Battalora has no disclosures. Amy Thomas has no disclosures.

4.8 References Cited


Table 4.1 Baseline patient demographics, characteristics, and medical history

<table>
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<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients studied</td>
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</tr>
<tr>
<td>Median age, years (range)</td>
<td>41.0 (25-55)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (93%)</td>
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<td>Race, n (%)</td>
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<tr>
<td>African American/African Heritage</td>
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</tr>
<tr>
<td>White/Caucasian/European Heritage</td>
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</tr>
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<tr>
<td>Not Hispanic or Latino</td>
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<tr>
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<tr>
<td>≥100,000 copies/mL, n (%)</td>
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<td>&lt;50 cells/mm³, n (%)</td>
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<td>≥200 cells/mm³, n (%)</td>
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<td>Adult CDC classifications for HIV infection, n (%)</td>
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<tr>
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<tr>
<td>Category B</td>
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<tr>
<td>No history or condition</td>
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</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation

*BMI = weight (kg)/height (m)²

**Percentages do not add to 100% due to rounding.

Abbreviation: IQR, interquartile range
Table 4.1 Baseline patient demographics, characteristics, and medical history, continued

<table>
<thead>
<tr>
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<td>4 (27%)</td>
</tr>
<tr>
<td>Median Weight (kg) (range)</td>
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</tr>
<tr>
<td>Exercise History</td>
<td></td>
</tr>
<tr>
<td>Often or very often</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Seldom or never</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Spine Total BMD (g/cm²)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.29 (1.17–1.39)</td>
</tr>
<tr>
<td>Spine Total T-score</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.60 (-0.40–1.50)</td>
</tr>
<tr>
<td>Spine Total Z-score</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.30 (-0.50–1.00)</td>
</tr>
<tr>
<td>Left Hip BMD (g/cm²)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.09 (0.99–1.16)</td>
</tr>
<tr>
<td>Left Hip T-score</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.30 (-0.70–0.40)</td>
</tr>
<tr>
<td>Right Hip BMD (g/cm²)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.11 (0.99–1.17)</td>
</tr>
<tr>
<td>Right Hip T-score</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.30 (-0.70–0.50)</td>
</tr>
<tr>
<td>Right Hip Z-score</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>-0.10 (-0.70-0.50)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range
Table 4.2 Changes in BMD and total body fat by body region over time

<table>
<thead>
<tr>
<th>Percent Change, Median (IQR):</th>
<th>Spine Total</th>
<th>Left Hip</th>
<th>Trunk</th>
<th>Limb Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 0 – 48</td>
<td>0.29 (%)</td>
<td>-1.25</td>
<td>-0.82</td>
<td>2.12</td>
</tr>
<tr>
<td></td>
<td>(-1.8-2.1)</td>
<td>(-2.5-0.2)</td>
<td>(-5.8-15.2)</td>
<td>(-4.8-15.8)</td>
</tr>
<tr>
<td>Weeks 0 – 96</td>
<td>-0.11 (%)</td>
<td>-1.75</td>
<td>-3.04</td>
<td>2.01</td>
</tr>
<tr>
<td></td>
<td>(-2.6-2.1)</td>
<td>(-2.5-0.2)</td>
<td>(-37.3-10.9)</td>
<td>(-13.9-21.1)</td>
</tr>
</tbody>
</table>

| Median Changes in BMD (grams/cm^2) and Total Body Fat (grams) by Body Region Over Time¹ |
|-----------------------------------------------|-------------|----------|-------|------------|
| Time                                          | Spine Total | Left Hip | Trunk | Limb Total |
| Baseline                                      | 1.29        | 1.09     | 15421.0 | 8413.0     |
|                                               | (1.17-1.39) | (0.99-1.16) | (10556-20180) | (6643-12184) |
| Week 48                                       | 1.31        | 1.10     | 17214.0 | 8591.0     |
|                                               | (1.15-1.36) | (1.00-1.15) | (8288-23285) | (6241-13819) |
| Week 96                                       | 1.31        | 1.09     | 12413.5 | 8477.0     |
|                                               | (1.17-1.34) | (0.98-1.17) | (6619-19996) | (6154-9098) |

¹ At Baseline and Week 48, n=15; at Week 96, n=14.
Figure 4.1. Box Plots of DEXA Measurements by Body Region and Visit – Median Percent Change from Baseline
CHAPTER 5

LOW BONE MINERAL DENSITY IS ASSOCIATED WITH INCIDENT FRACTURE RISK IN HIV-INFECTED ADULTS


Linda Battalora, Kate Buchacz, Carl Armon, Edgar T. Overton, John Hammer, Pragna Patel, Joan S. Chmiel, Kathy Wood, Timothy J. Bush, John T. Brooks, Benjamin Young for the HIV Outpatient Study (HOPS) and SUN Study Investigators

5.1 Abstract

Although the prevalence of both low bone mineral density (BMD) and bone fractures are increased among HIV-infected adults compared with the general population, no study has yet characterized their association in the context of HIV infection.

We analyzed available dual energy X-ray absorptiometry (DEXA) values of the hip (left femoral neck) and clinical data collected prospectively during 2004-2012 from two CDC-sponsored HIV cohort studies, the HOPS and the SUN. We assessed factors associated with low BMD (osteopenia or osteoporosis, defined by T-scores of $<-1.0$ to $>-2.5$, and $\leq -2.5$, respectively), using the Jochkheere-Terpstra test for ordered alternatives for continuous variables and the Cochran-Armitage test for categorical
variables. We analyzed the association of low BMD with subsequent incident fractures using Cox proportional hazards regression.

Among 1,008 patients (median age 42 [interquartile range (IQR)35-48] years, 83% male, 67% non-Hispanic white, median CD4+ cell count [CD4] 408 cells/mm³ [IQR 254-598]), 36.3% (n=366) had osteopenia and 2.9% (n=29) osteoporosis. During 5,032 person-years of observation after DEXA scanning, 95 incident fractures occurred, predominantly rib/sternum (n=18), hand (n=17), foot (n=15) and wrist (n=11). Low BMD was significantly (p<0.05) associated with increasing age, lower nadir CD4, history of fracture, and male-male sex HIV transmission risk. In unadjusted analyses, increasing age, current or prior tobacco smoking, hepatitis C co-infection, history of fracture, and low BMD (osteopenia or osteoporosis) were significantly associated with increased hazard of a new fracture. In multivariable analyses, only osteoporosis (adjusted hazard ratio [aHR] 3.04, 95% confidence interval [CI] 1.47-6.30) and increasing age (aHR 1.35 per 10 years, 95% CI 1.07-1.70) remained associated with incident fracture.

In a large convenience sample of HIV-infected adults in the U.S., low baseline BMD and increasing age were strongly associated with elevated risk of incident fracture, highlighting the potential value of DEXA screening in this population.

5.2 Introduction

Recent years have brought an increasing appreciation of deficits in bone health among persons living with human immune-deficiency virus - 1 (HIV). Studies in the United States have shown high prevalence of low bone mineral density (BMD) among persons living with HIV (Overton, CROI 2007; Brown and Qaqish, 2006; Tebas et al. 2000). This topic has been studied among various populations of HIV-infected
individuals, including ART naïve participants and those undergoing ART therapy (Bedimo et al. 2012; Looker et al. 1998; Tebas et al. 2000; McComsey et al. 2011). Increased bone fracture rates have been reported in multiple U.S. HIV cohorts (Triant et al. 2008; Yin et al. 2010; Young et al. 2011; Bedimo et al. 2012; Hansen et al. 2012; Womack et al. 2013). Our previous analysis revealed an increased risk of incident fractures among male and female HIV Outpatient Study (HOPS) participants compared with the general population (Young et al. 2011). This risk was associated with increasing age, lower nadir CD4 count, hepatitis C virus (HCV) infection, diabetes and substance abuse.

Although low bone mineral density is common among people living with HIV and increased bone fracture rates have been reported from multiple HIV cohorts, until now, no data have linked low BMD to incident fracture risk in HIV-infected populations. In this analysis, we characterized the relationship between low BMD and incident fracture risk in HIV-infected participants using data from two clinical HIV cohort studies funded by the Centers for Disease Control and Prevention (CDC).

5.3 Methods

This section provides a description of the two CDC-funded cohorts, definitions, and statistical analyses.

5.3.1 Study Populations

The HIV Outpatient Study (HOPS) is an ongoing prospective observational cohort study of HIV-infected adults that has accrued data longitudinally since 1993 (Moorman and Holmberg 1996). The HOPS includes data from eight clinics (university-based, public, and private) participating in the HOPS after January 1, 2006, located in
the following six cities: Chicago, IL; Denver, CO; Stony Brook, NY; Philadelphia, PA; Tampa, FL; and Washington, DC. Patient data, including demographic and social characteristics, symptoms, diagnoses, prescribed medications (including dose and duration), and laboratory values are abstracted from medical charts and entered by trained staff into a single database. These data are reviewed for quality and analyzed centrally at Cerner Corporation. Data quality assurance measures include supervisory reviews of randomly selected charts to ascertain accuracy and completeness of abstracted data, and centralized checks of data files to resolve discrepancies in diagnosis and treatment start and stop dates, and in diagnosis codes versus descriptive text field information. Annually, the institutional review boards (IRB) of the CDC (Atlanta, GA), Cerner Corporation (Vienna, VA), and each local site reviewed and approved the HOPS protocol and consents. The study protocol conforms to the guidelines of the United States (US) Department of Health and Human Services (DHHS) for the protection of human participants in research. The present analysis is based on the HOPS dataset updated as of September 30, 2012.

The Study to Understand the Natural History of HIV/AIDS in the ERA of Effective Therapy (SUN) is a prospective, observational cohort that monitors the clinical course of HIV-infected individuals treated with HAART from 7 HIV-specialty clinics in 4 US cities: St. Louis, Missouri; Providence, Rhode Island; Minneapolis, Minnesota; and Denver, Colorado (Vellozzi et al. 2009). Data collection (except imaging) occurred at the clinic site and coincided with subjects’ schedule of routine care. Imaging studies were obtained at a single site within each city. Six hundred ninety-five HIV-infected patients were enrolled from March 2004 through June 2006. The study's design, and its data
collection and management methods have been described previously (Vellozzi et al. 2009). Participants were generally healthy HIV-infected patients receiving routine outpatient care whose entire antiretroviral experience consisted only of HAART. Patient data, including sociodemographic characteristics and all symptoms, signs, diagnoses, treatments, and laboratory data, were abstracted from medical charts and entered into an electronic database by trained staff. These data were reviewed for quality and are analyzed centrally by Cerner staff. In addition to medical records abstraction, additional data were collected through periodic (6 monthly) physical examination, noninvasive imaging (echocardiogram, carotid intima-media thickness, coronary computed tomography, and dual-energy X-ray absorptiometry (DEXA)). The study protocol has been approved and is reviewed annually by the CDC and each site's IRB.

For the purposes of this analysis, we used data only from one HOPS site, which routinely offered and performed DEXA scans when screening indicated, and all the SUN study sites, which performed DEXA at each 6-monthly study visit. We defined our study population as HOPS patients seen at Denver Infectious Disease Consultants (HOPS-DIDC) with follow-up in 2008 or later and SUN patients with follow-up in 2004 or later, with at least one DEXA scan. The observation period began on January 1, 2008 or the first visit thereafter for HOPS patients, and on March 1, 2004 for SUN patients. Follow up extended to last patient contact or September 30, 2012 for HOPS-DIDC patients and June 30, 2012 for SUN patients.

DEXA data in the HOPS and SUN included values for BMD (g/cm²), T-score and Z-score for lumbar vertebrae one through five, and left or right femoral hip neck. In the HOPS-DIDC and SUN cohort, T-scores of the left femoral hip neck (or right femoral hip
neck if left was not available) were analyzed. Z-scores were also analyzed. For all DEXAs, the machine types used were either General Electric Lunar, or Hologic.

5.3.2 **Definitions**

We used the World Health Organization (WHO) definitions for normal BMD (BMD within 1 standard deviation (SD) of a young normal adult (T-score at -1.0 or above)), low bone mass (“osteopenia”) (BMD < 1.0 and > 2.5 SD below that of a young normal adult (T-score < -1.0 and > -2.5)), and osteoporosis (BMD of 2.5 SD or more below that of a young normal adult (T-score at or below -2.5)) (WHO Technical Report Series 843, 1994). The reference standard from which the T-score is calculated is the female, white, age 20-29 years, National Health and Nutrition Examination Survey (NHANES) III database (WHO Technical Report Series 843, 1994).

We analyzed the association between two main outcome variables, low BMD, defined as osteopenia (DEXA hip t-score < -1.0 and > -2.5) or osteoporosis (DEXA hip t-score ≤ -2.5) and any first incident fracture. In this analysis, incident fracture is defined as fracture that occurred in 2004 or later for SUN and in 2008 or later for HOPS and after first visit. Prevalent fracture is defined as fracture that occurred prior to 2004 for SUN and 2008 for HOPS or prior to first visit. Major osteoporotic fractures include hip, spine, shoulder and forearm. Age is defined as the age at baseline (at or closest to March 1, 2004 for SUN and January 1, 2008 for HOPS). Gender is defined as sex at birth.

Person years of observation were defined from March 1, 2004 to June 30, 2012, corresponding to the duration of the SUN Study follow up and from the first HOPS visit on or after January 1, 2008 after routine DEXA screening became available to HOPS-
DIDC and up to September 30, 2012. Baseline demographic and clinical values were those assessed closest to the baseline date, unless otherwise specified. Insurance status was classified as private, public or none (i.e., uninsured).

### 5.3.3 Statistical Analyses

We compared patient characteristics between groups using Yates corrected chi-square tests for categorical variables and Wilcoxon or Kruskal-Wallis tests for continuous variables. Among the three bone density categories, normal, osteopenia and osteoporosis, Jonckheere-Terpstra test of trend was used for continuous variables, and the Cochran-Armitage test of trend was used for categorical variables. We used Cox proportional hazards analyses to determine factors associated with incident fracture. In all modeling, variables with a univariate significance level (p-value) <0.05 were initially included in multivariable analyses. We constructed final multivariable models using backward manual selection procedures, retaining only those variables for which the significance level was <0.05. Descriptive data summaries, box plots, and univariate and multivariable Cox proportional hazards analyses were performed using statistical analysis system (SAS) version 9.3 (SAS Institute, Cary, NC). Yates corrected chi-square tests were performed using StatCalc (EpiInfo 2002 revision 2; Centers for Disease Control and Prevention, Atlanta, GA).

### 5.4 Results

We studied 1,008 patients (SUN, n=666; HOPS-DIDC, n=342) with at least one DEXA scan (baseline median age 42 [interquartile range (IQR) 35-48] years, 83% male sex, 67% non-Hispanic white, median CD4+ cell count (CD4) of 408 cells/mm³ [IQR 254-598; Table 5.1]. These subjects contributed 5,032 total patient-years of data with a
mean follow-up time of 4.99 years. Baseline BMD was categorized as normal in 60.8% (n=613), osteopenia 36.3%, and osteoporosis 2.9% (n=29). SUN and HOPS-DIDC patients showed similarity in proportions with osteopenia, osteoporosis, prevalent and incident fractures. HOPS-DIDC patients were significantly older, and more likely to be male, of white non-Hispanic race/ethnicity, have MSM HIV risk behavior, be privately insured, have higher baseline and nadir CD4+ cell counts, have a viral load < 400 copies/ml, more likely to have taken a tenofovir-containing HAART regimen, and less likely to be a current/prior smoker, have 14 or more alcoholic drinks per week, and have HCV co-infection (all p ≤ 0.01).

Low BMD (osteopenia or osteoporosis) was significantly (p<0.05) associated with increasing age, male sex, MSM HIV risk, lower nadir CD4+ cell counts, having a viral load < 400 copies/ml, having HCV co-infection, history of fracture, and inversely associated with heterosexual HIV transmission risk (Table 5.2). Low BMD was notably not associated with insurance payer, being a current/prior tobacco smoker, type of HAART used, or tenofovir use. The median ages of the patients in the three BMD classifications, i.e., normal, osteopenia and osteoporosis, were 39 years IQR (33-45), 44 years IQR (38-49) and 47 years (43-53), respectively.

Characteristics of patients who did and did not experience an incident fracture in the cohort were analyzed and reported in Table 5.3. Ninety-five incident fractures were reported. Of the patients reporting incident fracture (median age 43 years, IQR (38-50)), fractures occurred in 49 patients (51.6%) with normal bone density (hip T-score ≥ -1.0), 37 patients (39.0%) with osteopenia (hip T-score < -1.0) and 9 patients (9.5%) with osteoporosis (hip T-score < -2.5) (Table 5.3). The most frequent anatomical sites were:
rib/sternum (n=18), hand (n=17), foot (n=15) and wrist (n=11). Factors associated with incident fracture in univariate descriptive analyses included older age, being a prior or current smoker, having HCV co-infection, having a prior fracture, and presence of osteopenia or osteoporosis (all p < 0.05).

In unadjusted Cox proportional hazards regression analyses, factors associated with incident fracture were increasing age (hazard ratio [HR] = 1.41, 95% confidence interval [CI] = 1.13-1.76), current/prior tobacco smoking (HR = 1.60, 95% CI = 1.05-2.44) and presence of osteoporosis (HR = 3.98, 95% CI = 1.96-8.11) [Table 5.4].

In multivariable analyses, increasing age (adjusted Hazard Ratio [aHR] = 1.35 per 10 years age; 95% CI =1.07-1.70), being a current or prior smoker (aHR = 1.53, 95% CI =1.00-2.33) and DEXA T-score indicative of osteoporosis (aHR 3.04, 95% CI =1.47-6.30), were associated with incident fracture, but HCV co-infection and current or nadir CD4 were not [Table 5.4].

Baseline hip BMD T-scores were significantly lower among patients with incident fracture than those patients without incident fracture (Wilcoxon p-value < 0.001; Figure 5.1). Small sample size of fragility fractures ((hip, spine, forearm or shoulder; n=25) limited our ability to perform sensitivity analyses among this group.

5.5 Discussion

In this combined cohort of over one thousand individuals, abnormal BMD was found in a substantial minority of patients. Factors associated with low BMD in this cohort included increasing age, lower nadir CD4+ cell, MSM HIV risk, and prevalent and incident fracture. The findings of increasing age and lower nadir CD4+ cell count
associated with increased fracture risk in HIV-infected patients are consistent with previously reported findings (Young et al. 2011).

Although the inverse association of increasing age with decreasing T-score value is common in the literature, the relatively young age of this HIV-infected cohort warrants close scrutiny. These median ages of patients with low BMD in this cohort were below the minimum ages prescribed in clinical guidelines for DEXA screening in the general population (NOF 2013) as well as the HIV-infected population (IDSA 2013; EACS 2013).

Presently, diverse recommendations for DEXA screening exist based on age and clinical factors. The United States National Osteoporosis Foundation (NOF) recommends DEXA screening for osteoporosis in all women ≥ 65 years of age, men ≥ 70 years, and men and women ≥ 50 years if a fracture occurs or if other risk factors including rheumatoid arthritis or glucocorticoid use are observed (NOF 2013). NOF does not specifically address DEXA screening for HIV-infected individuals. The Infectious Diseases Society of America (IDSA) recommends bone densitometry screening for osteoporosis in postmenopausal women and men 50 years or older (Aberg et al. 2014; IDSA 2013). The European AIDS Clinical Society (EACS) recommends DEXA screening for any patient with one or more risk factors (i.e., postmenopausal women, men age ≥ 50 years, history of low impact fracture or high risk of falls, clinical hypogonadism and oral glucocorticoid use), preferably prior to ART initiation (EACS 2013). EACS provides detailed guidelines for screening and diagnosis of bone diseases (osteopenia, osteoporosis, osteomalacia and osteonecrosis) in HIV-infected patients (EACS 2013). McComsey and colleagues recommend DEXA
screening in HIV-infected men and women age ≥ 50 years predicated on the majority of HIV patients have an additional risk factor and fracture data suggesting that HIV and ART are linked to increased fracture risk (McComsey et al. 2010).

Our analysis is subject to several important limitations. Our cohort had a relatively few female study participants. Fractures occurring before entry into HOPS or SUN studies may be missing from medical records. Therefore, under-reporting of fractures may have occurred and consequently uncertainty as to whether incident fracture reported is a first fracture or a subsequent fracture. Incomplete reporting of anatomical site of fracture and limited number of fragility fractures precluded site-specific analyses. In these cohorts, incomplete capture of current/prior tobacco smoking may limit our ability to detect an effect. Lastly, HCV status was determined HCV seropositivity or detectable plasma HCV RNA but was unable to determine if chronic HCV infection was present.

Our analysis revealed low BMD and increased risk of incident fractures in HIV-infected persons at ages younger than 50 years, the minimum age recommended in these guidelines. While further studies are needed to confirm this observation, our findings suggest that DEXA screening be performed at diagnosis of or entry into care to ascertain baseline bone health in HIV-infected patients, regardless of age. In the interim, early detection of low BMD or risk of low BMD provides opportunity for earlier intervention to prevent fractures in HIV-infected patients.

5.6 Conclusion

In a large convenience sample of relatively young HIV-infected adults in the U.S., low baseline BMD and increasing age were strongly associated with elevated risk of
incident fracture. Presence of baseline osteoporosis was strongly associated with increased risk of incident fracture in this population of relatively young HIV-infected adults. Similar to previous analysis (Young et al. 2011), fracture risk was increased with increasing age. Early detection of low BMD or risk of low BMD may provide an opportunity for earlier intervention to prevent fractures in HIV-infected patients.

5.7 Acknowledgements

The authors thank the many SUN and HOPS patients for their participation in the studies and for the HOPS patients for their ongoing participation. We thank Rosa Franklin and Barbara Widick for their technical assistance. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

5.8 References Cited


Infectious Disease Society of America (ISDA) Practice Guidelines. 2013.  


Table 5.1 Demographic characteristics by study data source.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All study patients (N=1,008)</th>
<th>HOPS-DIDC (n=342)</th>
<th>SUN (n=666)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) or median (IQR)</td>
<td>N (%) or median (IQR)</td>
<td>N (%) or median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Median age*</td>
<td>42 (35-48)</td>
<td>44 (38-50)</td>
<td>40 (34-46)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>838 (83.1)</td>
<td>325 (95.0)</td>
<td>513 (77.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>674 (66.9)</td>
<td>281 (82.2)</td>
<td>393 (59.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>212 (21.0)</td>
<td>20 (5.9)</td>
<td>192 (28.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>92 (9.1)</td>
<td>36 (10.5)</td>
<td>56 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown race/ethnicity</td>
<td>30 (3.0)</td>
<td>5 (1.5)</td>
<td>25 (3.8)</td>
<td></td>
</tr>
<tr>
<td>MSM HIV risk</td>
<td>690 (68.5)</td>
<td>302 (88.3)</td>
<td>388 (58.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IDU HIV risk</td>
<td>58 (5.8)</td>
<td>8 (2.3)</td>
<td>50 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown HIV risk</td>
<td>62 (6.2)</td>
<td>9 (2.6)</td>
<td>53 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual HIV risk</td>
<td>198 (19.6)</td>
<td>23 (6.7)</td>
<td>175 (26.3)</td>
<td></td>
</tr>
<tr>
<td>First HOPS/SUN visit &lt; 2008</td>
<td>921 (91.4)</td>
<td>256 (74.9)</td>
<td>665 (99.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>First HOPS/SUN visit 2008-2009</td>
<td>68 (6.8)</td>
<td>67 (19.6)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>First HOPS/SUN visit ≥ 2010</td>
<td>19 (1.9)</td>
<td>19 (5.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Private Insurance*</td>
<td>590 (58.5)</td>
<td>289 (84.5)</td>
<td>301 (45.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Public Insurance*</td>
<td>264 (26.2)</td>
<td>39 (11.4)</td>
<td>225 (33.8)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown payer*</td>
<td>154 (15.3)</td>
<td>14 (4.1)</td>
<td>140 (21.0)</td>
<td></td>
</tr>
<tr>
<td>Median CD4+ cell count (cells/mm³)*</td>
<td>408 (254-598)</td>
<td>466 (316-642)</td>
<td>374 (232-562)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nadir CD4+ cell count (cells/mm³)</td>
<td>188 (71-299)</td>
<td>221 (73-335)</td>
<td>178 (71-275)</td>
<td>0.009</td>
</tr>
<tr>
<td>Viral load &lt; 400 copies/mL*</td>
<td>560 (55.6)</td>
<td>222 (64.9)</td>
<td>338 (50.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current/prior smoker</td>
<td>546 (54.2)</td>
<td>152 (44.4)</td>
<td>394 (59.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>14+ ETOH drinks/week</td>
<td>34 (3.4)</td>
<td>4 (1.2)</td>
<td>30 (4.5)</td>
<td>0.010</td>
</tr>
<tr>
<td>HAART type*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boosted PI</td>
<td>292 (29.0)</td>
<td>124 (36.3)</td>
<td>168 (25.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NNRTI</td>
<td>422 (41.9)</td>
<td>124 (36.3)</td>
<td>298 (44.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>260 (25.8)</td>
<td>88 (25.7)</td>
<td>172 (25.8)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>34 (3.4)</td>
<td>6 (1.7)</td>
<td>28 (4.2)</td>
<td></td>
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<tr>
<td>TDF-containing HAART</td>
<td>468 (46.4)</td>
<td>208 (60.8)</td>
<td>260 (39.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HCV co-infection (DX or +Lab)</td>
<td>123 (12.2)</td>
<td>21 (6.1)</td>
<td>102 (15.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prevalent fracture</td>
<td>60 (6.0)</td>
<td>19 (5.5)</td>
<td>41 (6.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>Normal bone density (hip t-score ≥ -1.0)</td>
<td>613 (60.8)</td>
<td>210 (61.4)</td>
<td>403 (60.5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Osteopenia (hip t-score &lt; -1.0)</td>
<td>366 (36.3)</td>
<td>121 (35.4)</td>
<td>245 (36.8)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis (hip t-score &lt; -2.5)</td>
<td>29 (2.9)</td>
<td>11 (3.2)</td>
<td>18 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Years follow-up, mean</td>
<td>4.99</td>
<td>3.05</td>
<td>5.99</td>
<td></td>
</tr>
<tr>
<td>Incident fracture</td>
<td>95 (9.4)</td>
<td>29 (8.5)</td>
<td>66 (9.9)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
** Yates corrected chi-square test for class variables, Wilcoxon rank-sum test for continuous variables
Table 5.2  Prevalence of factors associated with low BMD (osteopenia or osteoporosis, determined by DEXA hip t-score).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Osteoporosis (n=29)</th>
<th>Osteopenia (n=366)</th>
<th>Normal BMD (n=613)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) or median (IQR)</td>
<td>N (%) or median (IQR)</td>
<td>N (%) or median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Median age*</td>
<td>47 (43-52)</td>
<td>44 (38-49)</td>
<td>39 (33-45)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>27 (93.1)</td>
<td>324 (88.5)</td>
<td>487 (79.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>16 (55.2)</td>
<td>268 (73.2)</td>
<td>390 (63.6)</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>6 (20.7)</td>
<td>61 (16.7)</td>
<td>145 (23.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (24.1)</td>
<td>30 (8.2)</td>
<td>55 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown race/ethnicity</td>
<td>0 (0.0)</td>
<td>7 (1.9)</td>
<td>23 (3.8)</td>
<td></td>
</tr>
<tr>
<td>MSM HIV risk</td>
<td>21 (72.4)</td>
<td>265 (72.4)</td>
<td>404 (65.9)</td>
<td></td>
</tr>
<tr>
<td>IDU HIV risk</td>
<td>2 (6.9)</td>
<td>23 (6.3)</td>
<td>33 (5.4)</td>
<td>0.012</td>
</tr>
<tr>
<td>Other/Unknown HIV risk</td>
<td>2 (6.9)</td>
<td>28 (7.7)</td>
<td>32 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual HIV risk</td>
<td>4 (13.8)</td>
<td>50 (13.7)</td>
<td>144 (23.5)</td>
<td></td>
</tr>
<tr>
<td>First HOPS/SUN visit &lt; 2008</td>
<td>28 (96.6)</td>
<td>344 (94.0)</td>
<td>549 (89.6)</td>
<td>0.024</td>
</tr>
<tr>
<td>First HOPS/SUN visit 2008-2009</td>
<td>0 (0.0)</td>
<td>20 (5.5)</td>
<td>48 (7.8)</td>
<td></td>
</tr>
<tr>
<td>First HOPS/SUN visit ≥ 2010</td>
<td>1 (3.5)</td>
<td>2 (0.6)</td>
<td>16 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Private Insurance*</td>
<td>12 (41.4)</td>
<td>213 (58.2)</td>
<td>365 (59.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Public Insurance*</td>
<td>14 (48.3)</td>
<td>92 (25.1)</td>
<td>158 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown payer*</td>
<td>3 (10.3)</td>
<td>61 (16.7)</td>
<td>90 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Median CD4+ cell count (cells/mm$^3$)*</td>
<td>392 (168-624)</td>
<td>398 (247-598)</td>
<td>414 (258-594)</td>
<td>0.62</td>
</tr>
<tr>
<td>Nadir CD4+ cell count (cells/mm$^3$)</td>
<td>92 (15-274)</td>
<td>177 (57-285)</td>
<td>200 (87-305)</td>
<td>0.008</td>
</tr>
<tr>
<td>Viral load &lt; 400 copies/mL*</td>
<td>17 (58.6)</td>
<td>230 (62.8)</td>
<td>313 (51.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>AIDS DX*</td>
<td>4 (13.8)</td>
<td>49 (13.4)</td>
<td>127 (20.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Current/prior smoker</td>
<td>17 (58.6)</td>
<td>209 (57.1)</td>
<td>320 (52.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>14+ ETOH drinks/week</td>
<td>1 (3.5)</td>
<td>19 (5.2)</td>
<td>14 (2.3)</td>
<td>0.033</td>
</tr>
<tr>
<td>HAART type*</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Boosted PI</td>
<td>3 (10.3)</td>
<td>104 (28.4)</td>
<td>185 (30.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>NNRTI</td>
<td>14 (48.3)</td>
<td>155 (42.4)</td>
<td>253 (41.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (41.4)</td>
<td>96 (26.2)</td>
<td>152 (24.8)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0 (0.0)</td>
<td>11 (3.0)</td>
<td>23 (3.8)</td>
<td></td>
</tr>
<tr>
<td>TDF-containing HAART</td>
<td>11 (37.9)</td>
<td>165 (45.1)</td>
<td>292 (47.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>HCV co-infection (DX or +Lab)</td>
<td>8 (27.6)</td>
<td>53 (14.5)</td>
<td>62 (10.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Prevalent fracture</td>
<td>6 (20.7)</td>
<td>24 (6.6)</td>
<td>30 (4.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Incident fracture</td>
<td>9 (31.0)</td>
<td>37 (10.1)</td>
<td>49 (8.0)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
**Yates corrected chi-square test for class variables, Jonckheere-Terpstra test for individual continuous variables, Cochran-Armitage test for individual categorical variables.
Table 5.3 Baseline patients characteristics among patients who did and did not experience a fracture during follow-up.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fracture (n=95) N (%) or IQR</th>
<th>No Fracture (n=913) N (%) or IQR</th>
<th>Yates corrected p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age*</td>
<td>43 (38-50)</td>
<td>41 (34-47)</td>
<td>0.007</td>
</tr>
<tr>
<td>Male sex</td>
<td>82 (86.3)</td>
<td>756 (82.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>65 (68.4)</td>
<td>609 (66.7)</td>
<td>0.86</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>18 (19.0)</td>
<td>194 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>10 (10.5)</td>
<td>82 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown race/ethnicity</td>
<td>2 (2.1)</td>
<td>28 (3.1)</td>
<td></td>
</tr>
<tr>
<td>MSM HIV risk</td>
<td>67 (70.5)</td>
<td>623 (68.2)</td>
<td>0.051</td>
</tr>
<tr>
<td>IDU HIV risk</td>
<td>8 (8.4)</td>
<td>50 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown HIV risk</td>
<td>1 (1.1)</td>
<td>61 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual HIV risk</td>
<td>19 (20.0)</td>
<td>179 (19.6)</td>
<td></td>
</tr>
<tr>
<td>First HOPS/SUN visit &lt; 2008</td>
<td>91 (95.8)</td>
<td>830 (90.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>First HOPS/SUN visit 2008-2009</td>
<td>4 (4.2)</td>
<td>64 (7.0)</td>
<td></td>
</tr>
<tr>
<td>First HOPS/SUN visit ≥ 2010</td>
<td>0 (0.0)</td>
<td>19 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Private Insurance*</td>
<td>51 (53.7)</td>
<td>539 (59.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Public Insurance*</td>
<td>32 (33.7)</td>
<td>232 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown payer*</td>
<td>12 (12.6)</td>
<td>142 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Median CD4+ cell count (cells/mm$^3$)*</td>
<td>427 (276-660)</td>
<td>406 (253-588)</td>
<td>0.27</td>
</tr>
<tr>
<td>Nadir CD4+ cell count (cells/mm$^3$)</td>
<td>189 (51-300)</td>
<td>188 (72-299)</td>
<td>0.82</td>
</tr>
<tr>
<td>Viral load &lt; 400 copies/mL*</td>
<td>57 (60.0)</td>
<td>503 (55.1)</td>
<td>0.42</td>
</tr>
<tr>
<td>AIDS DX*</td>
<td>17 (17.9)</td>
<td>163 (17.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Current/prior smoker</td>
<td>62 (65.3)</td>
<td>484 (53.0)</td>
<td>0.030</td>
</tr>
<tr>
<td>14+ ETOH drinks/week</td>
<td>3 (3.2)</td>
<td>31 (3.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>HAART type*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boosted PI</td>
<td>20 (21.1)</td>
<td>272 (29.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>NNRTI</td>
<td>49 (51.6)</td>
<td>373 (40.9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>22 (23.2)</td>
<td>238 (26.1)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (4.2)</td>
<td>30 (3.3)</td>
<td></td>
</tr>
<tr>
<td>TDF-containing HAART</td>
<td>42 (44.2)</td>
<td>426 (46.7)</td>
<td>0.73</td>
</tr>
<tr>
<td>HCV co-infection (DX or +Lab)</td>
<td>19 (20.0)</td>
<td>104 (11.4)</td>
<td>0.023</td>
</tr>
<tr>
<td>Prevalent fracture</td>
<td>12 (12.6)</td>
<td>48 (5.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Normal bone density (hip t-score ≥ -1.0)</td>
<td>49 (51.6)</td>
<td>564 (61.8)</td>
<td></td>
</tr>
<tr>
<td>Osteopenia (hip t-score &lt; -1.0)</td>
<td>37 (39.0)</td>
<td>329 (36.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Osteoporosis (hip t-score &lt; -2.5)</td>
<td>9 (9.5)</td>
<td>20 (2.2)</td>
<td></td>
</tr>
</tbody>
</table>

* At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
Table 5.4 Association between low bone mineral density and other factors, and incident fractures.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate HR (95% CI)</th>
<th>Multivariable HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.41 (1.13-1.76)</td>
<td>1.35 (1.07-1.70)</td>
<td>0.011</td>
</tr>
<tr>
<td>CD4+ count (per 100 cells)</td>
<td>1.04 (0.97-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir CD4+ count (per 100 cells)</td>
<td>1.00 (0.88-1.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.66 (0.37-1.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDU HIV risk (vs. MSM HIV risk)</td>
<td>1.38 (0.66-2.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public insurance (vs. private/other)</td>
<td>1.26 (0.82-1.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1.62 (0.98-2.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/prior smoker</td>
<td>1.64 (0.99-2.71)</td>
<td>1.53 (1.00-2.33)</td>
<td>0.048</td>
</tr>
<tr>
<td>Osteopenia*</td>
<td>1.21 (0.79-1.85)</td>
<td>1.04 (0.67-1.62)</td>
<td>0.85</td>
</tr>
<tr>
<td>Osteoporosis**</td>
<td>3.98 (1.96-8.11)</td>
<td>3.04 (1.47-6.30)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* Defined as T-score of < -1.0, based on hip measurement.

** Defined as T-score of < -2.5, based on hip measurement. With osteopenia in the model, the referent patients are those with hip T-score ≥ -1.0.
Figure 5.1  Hip BMD T-score distribution by incident fracture.
CHAPTER 6

NEW FRACTURE RISK AND FRAX 10-YEAR PROBABILITY OF FRACTURE IN HIV-INFECTED ADULTS

A paper to be submitted to Clinical Infectious Diseases. Abstract orally presented at the Joint Session of 14th European AIDS Conference and 15th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV, 17 October 2013, Brussels, Belgium and during Poster Session P-Q5 at the Conference on Retroviruses and Opportunistic Infections, 6 March 2014, Boston, Massachusetts, United States. Abstract to be presented at the International Society for Pharmacoconomics and Outcomes Research (ISPOR), May 31-June 4, 2012, Montreal, QC, Canada, Poster Session V

Linda A. Battalora, Kate Buchacz, Carl Armon, Edgar T. Overton, John Hammer, Pragna Patel, Joan S. Chmiel, Kathy Wood, John T. Brooks, Benjamin Young for the HIV Outpatient Study (HOPS) and SUN Study Investigators

6.1 Abstract

The prevalence of low bone mineral density (BMD) and fracture risk is elevated among human immunodeficiency virus (HIV)-infected persons. FRAX reliably predicts 10-year fracture risk for adults in the general population. However, FRAX’s utility for HIV-infected adults has not been assessed. Using dual energy X-ray absorptiometry (DEXA) BMD values of the left femoral neck, and clinical data collected prospectively during 2004-2012 from two CDC-sponsored HIV cohorts, we calculated the initial FRAX 10-year risk of a major osteoporotic fracture.

One thousand six participants contributed 5022 patient-years (py) of follow-up (83% male; 67% non-Hispanic white; median age at DEXA scan was 42 years [interquartile range (IQR) 35-48]; median CD4+ cell count 408 cells/mm³ [IQR 255-600]). Participants had median (IQR) values of 0.90 g/cm² for BMD (IQR: 0.80-1.00)
and 1.9 for FRAX score (IQR: 1.4-3.2). Median FRAX scores were higher for those who had any subsequent new fracture vs. those who did not (Wilcoxon rank sum test: p<0.01). During a median of 4.2 (IQR 3.0-7.7) years of observation after initial DEXA, 95 participants (9.4%) had any new fracture: 7.1% occurred among persons with FRAX score <3% (1.39 per 100py) and 15.3% among persons with FRAX score ≥3% (3.27 per 100py). New major osteoporotic fractures were observed among 1.5% of persons with FRAX score <3% (0.30 per 100py), and among 4.9% (1.04 per 100py) of persons with FRAX score ≥3%. In multivariate analyses, having a prior fracture (adjusted hazard ratio [aHR] 2.02, 95% confidence interval [CI]: 1.09-3.71), older age (aHR 1.30 per 10 years, 95% CI: 1.04-1.62), and lower BMD (aHR 0.14 per g/cm², 95% CI: 0.03-0.59) were associated with risk of any new fracture. In a separate model, having FRAX score ≥ 3% vs. FRAX of < 3.0% was associated with any new fracture (HR 2.31, 95% CI: 1.54-3.46).

In this large convenience sample of relatively young HIV-infected U.S. adults, a FRAX score ≥3%, low baseline BMD, history of prior fracture, and increased age were significantly associated with elevated risk of new fracture.

### 6.2 Introduction

There is an increasing appreciation of deficits in bone health among persons living with HIV. Studies in the United States have shown high prevalence of low bone mineral density (BMD) among persons living with HIV (Overton, CROI 2007; Brown and Qaqish, 2006; Tebas et al. 2000). This topic has been studied among various populations of HIV-infected individuals, including ART naïve participants and those undergoing ART therapy (Bedimo et al. 2012; Looker et al. 1998; Tebas et al. 2000;
McComsey et al. 2011). Increased bone fracture rates have been reported in multiple U.S. HIV cohorts (Triant et al. 2008; Yin et al. 2010; Young et al. 2011; Bedimo et al. 2012; Hansen et al. 2012; Womack et al. 2013). Our previous analysis revealed an increased risk of incident fractures among male and female HIV Outpatient Study (HOPS) participants compared with the general population (Young et al. 2011). This risk was associated with increasing age, lower nadir CD4 count, hepatitis-C virus (HCV) infection, diabetes and substance abuse.

In a large sample of HIV-infected adults in the U.S., we found that low baseline BMD and increasing age were strongly associated with elevated risk of incident fracture (Battalora, CROI 2014). Early detection of low BMD or risk of low BMD may provide an opportunity for earlier intervention to prevent fractures in HIV-infected patients. The World Health Organization (WHO) Fracture Risk Algorithm (FRAX®) (FRAX) reliably predicts the 10-year fracture risk for adults in the general population (NOF 2013). The algorithm calculates the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (spine, forearm, hip, or shoulder fracture). Multiple FRAX models have been developed based on cohorts in Europe, North America, Asia, Australia, Latin America and Oceania.

The utility of FRAX for HIV-infected adults has not been assessed. In this analysis, we calculated baseline FRAX 10-year probability of major osteoporotic fracture (hip, spine, shoulder or forearm) in HIV-infected participants using data from two clinical HIV cohort studies funded by the Centers for Disease Control and Prevention (CDC) and contrasted these findings with observed incident fractures.
6.3 Methods

This section provides a description of the two CDC-funded cohorts, definitions, and statistical analyses.

6.3.1 Study Population

The HIV Outpatient Study (HOPS) is an ongoing prospective observational cohort study of HIV-infected adults that has accrued data longitudinally since 1993 (Moorman and Holmberg 1996). The HOPS includes data from eight clinics (university-based, public, and private) participating in the HOPS after January 1, 2006, located in six US cities. Annually, the institutional review boards (IRB) of the CDC (Atlanta, GA), Cerner Corporation (Vienna, VA), and each local site reviewed and approved the HOPS protocol and consents. The study protocol conforms to the guidelines of the United States (US) Department of Health and Human Services (DHHS) for the protection of human participants in research. The present analysis is based on the HOPS dataset updated as of September 30, 2012.

The Study to Understand the Natural History of HIV/AIDS in the ERA of Effective Therapy (SUN) is a prospective, observational cohort that monitors the clinical course of HIV-infected individuals treated with HAART from 7 HIV-specialty clinics in 4 US cities (Vellozzi 2009). Six hundred ninety-five HIV-infected patients were enrolled from March 2004 through June 2006. Participants were generally healthy HIV-infected patients receiving routine outpatient care whose entire antiretroviral experience consisted only of HAART. Dual-energy X-ray absorptiometry (DEXA) scans were performed every six months as part of the study protocol. The study protocol has been approved and is reviewed annually by the CDC and each site's IRB.
For the purposes of this analysis, we used data only from one HOPS site, which routinely offered and performed DEXA scans when screening indicated, and all of the SUN sites which performed DEXA at each 6-monthly study visit. We defined our study population as HOPS patients seen at the Denver Infectious Disease Consultants site (HOPS-DIDC) with follow-up in 2008 or later and SUN patients with follow-up in 2004 or later, with at least one DEXA scan. The observation period began on January 1, 2008 or the first visit thereafter for HOPS patients, and on March 1, 2004 for SUN patients. Follow up extended to last patient contact or September 30, 2012 for HOPS-DIDC patients and June 30, 2012 for SUN patients.

DEXA data in the HOPS and SUN included values for BMD (g/cm²), T-score and Z-score for lumbar vertebrae one through five, and left or right femoral hip neck. In the HOPS-DIDC and SUN cohort, T-scores of the left femoral hip neck (or right femoral hip neck if left was not available) were analyzed. Z-scores were also analyzed. For all DEXAs, the machine types used were either General Electric Lunar, or Hologic.

6.3.2 Definitions

We used the World Health Organization (WHO) definitions for normal BMD (BMD within 1 standard deviation (SD) of a young normal adult (T-score at -1.0 or above)), low bone mass (“osteopenia”) (BMD < 1.0 and > 2.5 SD below that of a young normal adult (T-score < -1.0 and > -2.5)), and osteoporosis (BMD of 2.5 SD or more below that of a young normal adult (T-score at or below -2.5)) (See Assessment of Fracture risk and its Application to screening for Postmenopausal Osteoporosis. 1994. WHO Technical Report Series 843, 1994).
In this analysis, incident fracture is defined as fracture that occurred in 2004 or later for SUN and in 2008 or later for HOPS and after first visit. Prevalent fracture is defined as fracture that occurred prior to 2004 for SUN and 2008 for HOPS or prior to first visit. Major osteoporotic fractures include hip spine, shoulder and forearm. Age is defined as the age at baseline (at or closest to March 1, 2004 for SUN and January 1, 2008 for HOPS). Gender is defined as sex at birth.

The observation period was from March 1, 2004 to June 30, 2012, corresponding to the duration of the SUN follow up and from the first HOPS visit on or after January 1, 2008 after routine DEXA screening became available to HOPS-DIDC and up to September 30, 2012. Baseline demographic and clinical values were those assessed closest to the baseline date, unless otherwise specified.

In these analyses, we used the U.S-adapted WHO FRAX algorithm that is calibrated to U.S. fracture and mortality rates (NOF 2013). FRAX calculation tool risk factors included age, sex, weight (kg), height (cm), previous fracture, parent fractured hip, current tobacco smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol 3 or more units/day and BMD. The FRAX definitions of these factors were adopted in this analysis and are provided below. From the FRAX® World Health Organization Fracture Risk Assessment Tool. [http://www.shef.ac.uk/FRAX/](http://www.shef.ac.uk/FRAX/).

**Accessed April 7, 2014:**

- "Age is defined in years between 40 and 90. Ages below or above automatically default to 40 and 90, respectively;
• Previous fracture means a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma that, in a healthy individual, would not have resulted in a fracture;

• Parent fractured hip refers to mother’s or father’s history of hip fracture. (Current smoking requires a yes or no answer);

• Glucocorticoids refer to patient exposure to oral glucocorticoids or patient has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5m daily or more (or equivalent does of other glucocorticoids);

• Rheumatoid arthritis refers to patient’s confirmed diagnosis of the condition;

• Secondary osteoporosis means the patient has a disorder strongly associated with osteoporosis, including type 1 (insulin dependent) diabetes, osteogenesis imperfect in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (< 45 years), chronic malnutrition, or malabsorption and chronic liver disease;

• Alcohol consumption is defined as 3 or more units /day where a unit of alcohol may vary slightly from 8-10 g of alcohol in different countries;

• BMD is defined in units of g/cm² and measurements are taken from the femoral neck. If BMD is not available, then T-score based on the NHANES III female reference population is entered.”

HCV was recorded in HOPS and SUN Study charts or in discharge records as either a diagnosis of HCV infection, or evidence of HCV seropositivity or detectable plasma HCV RNA.

6.3.3 Statistical Analyses

Using dual energy X-ray absorptiometry (DEXA) BMD values of the left femoral neck, and clinical data collected prospectively during 2004-2012 from two CDC-sponsored HIV cohorts, we calculated the initial FRAX 10-year risk of a major osteoporotic fracture (i.e., of the hip, spine, forearm, or shoulder). We compared patient characteristics by four FRAX ranges chosen to have similar numbers of patients in each of the four groups, and used Yates-corrected chi-square test or Fisher Exact test for class variables, Jonckheere-Terpstra test for individual continuous variables or Cochran-Armitage test for individual categorical variables to compare the four groups.

We assessed rates of any new bone fracture and major osteoporotic fracture per 100 person-years (py) of follow-up, stratified by initial FRAX-score intervals, and used Cox proportional hazards models to identify clinical and demographic risk factors for any new fracture. We created 2 multivariable models using the Cox proportional hazards analyses. Model 1 included all factors required by the FRAX software and additional disease-specific factors of viral load, HCV co-infections, CD4+ cell counts, and antiviral use. Model 2 included the FRAX 10-year probability and disease specific factors significant in the first multivariable model and not required by the FRAX tool, if any.

In all modeling, variables with a univariate significance level (p-value) <0.05 were initially included in multivariable analyses. We constructed final multivariable models using backward manual selection procedures, retaining only those variables for which
the significance level was <0.05. Descriptive data summaries, box plots, and univariate and multivariable Cox proportional hazards analyses were performed using statistical analysis system (SAS) version 9.3 (SAS Institute, Cary, NC). Yates corrected chi-square tests were performed using StatCalc (EpiInfo 2002 revision 2; Centers for Disease Control and Prevention, Atlanta, GA).

6.4 Results

The patient characteristics are described in Table 6.1. Among 1,006 participants who contributed 5,022 person-years of follow-up, 83% were male, 67% were non-Hispanic white, median age at date of DEXA scan was 42 years, and median CD4+ cell count was 408 cells/mm$^3$. By increasing FRAX range, patients were significantly older, more likely to be male and of non-Hispanic white race/ethnicity, more likely to have MSM HIV risk, more likely to be privately insured, have higher median baseline CD4+ cell counts, more likely to have baseline viral loads < 400 copies/ml, more likely to have osteopenia or osteoporosis, and more likely to have a prevalent fracture.

During follow-up, patients with FRAX range > 3% were more likely to have an incident fracture. There were 95 incident fractures reported in the combined SUN/HOPS-DIDC cohort (Table 6.2). During a median of 4.2 years of observation after initial DEXA, 95 (9.4%) of patients had an incident fracture, 7.1% with FRAX 10-year probability <3% (1.39/100py) and 15.3% with FRAX 10-year probability ≥3% (3.27/100py), and new major osteoporotic fractures were observed among 1.5% with FRAX 10-year probability <3% (0.3/100py) and among 4.9% (1.04/100py) with FRAX 10-year probability ≥3%.

The mean FRAX 10-year probabilities among patients with no incident fracture
(n=911), any incident fracture (n=95), or incident major osteoporotic fracture (n=25) were 2.5%, 3.4%, and 4.8%, respectively (Figure 6.1). Figure 6.2 describes SUN/HOPS-DIDC incident fracture proportion and rate by FRAX 10-year probability (%) range among the 1,006 patients. Figure 6.1 indicated that incidence of fracture was statistically greater among those with FRAX 10-year probability of 3.0% or greater compared to those with FRAX 10-year probabilities < 3%.

In multivariable analysis of the first model, having a prior fracture, increasing age, and lower BMD were associated with incident fracture. In the second model, having a FRAX 10-year probability ≥3% vs. FRAX 10-year probability <3% was associated with any new fracture (Table 6.3).

### 6.5 Discussion

An awareness of bone health among people living with HIV is heightened with the knowledge of increased fracture risk, particularly among an aging population. Algorithms can be useful in predicting risk, but have not yet been assessed in the HIV population. FRAX is widely used to predict the 10-year fracture risk for adults in the general population (NOF 2013). The utility of FRAX for HIV-infected adults has not been determined. In our SUN/HOPS-DIDC cohort, we found that over a median of 4.2 years of observation nearly 10% of patients had an incident fracture, 7.1% with FRAX 10-year probability <3% (1.39/100py) and 15.3% with FRAX 10-year probability ≥3% (3.27/100py). New major osteoporotic fractures were observed among 1.5% with FRAX 10-year probability <3% (0.3/100py) and among 4.9% (1.04/100py) with FRAX 10-year probability ≥3%. Incidence of fracture was statistically greater among those with FRAX 10-year probability of ≥3% to those with FRAX 10-year probabilities <3%. A two-fold
increase in rate of incidence fracture was observed in participants with FRAX 10-year probability of ≥3%.

While the strengths of this study include the large sample size and long follow up time, our analysis is subject to important limitations. Our sample population had relatively few women, and fractures that may have occurred before entry into the cohort studies may be missing from medical records. Incident fracture events may have been incompletely captured, if not diagnosed by or reported to HOPS or SUN clinics. FRAX tool risk factor of parent fractured hip unavailable in HOPS and SUN data. In HOPS and SUN, we have all fractures incidence, while FRAX focuses on risk of major osteoporotic fractures only. Incomplete reporting of anatomical site of fracture and limited number of major osteopathic fractures (n=25) precluded site-specific analyses.

6.6 Conclusions

In a large convenience sample of 1,006 relatively young HIV-infected U.S. adults who contributed 5,022 person-years of follow-up, increasing baseline FRAX 10-year probability was consistently associated with increased rates of incident fractures. Subjects with FRAX 10-year probability of ≥3% had over 2-fold higher rates of incident fracture than those with lower FRAX scores. A FRAX score ≥ 3%, low baseline BMD, history of prior fracture, and increased age were significantly associated with elevated risk of new fracture.

Taken together, these data highlight the association of low BMD and risk of bone fractures. Future research needs to be directed at improving the predictive value of clinical algorithms in the field and the factors that contribute to heightened fracture risk.
6.7 Acknowledgements

The authors thank the SUN and HOPS patients for their participation in the studies and for the HOPS patients for their ongoing participation. We also thank Rosa Franklin and Barbara Widick for their research support. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

6.8 References Cited


Moorman AC, Holmberg SD, Marlowe SI, et al. Changing conditions and treatments in a


Table 6.1 Patient characteristics FRAX 10-year probability (%), (N=1,006)

<table>
<thead>
<tr>
<th>Patient characteristics n (%) or median (IQR)</th>
<th>All study patients (n=1,006)</th>
<th>FRAX range 0%-1.4% (n=263)</th>
<th>FRAX range &gt;1.4%-1.9% (n=243)</th>
<th>FRAX range &gt;1.9%-3.0% (n=231)</th>
<th>FRAX range &gt;3.0% (n=269)</th>
<th>p-value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age*</td>
<td>41.7 (35.2-48.0)</td>
<td>36.4 (29.1-41.7)</td>
<td>36.7 (31.6-41.1)</td>
<td>43.5 (39.8-46.9)</td>
<td>50.6 (46.1-55.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>837 (83.2)</td>
<td>178 (67.7)</td>
<td>202 (83.1)</td>
<td>208 (90.0)</td>
<td>249 (92.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>169 (16.8)</td>
<td>85 (32.3)</td>
<td>41 (16.9)</td>
<td>23 (10.0)</td>
<td>20 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>673 (66.9)</td>
<td>18 (6.8)</td>
<td>201 (82.7)</td>
<td>205 (88.7)</td>
<td>249 (92.6)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>212 (21.1)</td>
<td>159 (60.5)</td>
<td>26 (10.7)</td>
<td>16 (6.9)</td>
<td>11 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>91 (9.1)</td>
<td>65 (24.7)</td>
<td>11 (4.5)</td>
<td>7 (3.0)</td>
<td>8 (3.0)</td>
<td></td>
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<tr>
<td>Other/unknown</td>
<td>30 (3.0)</td>
<td>21 (8.0)</td>
<td>5 (2.1)</td>
<td>3 (1.3)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>HIV Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IDU</td>
<td>58 (5.8)</td>
<td>19 (7.2)</td>
<td>10 (4.1)</td>
<td>15 (6.5)</td>
<td>14 (5.2)</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>689 (68.5)</td>
<td>114 (43.4)</td>
<td>179 (73.7)</td>
<td>183 (79.2)</td>
<td>213 (79.2)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>197 (19.6)</td>
<td>102 (38.8)</td>
<td>43 (17.7)</td>
<td>24 (10.4)</td>
<td>28 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>62 (6.2)</td>
<td>28 (10.7)</td>
<td>11 (4.5)</td>
<td>9 (3.9)</td>
<td>14 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Insurance*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Private</td>
<td>589 (58.6)</td>
<td>94 (35.7)</td>
<td>161 (66.3)</td>
<td>153 (66.2)</td>
<td>181 (67.3)</td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>263 (26.1)</td>
<td>107 (40.7)</td>
<td>47 (19.3)</td>
<td>43 (18.6)</td>
<td>66 (24.5)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>154 (15.3)</td>
<td>62 (23.6)</td>
<td>35 (14.4)</td>
<td>35 (15.2)</td>
<td>22 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Median CD4+ cell count (cells/mm$^3$)*</td>
<td>408 (254-598)</td>
<td>354 (209-528)</td>
<td>419 (258-588)</td>
<td>430 (294-619)</td>
<td>447 (269-673)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nadir CD4+ cell count (cells/mm$^3$)</td>
<td>188 (71-298)</td>
<td>179 (58-275)</td>
<td>195 (86-316)</td>
<td>205 (79-298)</td>
<td>168 (59-305)</td>
<td>0.58</td>
</tr>
<tr>
<td>Viral load &lt; 400 copies/ml*</td>
<td>560 (55.7)</td>
<td>114 (43.4)</td>
<td>117 (48.2)</td>
<td>139 (60.2)</td>
<td>190 (70.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current/prior tobacco smoker</td>
<td>546 (54.3)</td>
<td>136 (51.7)</td>
<td>130 (53.5)</td>
<td>130 (56.3)</td>
<td>150 (55.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>14+ alcoholic drinks/week</td>
<td>34 (3.4)</td>
<td>10 (3.8)</td>
<td>4 (1.7)</td>
<td>9 (3.9)</td>
<td>11 (4.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>HAART type*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>Boosted PI</td>
<td>292 (29.0)</td>
<td>83 (31.6)</td>
<td>73 (30.0)</td>
<td>65 (28.1)</td>
<td>71 (26.4)</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>420 (41.8)</td>
<td>111 (42.2)</td>
<td>103 (42.4)</td>
<td>92 (39.8)</td>
<td>114 (42.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>260 (25.8)</td>
<td>61 (23.2)</td>
<td>57 (23.5)</td>
<td>63 (27.3)</td>
<td>79 (29.4)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>34 (3.4)</td>
<td>8 (3.0)</td>
<td>10 (4.1)</td>
<td>11 (4.8)</td>
<td>5 (1.9)</td>
<td></td>
</tr>
<tr>
<td>TDF-containing HAART</td>
<td>467 (46.4)</td>
<td>114 (43.4)</td>
<td>120 (49.4)</td>
<td>100 (43.3)</td>
<td>133 (49.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>HCV co-infection (DX or +Lab)</td>
<td>123 (12.2)</td>
<td>31 (11.8)</td>
<td>23 (9.5)</td>
<td>32 (13.9)</td>
<td>37 (13.8)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

* At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
† Yates corrected chi-square test or Fisher Exact test for class variables, Jonckheere-Terpstra test for individual continuous variables, Cochran-Armitage test for individual categorical variables.
Table 6.1 Patient characteristics FRAX 10-year probability (%), (N=1,006), continued

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All study patients (n=1,006)</th>
<th>FRAX range 0%-1.4% (n=263)</th>
<th>FRAX range &gt;1.4%-1.9% (n=243)</th>
<th>FRAX range &gt;1.9%-3.0% (n=231)</th>
<th>FRAX range &gt;3.0% (n=269)</th>
<th>p-value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Mineral Density ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>611 (60.7)</td>
<td>203 (77.2)</td>
<td>204 (84.0)</td>
<td>127 (55.0)</td>
<td>77 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Osteopenia</td>
<td>366 (36.4)</td>
<td>60 (22.8)</td>
<td>36 (14.8)</td>
<td>101 (43.7)</td>
<td>169 (62.8)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>29 (2.9)</td>
<td>0 (0.0)</td>
<td>3 (1.2)</td>
<td>3 (1.3)</td>
<td>23 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Prevalent fracture</td>
<td>60 (6.0)</td>
<td>2 (0.8)</td>
<td>6 (2.5)</td>
<td>7 (3.0)</td>
<td>45 (16.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>During follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total person-years of observation</td>
<td>5,022</td>
<td>1,394</td>
<td>1,211</td>
<td>1,170</td>
<td>1,248</td>
<td></td>
</tr>
<tr>
<td>Incident fracture</td>
<td>95 (9.4)</td>
<td>19 (7.2)</td>
<td>17 (7.0)</td>
<td>16 (6.9)</td>
<td>43 (16.0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
† Yates corrected chi-square test or Fisher Exact test for class variables, Jonckheere-Terpstra test for individual continuous variables, Cochran-Armitage test for individual categorical variables.
‡ Normal bone mineral density: hip T-score ≥ -1.0; Osteopenia: hip T-score < -1.0; Osteoporosis: hip T-score < -2.5.

Table 6.2 Incidence of bone fractures by baseline FRAX 10-year probability (%), (N=1,006; 95 incident fractures)

<table>
<thead>
<tr>
<th>FRAX 10-year probability</th>
<th>0% to 1.4%</th>
<th>&gt;1.4% to 1.9%</th>
<th>&gt;1.9% to 3.0%</th>
<th>≥3.0% (max. value=26%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>263</td>
<td>243</td>
<td>212</td>
<td>288</td>
</tr>
<tr>
<td>Number of incident fractures</td>
<td>19</td>
<td>17</td>
<td>15</td>
<td>44</td>
</tr>
<tr>
<td>% Patients with incident fractures</td>
<td>7.2%</td>
<td>7.0%</td>
<td>7.1%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Person-years (py) of observation</td>
<td>1,394</td>
<td>1,211</td>
<td>1,072</td>
<td>1,346</td>
</tr>
<tr>
<td>Median (IQR) observation, years</td>
<td>5.7 (2.9-7.9)</td>
<td>4.2 (2.9-7.8)</td>
<td>4.2 (3.0-7.7)</td>
<td>4.0 (3.1-7.6)</td>
</tr>
<tr>
<td>Mean (min-max) observation, years</td>
<td>5.3 (0.1-8.5)</td>
<td>5.0 (0.0-8.5)</td>
<td>5.1 (0.2-8.5)</td>
<td>4.7 (0.0-8.5)</td>
</tr>
<tr>
<td>Incidence per 100 py</td>
<td>1.36</td>
<td>1.40</td>
<td>1.40</td>
<td>3.27</td>
</tr>
</tbody>
</table>
Table 6.3 Cox proportional hazards analyses of factors associated with incident fractures (N = 1,006; 95 incident fractures)

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Univariate HR (95% CI)</th>
<th>p-value</th>
<th>Multivariable HR (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>MODEL 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FRAX tool risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age per 10 years</td>
<td>1.41 (1.13-1.76)</td>
<td>0.002</td>
<td>1.30 (1.04-1.62)</td>
<td>0.022</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.51 (0.84-2.72)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight in kg.</td>
<td>1.00 (0.99-1.01)</td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height in cm.</td>
<td>1.00 (0.98-1.02)</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous fracture</td>
<td>2.42 (1.32-4.43)</td>
<td>0.004</td>
<td>2.02 (1.09-3.71)</td>
<td>0.025</td>
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<tr>
<td>Current/prior tobacco smoker</td>
<td>1.59 (1.04-2.43)</td>
<td>0.031</td>
<td></td>
<td></td>
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<tr>
<td>Taking glucocorticoids &gt; 90 days</td>
<td>1.40 (0.44-4.43)</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.11 (0.15-7.93)</td>
<td>0.92</td>
<td></td>
<td></td>
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<tr>
<td>Secondary osteoporosis</td>
<td>1.09 (0.68-1.74)</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14+ alcoholic drinks/week</td>
<td>0.83 (0.26-2.63)</td>
<td>0.75</td>
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<tr>
<td>BMD in g/cm²*</td>
<td>0.09 (0.02-0.37)</td>
<td>&lt; 0.001</td>
<td>0.14 (0.03-0.59)</td>
<td>0.007</td>
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<td><strong>Disease specific factors</strong></td>
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<tr>
<td>Viral load &lt; 400 copies/mL*</td>
<td>1.16 (0.77-1.75)</td>
<td>0.48</td>
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<tr>
<td>HCV co-infection</td>
<td>1.63 (0.99-2.70)</td>
<td>0.06</td>
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<tr>
<td>Nadir CD4 cell count per 100 cells/mm³*</td>
<td>1.00 (0.88-1.14)</td>
<td>1.00</td>
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<tr>
<td>CD4 cell count per 100 cells/mm³*</td>
<td>1.04 (0.97-1.11)</td>
<td>0.24</td>
<td></td>
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<tr>
<td>TDF-containing HAART, years*</td>
<td>0.94 (0.74-1.19)</td>
<td>0.59</td>
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<td><strong>MODEL 2</strong></td>
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<td><strong>FRAX 10-year probability (%)</strong></td>
<td>referent</td>
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<tr>
<td>0% to &lt; 3%</td>
<td>2.31 (1.54-3.46)</td>
<td>&lt; 0.001</td>
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Abbreviations: HR, hazard ratio; CI, confidence interval; HCV, hepatitis-C virus; BMD, bone mineral density; TDF, tenofovir difumarate.
* At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS
Figure 6.1 FRAX 10-year probability (%) distribution and occurrence of new fracture among 1,006 HIV-infected patients
Figure 6.2 SUN/DIDC-HOPS incident fracture proportion and rate by FRAX 10-year probability (5) range (N=1,006; 95 incident fractures)
CHAPTER 7
BONES, FRACTURES, ANTIRETROVIRAL THERAPY AND HIV

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7.1 Abstract

The course of HIV infection has been dramatically transformed by the success of antiretroviral therapy from a universally fatal infection to a manageable chronic disease. With these advances in HIV disease management, age-related comorbidities, including metabolic bone disease, have become more prominent in the routine care of persons living with HIV infection. Recent data has highlighted the role of the HIV virus, initiation of antiretroviral therapy, and HCV co-infection in bone mineral density (BMD) loss and fracture incidence. Additionally, the underlying mechanism for the development of metabolic bone disease in the setting of HIV has received considerable attention. This review will highlight recently published and presented data and synthesize the current state of the field. These data highlight the need for pro-active prevention for fragility fractures.

7.2 Introduction

Among individuals who successfully engage in HIV care, combination antiretroviral therapy (ART) has resulted in dramatic reductions in HIV-associated morbidity and mortality, increased life expectancy, and an increase in age-related comorbidities. Clinicians are reporting a premature aging phenotype among HIV-
infected individuals manifest by an increasing incidence of therapy-related metabolic complications, including frailty, neurocognitive dysfunction, hyperlipidemia, insulin resistance, diabetes mellitus, cardiovascular disease, osteoporosis and related fractures (Effros et al. 2008; Onen, et al. 2010). Specifically, low bone mineral density (BMD) is a frequent complication of HIV infection and/or its treatment with ART (Brown and Qaqish 2006). Several cohort studies have reported that a majority of HIV-infected persons have low BMD despite the fact that most of the HIV-infected persons included in these studies were under the age of 50, an age below which osteoporosis is a rare diagnosis in the general population (Overton et al. 2007; Guaraldi et al. 2006). Metabolic bone disease may have a dramatic impact on the health of the HIV population, as multiple studies show that HIV-infected individuals experience significantly elevated rates of bone fractures (Triant et al. 2008). This review will focus on recent data related to three areas of interest for HIV-related metabolic bone disease: the effects of specific antiretroviral strategies, possible mechanisms for BMD loss, and the risk of fracture.

### 7.3 ART and Bone Loss

The expanding list of available antiretroviral agents allows providers to develop a myriad of virologically suppressive regimens but how do these affect bone health? Given that tenofovir (TDF) has been consistently associated with BMD loss, numerous studies have looked at alternatives to this agent. One approach is switching from TDF to an alternative agent. At CROI 2012, Negredo et al. reported on a small study assessing 54 persons on a suppressive TDF-containing regimen who either continued TDF (n=28) or switched to abacavir (ABC, n=26) (Negredo et al. 2013). Those persons who switched to ABC had a 2.1% increase in BMD at the femoral neck whole there was no
change in the TDF group (p=0.04). In the lumbar spine, the ABC switch group experienced a 0.2% increase in BMD at 48 weeks while the TDF group had a 2.9% decrease in BMD (p=0.09). At CROI 2013, Bloch et al. reported on a study evaluating an open-label switch from TDF to raltegravir (RAL), an integrase inhibitor, in 37 persons with fully suppressed HIV viremia and femoral neck T score < -1.0 (Bloch et al. 2012). There were significant increases in BMD at lumbar spine, femoral neck and total hip (1.5%, 2.1%, and 2.5%, respectively; p <0.05 for all). Markers of both bone formation (osteocalcin) and resorption (N-telopeptide and bone alkaline phosphatase (BAP)) declined significantly at both week 24 and 48. These studies suggest that switch strategies may be an effective approach to mitigate TDF-associated bone loss.

Given the specific concern of bone toxicity from nucleoside/tide reverse transcriptase inhibitors (NRTIs), other studies have evaluated bone markers during treatment with novel NRTI-sparing regimens. The RADAR Study, presented at IAS 2013, presents a cautionary tale (Bedimo et al. 2013). Ritonavir-boosted darunavir (DRV/rtv) was paired with either RAL or tenofovir/emtricitabine (TDF/FTC) in 80 ART-naïve persons. After 48 weeks of treatment, the RAL arm was associated with a 1.2% increase in total body BMD while the TDF/FTC arm experienced a 0.7% loss. Bone biomarkers remained stable over 48 weeks for the RAL arm but increased significantly in the TDF/FTC arm. Unfortunately, the RAL arm was less effective at maintaining HIV virologic suppression (63% vs. 83% at 48 weeks, p =0.045) highlighting the importance in focusing first on virologic success before considering metabolic consequences.

Data from virologically successful NRTI-sparing regimen have also been presented. Hoy et al. presented 96 week data from the SECOND-LINE study at IAS
2013 comparing two second line regimens: lopinavir/rtv (LPV/rtv) combined with either RAL or 2 or 3 NRTIs (Martin et al. 2013). Those persons randomized to the NRTI arm had significantly greater bone loss at both the proximal femur (-5.2% vs. -2.9%, p<0.001) and the lumbar spine (-4.2% vs. -2.0%, p< 0.001). A multivariate analysis found that BMD loss was independently associated with lower BMI, exposure to TDF, and non-Asian ethnicity. Another NRTI-sparing study (INROADS) was presented at the 15th International Workshop on Comorbidities and Adverse Reactions (Overton et al. 2013). In this single arm study, 54 HIV-infected persons (12 ART naïve persons with baseline resistance to NNRTIs and 42 persons with previous failure to PI-based ART) were given DRV/rtv with etravirine. At 48 weeks, there was no change in median BMD at the total hip (1.0 g/cm² at both time points) and a non-significant decline in BMD at the lumbar spine (1.2 to 1.1 g/cm²). Taken together, these three studies highlight than BMD loss can be reduced by the selection of NRTI-free (specifically TDF) regimen.

Alternative NRTI strategies for ART naïve subjects have also been explored. Moyle and colleagues recently published 96-week data from an open label randomized study that evaluated bone, renal and metabolic consequences of treatment with efavirenz paired with either TDF/FTC or abacavir/lamivudine (ABC/3TC) (Moyle et al. 2013). Of 385 subjects enrolled, 249 completed the study. Total hip BMD declined in both groups with the greatest decline in the first 48 weeks and stabilization in the second 48 weeks. At 96 weeks, total hip BMD loss was significantly greater in the TDF/FTC arm compared to the ABC/3TC arm (-3.6% vs. -2.2%. p<0.001). Similarly, ABC/3TC has was associated with less bone loss at the lumbar spine (-0.8% vs. -1/9%, p=0.112). Wohl recently presented data from the ASSURE Study comparing unboosted
atazanavir (ATV) with ABC/3TC to ritonavir-boosted atazanavir (ATV/rtv) with TDF/FTC in 296 ART-naïve subjects who were HLA B*5701 negative (Wohl et al. 2013). In this study, changes in markers of bone formation and turnover were evaluated. In the ABC/3TC arm, there were reductions in markers of bone formation (osteocalcin) and bone resorption (C-telopeptide and BAP) as well as parathyroid hormone while the markers were relatively stable in the TDF/FTC arm. The differences in the changes in these markers was highly significant (p<0.001 for all). The mean 25-OH vitamin D levels declined for the ABC/3TC group (28 to 25 ng/mL) and increased for the TDF/FTC/rtv group (26 to 29 ng/mL, p< 0.05 for both). These two studies confirm previous studies highlighting that ABC/3TC is associated with less BMD decline and bone turnover than TDF/FTC (McComsey et al. 2011; Brown et al. 2011).

Perhaps more provocative on the ART front has been the arrival of tenofovir alafenamide fumarate (TAF), an investigational tenofovir prodrug. Zolopa shared the 24-week data from the phase 2 trial at CROI 2013 comparing TAF vs. TDF combined with elvitegravir, cobicistat, and emtricitabine in ART naïve persons (Zolopa et al. 2013). Bone loss was significantly reduced with TAF at both the lumbar spine and (-0.8% vs. -2.5%, p=0.002) and total hip (-0.3% vs. -2.0%, p<0.001). Subsequent 48 week data from this study confirmed the superiority of TAF over TDF at both total hip (-0.6% vs. -2.4%, p<0.001) and lumbar spine (-1.0% vs. -3.4%, p< 0.001) (Sax et al. 2013). Specifically, no decline in total hip BMD was reported in 32% of TAF arm compared to only 7% of TDF arm (p<0.001). Markers of bone formation and resorption increased to a greater degree over the 48 weeks in the TDF arm: P1NP (109% vs. 169% baseline
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value) and CTx (119% vs. 178%, p < 0.001 for both). Taken as a whole, TDF-sparing regimens, regardless of the agents chosen, significantly reduce BMD loss.

7.4 Mechanisms Behind Bone Loss

The pathogenesis of bone disease among people living with HIV is unclear, but an area of active research. Several groups have focused on different aspects of the pathogenesis. Failure to reach peak BMD is commonly cited as a cause for the low BMD in persons who are infected with HIV before age 30, the age at which peak BMD is achieved. Tanchaweng presented data on changes in BMD among 46 HIV-infected Thai adolescents (Tanchaweng et al. 2013). At a median age of 14.5 years, 23% had low BMD (defined as a z-score < -2.0) and 19% had low BMD when re-evaluated 2 years later. Only male sex was associated with low BMD. Notably no ART agents, and specifically TDF, were associated with low BMD. In another cohort study, Yin and colleagues compared BMD in 30 HIV-infected youth with 15 uninfected youth (ages 20-25) (Yin et al. 2013). The HIV-infected youth were all receiving ART; 15 were infected perinatally and 15 during adolescence. By routine DXA scanning, the HIV-infected youth had lower z-scores at all sites evaluated (spine, total hip, radius). CTX, a marker of bone resorption, was significantly higher in the HIV-infected youth. These investigators also utilized high resolution CT scanning at the distal radius and tibia and demonstrated that HIV-infected youth had reduced trabecular BMD and cortical thickness at these sites indicating not only a reduction in bone mass but also in bone strength. In another observational study presented at CROI, Jiminez reported BMD data from a cohort of 24 perinatally infected children and identified low BMD (defined as z-score < -1.0) in 38% of the cohort (Jiminez et al. 2013). Low BMD was associated with nadir CD4 count and
time with detectable HIV viremia but no relationship to TDF exposure or markers of systemic inflammation. Taken as a whole, these studies indicated that a significant proportion of HIV-infected youth are failing to achieve peak BMD although the factors driving this process remain to be fully elucidated.

The association between the severity of HIV disease and lower BMD is well established. A recent analysis by Grant and colleagues from the AIDS Clinical Trials Group demonstrates that the loss of BMD with ART initiation is greatest for those individuals with low CD4 cell counts, particularly those persons with a CD4 count < 50 cells/mm³ (Grant et al. 2013). Additional factors that were independently associated with BMD loss included older age, female sex, lower BMI, higher HIV-1 plasma viral loads, initiation of protease inhibitor, and initiation of TDF. A separate analysis by Erlandsen et al. (CROI 2013) confirmed the relationship between low nadir CD4 levels and BMD loss during ART initiation (Erlandsen et al. 2013).

Another mechanistic study presented at CROI 2013 focused on the role of B cells play in osteoclast activation and increased bone resorption. Titanji reported on a cross sectional evaluation including 45 HIV-infected and 45 seronegative persons (Titanji et al. 2013). When they evaluated the B cells from these two groups, intracellular levels of osteoprotegerin (OPG) was reduced and receptor activator of nuclear factor kappa-B ligand (RANKL) was increased with HIV infection. RANKL binds to osteoclasts to increase bone formation while OPG binds to RANKL to prevent its action on osteoclasts. The HIV-infected persons had elevated markers of bone turnover (CTX) while markers of bone formation (osteocalcin) were similar between the groups. These data suggest that aberrant B cell activity in HIV infection contributes to bone loss by
increasing osteoclast activity. Given that B cell dysfunction is a prominent component of advanced HIV disease, this may partially explain why advanced HIV disease is associated with the greater BMD loss.

As noted above in the study by Grant et al, an association between protease inhibitors and low BMD has long been recognized (Brown and Qaqish 2006; Tebas et al. 2000). A provocative presentation at CROI 2013 by Beaufere et al focused on the toxicity of HIV proteins and two boosted PIs (ATV/rtv and DRV/rtv) on osteoblast and adipocyte development (Hernandez-Vallejo et al. 2013). Both cells are derived from the mesenchymal stem cells (MSC). In the presence of HIV proteins or these boosted PIs, the MSCs lost proliferative capacity, increased reactive oxygen species production, increased expression of senescence markers and markers of cellular aging (farnesylated pre-lamin A). Strikingly, the differentiation into osteoblasts and adipocytes was greatly reduced as a consequence. Hence, the authors provide a potential mechanism by which this class of agents potentially induces bone loss: a reduction in bone formation due to inhibition of osteoblast formation and imbalance towards bone turnover. A final experiment by this group demonstrated that the disruption of osteoblast formation was corrected by administration of pravastatin suggesting that bone loss due to PIs could be abrogated by blocking the mevalonic acid pathway and hence demonstrating positive non-lipid effects of statins.

Clearly, certain antiretroviral agents that induce less bone loss than TDF but we must be mindful to select an ART regimen that will durably suppress HIV viremia. The next steps are trying to understand the causes of bone loss among our patients and the mechanisms behind this process. To further explore the reduced loss of BMD with TAF,
Liu et al studied the *in-vitro* effects of TAF on osteoblasts at concentrations that are achieved with oral therapy (Liu et al. 2013). First, the authors demonstrated that *in-vitro* drug levels achieved in osteoblasts are similar to *in-vivo* levels achieved in lymphocytes. Secondly at clinically relevant concentrations, TAF induced no cytotoxic effects on osteoblasts with normal cell viability *in-vitro*. Thus, a possible explanation for the improved BMD outcomes seen with TAF as compared to TDF related to lessened osteoblast toxicity and hence normal bone turnover.

Taken together, these studies highlight several key aspects of bone disease pathogenesis: 1) initiating ART earlier in HIV disease progression makes a positive impact on preservation of BMD, 2) we should not forget the relationship between lean body mass and BMD and to counsel patients to perform weight-bearing exercise, and 3) as noted above, the selection of initial regimen plays a big role in bone health. If we have equivalent regimen for viral efficacy, we should consider regimens with better toxicity profiles.

### 7.5 HIV and Fractures

While BMD loss, ART effects and mechanism of this process are intriguing, the key question for many has been: does this loss of BMD lead to increased fractures? This year, the National Osteoporosis Foundation (NOF) included HIV infection and ART as risk factors for osteoporosis and fragility fractures (NOF 2013). In support of this, several cohort studies have previously concluded that when matched for age and gender, people living with HIV are at greater risk of bone fractures. For example, a nearly 3-fold increase in incident fracture rates was identified among participants in the HIV Outpatient Study (HOPS) as compared to the National Hospital Ambulatory Medical
Care Survey (NHAMCS-OPD), a representative sample of the U.S. general population. This study suggested that younger HIV-infected adults, particularly those between the ages of 25-54 years of age, are at an increased risk of bone fracture (Young et al. 2011).

Interesting data was presented at CROI 2013. Warriner reported a study using US Medicare data in a cohort of 2.5 million HIV-negative and 13,000 HIV-infected persons. In the final adjusted model, risk of any fracture was approximately 50% higher in HIV-infected compared with the HIV-uninfected population. This risk was greater for older HIV-infected patients (> 65 years; relative risk, 1.52, 95% CI (1.34, 1.73)) but still present for younger HIV-infected patients (<65 years; 1.32 (1.21, 1.45)) and the authors suggest that osteoporotic fractures may occur at younger age in HIV-infected persons (Warriner et al. 2013). Gotti provided data demonstrating the need to consider occult spinal fractures. In a cohort of 175 HIV-infected and 120 uninfected age-matched patients, 30% of HIV-infected patients had morphometric vertebral fractures compared with 4% of the uninfected patients. Vertebral fracture risk factors included age, osteoporosis, BMI >25, AIDS event and TDF. The authors suggest that screening for vertebral fractures are useful and may provide rationale to begin earlier treatment in patients with osteopenia (Gotti et al. 2013).

At the 2013 Joint Session of the 15th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV and the 14th European AIDS Conference, Battalora reported on fracture risk among 1008 participants (median baseline age 42 years) from two Centers of Disease Control and Prevention (CDC)-funded cohorts in the US that had baseline DEXA testing (Battalora et al. 2013). During 5,032 person-years of
observation, 95 incident fractures occurred, including rib/sternum (n=18), hand (n=17), foot (n=15) and wrist (n=11). In multivariable analyses, baseline osteoporosis (adjusted hazard ratio [aHR] 3.04, 95% confidence interval [CI] 1.47-6.30) and increasing age (aHR 1.35 per 10 years, 95% CI 1.07-1.70) were associated with incident fracture. These data provide an important link between the presence of low BMD and risk of future fracture, even among young adults.

The role of specific ARVs and relationship to therapy initiation remains an area of controversy. A recent publication from the Veteran’s Health Administrative Data Clinical Case Registry (VHA CCR), Bedimo and colleagues characterized the risk of osteoporotic fractures (defined as wrist, vertebral or hip fracture) among a cohort of 56,600 HIV-infected veterans identified in the Veteran’s Health Administrative Data Clinical Case Registry (VHA CCR) (Bedimo et al. 2012). Cumulative exposure to the antiretrovirals TDF and LPV/rtv were both independently associated with fracture. Another recent publication evaluated fracture risk after ART initiation among 4640 HIV-infected individuals (Yin et al. 2012), identifying 135 persons who experienced 151 incident fractures occurring a median 2.3 years after ART initiation. Fracture rates were significantly higher in the first 2 years after ART initiation compared to subsequent time periods. Interestingly, type of ART, baseline CD4 count or HIV viral loads were not associated with fracture incidence. The authors suggest that BMD decline with ART initiation is linked with change in bone mass and quality leading to increased fracture risk. Further, as patient health improves over time with ART, the risk of falls and subsequent fractures may decrease with overall improved health suggesting there may be a catabolic window after ART initiation that leaves patients susceptible to fracture.
Several studies focused on the contribution of chronic hepatitis C virus (HCV) and fracture risk among HIV-infected person. In an analysis utilizing Medicaid data from 5 states comparing fracture rates among 36,950 HCV/HIV co-infected, 276,901 HCV monoinfected, 95,827 HIV monoinfected and 3,110,904 HCV/HIV-uninfected persons, Lo Re and colleagues found that fracture incidence rates were lowest among uninfected persons (1.29 events/1,000 person-years), and increased with either HIV infection (1.95 events/1,000 person-years) or HCV infection (2.69 events/1,000 person-years) (Lo Re et al. 2012). Increasing relative hazards of hip fracture were found in HCV/HIV co-infection compared with those with HCV monoinfection (HR 1.38; 95% CI 1.25-1.53), those with HIV monoinfection (HR 1.76, 95% CI 1.44-2.16, in women; HR 1.36, 95% CI 1.20-1.55, in men), and those without HCV/HIV infection (HR 2.65, 95% CI 2.21-3.17, in women; HR 2.20, 95% CI 1.97-2.47 in men). Hansen et al. similarly evaluated fracture risk among a cohort that included HIV-infected, HIV/HCV coinfected, and uninfected persons (Hansen et al. 2012). HIV-infected patients had increased risk of fracture (incidence rate ratio, IRR, 1.5; 95% CI 1.4-1.7) compared with uninfected subjects. Relative risk was lower in HIV monoinfected patients (IRR 1.3; 95% CI 1.2-1.4) than in HIV/HCV-coinfected patients (IRR 2.9; 95% CI 2.5-3.4). The increased fracture risk with HCV infection and with HIV infection appears to be additive with HIV infection.

Analysis of fracture risk factors among HIV-infected veterans followed in the VHA CCR found that HCV co-infection was associated with a 24% increased relative risk of osteoporotic fracture over HIV alone and HCV is an independent risk factor for fracture when the model is controlled for cirrhosis (Maalouf et al. 2013). Womack and colleagues assessed the risk for first fragility fracture among 40,115 HIV-infected
veterans followed in the Veterans Aging Cohort Study (VACS) and failed to confirm the association with HCV infection (Womack et al. 2013). This study included 588 fragility fractures (210 hip, 111 vertebral, and 267 upper arm fractures) and included a majority of persons with uncontrolled HIV viremia. The authors speculated that by accounting for fibrosis using the FIB-4 in the models reduced any impact of HCV infection. These disparate results raise questions related to the overall impact of chronic HCV infection on metabolic bone disease. Additional research is warranted to determine whether the role of HCV is attributable to fibrosis and the development of cirrhosis rather than a specific viral effect.

7.6 Conclusions

It is clear that HIV, particularly advanced disease, and ART initiation play a significant role in the bone health of people living with HIV infection. We must be wise in assessing baseline risk factors and our selection of initial ART selection to achieve virologic success and minimize potential metabolic toxicities such as low BMD and subsequent fractures. ART initiation not only induces a 2-6% loss in BMD but also leaves patients susceptible to fractures in this early catabolic window period. The mechanisms causing bone loss in our patient are likely complex and include viral, medication, host and environmental factors. We must take a proactive approach to prevention to minimize consequences of bone loss and the morbidity associated with fragility fractures (McComsey et al. 2010).
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Young B, Dao CN, Buchacz K, Baker R, Brooks JT; HIV Outpatient Study (HOPS) Investigators. Increased rates of bone fracture among HIV-infected persons in


CHAPTER 8
GENERAL CONCLUSIONS

8.1 General Discussion

The analyses and findings in the chapters of this thesis demonstrate the increasing interest in and growing body of literature related to bone health in HIV-infected adults of which the author, in multiple collaborations, has contributed. Early detection of bone disease and in particular, osteoporosis, and treatment is tied to economic factors that impact the workplace, the worker, as well as society as discussed in the oil and gas project development context in Chapter 2. Ongoing research is needed to observe changes in BMD in HIV-infected participants using particular ART regimens such as the SHIELD clinical trial described in Chapter 4. The novel findings in Chapter 5 that low baseline BMD and increasing age are strongly associated with elevated risk of incident fracture encourage further research studies to confirm this observation and suggest the need to perform DEXA screening in all HIV-infected adults, regardless of age. FRAX, a diagnostic tool to predict 10-year probability of fracture, is used globally as described in Chapter 6. The need exists to develop a FRAX model specific to the HIV-infected population. Much progress has been made in treating multiple non-AIDS comorbidities described in Chapters 2, 3, and 7, but pivotal questions remain as to the cause or causes of these illnesses. Is it the virus? Is it the host? Is it ART? Is it more than one of these factors or all of them? As the numbers of aging HIV-infected individuals increase, there is a growing need for primary and long-term care of these individuals calling into play once again economic factors that impact the individual, the workplace and society as a whole.
The Appendices at the end of the thesis include a discussion of HIV, immune system components and ART (Appendix A), statistical methods used in the works included in this thesis (Appendix B), SUN and HOPS patient consents (Appendix C) and permissions to use my previously published material (Appendix D).

8.2 Recommendations for Future Research

Future research using SUN/HOPS cohort data includes analyses of the impact of osteoporosis treatment on a large scale and particularly on fracture risk, the association between FRAX and mortality after fracture, and DEXA utilization/cascade of care analysis: How many subjects do we anticipate in HOPS will have abnormal bone density? What proportion of those at risk (or eligible) for DEXA have been screened? What proportion of those with osteopenia or osteoporosis are smokers, have low testosterone and other modifiable risk factors? What proportion of those with osteoporosis have had testosterone and vitamin D checked? Results from research in these areas will expand the literature providing clinicians with guidance for early prevention of or treatment of osteoporosis.
The United States (U.S.) Centers for Disease Control and Prevention (CDC) recently reported that 1,178,350 persons aged 13 and older were living with HIV infection in the U.S. at the end of year 2008 (CDC 2014). Of these persons, 20% had undiagnosed HIV infections (CDC 2014). The CDC reported in 2009, there were 48,100 new HIV infections and of these new infections, 61% occurred in gay and bisexual men (CDC 2014). Black/African American men and women had an HIV incidence rate seven times higher than Caucasians in 2009 (CDC 2014). The estimate of cumulative number of acquired immune deficiency syndrome (AIDS) diagnoses in the U.S. and dependent areas (America Samoa, Guam, the Northern Mariana Islands, Puerto Rico, and the U.S. Virgin Islands) was 1,108,611 diagnoses (CDC 2014).

Each year, 50,000 people In the United States (US) become infected with the HIV-1 virus (NIAID 2014). Based on 2012 statistics, it is estimated that 35.3 million people are living with HIV (PLWH) worldwide. Only 9.7 million have access to antiretroviral therapy (ART) and they are living in low- and middle-income countries (WHO 2014). Latest statistics report that 1.7 million people died from AIDS-related causes (NIAID 2014). Once thought of as a disease of select populations, HIV has infiltrated every age group, race, and ethnicity. Its impacts are far-reaching, globally and locally, as the cost is not only to its host but to society as a whole.

Human Immunodeficiency Virus – 1 (HIV)

Human Immunodeficiency Virus–1 (HIV) is a retrovirus, a virus that contains ribonucleic acid (RNA) as its genetic material (Kindt et al. 2007; Campbell and Reece
Infection occurs when the virus enters the host cell and is reverse-transcribed by the enzyme reverse transcriptase to a complementary DNA copy (cDNA copy) of the viral RNA genome (Kindt et al. 2007; Campbell and Reece 2005). This cDNA copy or provirus integrates with the cell genome and is replicated with the cell's DNA (Kindt et al. 2007; Campbell and Reece 2005). The provirus generates progeny virions and one of two processes may occur. The cell lyses or latency occurs until a regulatory signal (Kindt et al. 2007; Campbell and Reece 2005) prompts the provirus to begin expression (Kindt et al. 2007; Campbell and Reece 2005). (See Figures A.1 and A.2.)

HIV is a lentivirus distinguished by the lengthy period between initial infection and onset of clinical symptoms (Kindt et al. 2007; Campbell and Reece 2005). Acquired immunodeficiency syndrome (AIDS) results from HIV infection. Other animal retroviruses exist, such as the feline and bovine immunodeficiency viruses, but HIV will not replicate in these or other animal models (Kindt et al. 2007; NIAID 2014). Were HIV to replicate in animal models, advancements in the development of antiretroviral therapy and possibly a cure would be underway.

HIV can be detected by electron microscopy. Its appearance is spherical and the diameter of one HIV virion is approximately 100-150 billionths of a meter (AVERT 2014). A viral envelope or coat comprised of fatty material surrounds the virion, and spike-like protrusions are embedded in the coat (AVERT 2014). These spikes are made of glycoproteins (gp) gp120 and gp41 (AVERT 2014). A matrix layer lies beneath the viral envelope and is comprised of gp17 (AVERT 2014). The core of the virion, also referred to as the capsid, is comprised of protein (p) p17 (AVERT 2014). HIV requires three enzymes for replication – reverse transcriptase, integrase and protease which are
located in the virion core (AVERT 2014). Also within the core are two strands of
identical single strand RNA (ssRNA) (AVERT 2014). (See Figures A-1 and A-2.)

FIGURE A-2: Human Immunodeficiency Virus Life Cycle
(Source: National Institute of Allergy and Infectious Diseases. 
HIV comprises nine genes whereas the human genome comprises 20,000-25,000 genes (AVERT 2014). The genes are categorized according to function wherein three genes, *gag*, *pol* and *env* code for structural proteins for new HIV virions and the remaining six genes, *tat*, *rev*, *nef*, *vir*, *vpr* and *vpu*, code for proteins involved in infection, viral replication, or disease (AVERT 2014).

**HIV Infection and Immune System Components**

The intricacy of HIV infection is manifested in its effect on the human immune system. Multiple key system components are affected by the virus including T-cells, B-cells, cytokines, monocytes and dendritic cells. Infection involves viral attachment and entry into target cells and use of proteins that are part of the immune system (Kindt et al. 2007; Campbell and Reece 2005).

**Humoral Response**

Within a few days of HIV infection, the immunoglobulin M (IgM) class of antibodies first appear to defend against core HIV or *gag* proteins as well as viral surface envelope (*env*) glycoproteins (Dolin et al. 2003; NIAID 2014). The appearance of IgM antibodies is transient and followed by the appearance and longer duration of the IgG class of antibodies. IgG antibodies to *gag* (p24) and *env* (gp160, 120, 41) are among the first identified and are followed by antibodies against HIV viral enzymes (Dolin et al. 2003). Identification of antibodies may be within days or weeks of infection. They are detected by antibody blood tests including the HIV antibody enzyme immunoassay (EIA), the immunofluorescent assay (IFA) and Western blot (Dolin et al. 2003). A classification of “seropositive” is given to an individual in which the presence of HIV protein antibodies are detected by EIAs, typically at three months after infection.
(Dolin et al. 2003).

**T-cells**

HIV targets T-cells that have CD4 antigen on their surface by binding to the surface of CD4 cells, entering them, infecting them, and resulting in cell damage (Kindt et al. 2007). Cells that have CD4 on their surface may be infected by HIV due to the affinity binding of the *env* protein of HIV-1 to the cell surface of CD4 molecules (Kindt et al. 2007). Other cell surface molecules such as coreceptors present on T-cells and monocytes are also required for HIV infection to occur (Kindt et al. 2007).

As the CD4 cells multiply to fight the infection, they also generate more HIV copies. De Vita et al. report that at advanced stages, $10^9$ new HIV virions emerge and $2 \times 10^9$ CD4-positive (CD4+) T-cells cycle daily with a half-life of 2 days for both the virions and the CD4+ T-cells (De Vita et al. 1997). Eventually the number of healthy CD4 cells declines (NIAID 2014). A baseline measurement of CD4 cell count is taken at diagnosis of HIV, within two to eight weeks after starting or changing treatment, and every three to six months afterward (US DHHS 2014). A normal CD4 count is from 500 to 1,000 cells per cubic millimeter (cells/mm³) of blood. Antiretroviral therapy (ART) is recommended when the CD4 count is between 200 to 500 cells per cubic millimeter of blood (US DHHS 2014). A patient with a CD4 count less than 200 cells/mm³ of blood is classified as having AIDS (US DHHS 2014). The immune system is severely weakened at this stage and the patient is at high risk for opportunistic diseases including tuberculosis, pneumonia, severe wasting diarrhea, or certain malignancies (US DHHS 2014).
Chemokines, Cytokines and Chemokine Coreceptors

Certain cytokines, chemokines and chemokine receptors, CXC and CC, also play a role in HIV infection. Chemokine receptor, CXCR4 serves as a coreceptor for HIV on T-cells, identified as the “T-tropic” strain of HIV. An analogous receptor, CCR5, serves as a coreceptor for HIV on macrophages, identified as the “M-tropic” strain of HIV (Kindt et al. 2007). In vitro studies have shown that some chemokines have an inhibitory effect on viral replication while some proinflammatory cytokines promote viral replication (Kindt et al. 2007). Both of these mechanisms occur with HIV. The chemokine ligands that normally bind to chemokine receptors CXCR4 and CCR5 compete with HIV to bind and they succeed. However, additionally, proinflammatory cytokines induce increased expression of the coreceptors so that HIV has a better chance of binding to the surplus coreceptors (Kindt et al. 2007). Thus, viral entry takes places with the assistance of the CXCR4 and CCR5 chemokines coreceptors.

Further, correlations exist between the type of coreceptor and the ability to induce syncytia. Syncytia formation occurs when the HIV viral envelope protein gp120 on the surface of infected cells with CD4 binds to the coreceptors on the surface of other cells that may or may not be infected (Kindt et al. 2007). Once bound, cell adhesion molecules (CAMs) assist in forming a syncytia, a spherical mass with a burstable membrane (Kindt et al. 2007). Chemokine coreceptor CXCR4, present on T-cells, is linked with syncytia-inducing (SI) ability (Kindt et al. 2007) and chemokine coreceptor CCR5, present on monocytes, is linked with non-syncytium-inducing (NSI) strains of HIV (Kindt et al. 2007). Selection of coreceptors and the occurrence of syncytia formation is linked to the V3 loop region of the HIV viral envelope protein
Cytotoxic T-lymphocytes (CTLs)

With a few months of HIV infection and during the later chronic stage, responses in the peripheral blood by CD8+ cytotoxic T-lymphocytes are detected (Mandell et al. 2005). However, HIV circumvents restrictions on viral replication through viral mediated, quantitative and qualitative defects in these CD8+ T-cell responses (Mandell et al. 2005). Some weaknesses in host CD8+ T-cell responses include the down-regulation by nef, tat and vpu of MHC class 1 molecule surface expression thereby lessening the likelihood of recognition of infected cells. Additionally, during the course of infection, there may be insufficient numbers available of HIV-specific CTLs (Mandell et al. 2005). Further, the HIV-specific T-cells may not mature or may lack avidity (Mandell et al. 2005).

Reservoirs of Infection

Dendritic cells carry HIV to the lymphoid organs and provide a costimulatory signal to T-cells upon contact with them (WHO 2014). Once T-cell activation commences, the virus replicates and the host immune response, involving both antibody and cytotoxic CD8+ T-lymphocytes, attempts to counterbalance the viral replication (WHO 2014). Viremia, or an initial burst of high levels of virus in circulation is identified, followed by a steady state period of viral level in circulation (WHO 2014). During this steady state period, clinical symptoms of the disease are not apparent. However, viral replication continues during this period and the viral load, the number of copies of the viral genome in plasma, can be quantified using Polymerase Chain Reaction (PCR)-based assays (WHO 2014).
HIV may be harbored in various regions of the body as a result of infected macrophages (Reese and Betts 1996). Reservoirs for infected macrophages include the bone marrow cells, myocardial cells, gastrointestinal lining cells and the brain – the latter possibly resulting in AIDS induced dementia (Reese and Betts 1996). Resting CD4⁺ cells and lymphoid tissue are also common reservoirs for HIV (Mandell et al. 2005).

**HIV and Cell Death**

Damage to CD4⁺ T-cells and other cells results in programmed cell death or apoptosis (NIAID 2014). Cells that are not infected by HIV but have HIV bound to their surfaces and consequently antibodies, may be attacked by natural killer cells (NK cells) through the mechanism of antibody-dependent cell-mediated cytotoxicity (ADCC) (NIAID 2014). HIV also causes death of immune precursor cells and their locations of origin, the bone marrow and thymus (NIAID 2014).

**Clinical Aspects of HIV**

There are three stages of HIV infection: acute primary infection, clinical latency, and progression from HIV to AIDS (NIAID 2014; WHO 2014). In the acute primary phase, the HIV viral load increases and spreads within the body to lymphoid (thymus, spleen, lymph nodes) organs and other locations. The humoral response begins within two to four weeks of viral exposure followed by a decrease in viral load. In some individuals, the CD4⁺ T-cell count may revert to its original count (NIAID 2014).

The second phase in the progression of HIV is the clinical latency period which can last as long as ten years. Within zero to eight weeks, “seroconversion” takes place and an individual infected with HIV may be identified as seropositive for HIV. Although
symptoms may not occur, the virus continues to replicate in the lymphoid organs (NIAID 2014; AVERT 2014; Kindt et al. 2007).

Finally, HIV progresses to the disease stage, or AIDS when the CD4+ T-cells count is less than 200 cells/mm³ and the infected individual has one or more opportunistic infections. Some common opportunistic infections include Candida albicans, tuberculosis, pnueomnia, severe wasting diarrhea, and various malignancies such as Karposi’s sarcoma may also present (AVERT 2014; Kindt et al. 2007).

**Antiretroviral Therapy (ART)**

Treatment of HIV infection has followed a path of rapid development – from no treatment in the early 1980s resulting in death, to onerous treatments involving cumbersome doses of pills with severe side effects in the 1990s, to “user friendly” treatments taken in one-a-day pills without less side effects in the 2000s. Presently, combinations of antiretroviral therapy or cART and highly active antiretroviral therapy (HAART) are being used. However, resistance to viral mutations poses obstacles in ongoing drug therapy development. Below is a summary of the commonly prescribed ART and their drug interaction targets (Dolin et al. 2003).

**Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**

One of the first drugs designed to combat HIV/AIDS was azidothymidine (zidovudine) commonly known as AZT. AZT is a nucleoside reverse transcriptase inhibitor or NRTI. The objective of AZT is to terminate the growing cDNA chain of the retrovirus. Integration of AZT into the DNA of the host also causes unintended cell death. Precursors of red blood cells are sensitive to AZT and long term use may result in anemia. More recent NRTIs include Didanosine, Azlcitabine, Stavudine, Lamivudine,
Abacavir and Emtricitabine (Farnan et al. 2012; Kindt et al. 2007).

**Nucleotide Analog Reverse Transcriptase Inhibitors**

The previous described family of NRTIs, require the conversion of nucleoside analogs to nucleotide analogs which occurs in the body. The *nucleotide* analog reverse transcriptase inhibitor form of ART supersedes this step by introducing a nucleotide analog to the body. Presently the Food and Drug Administration (FDA) approved only one drug of this kind, Tenofovir, which is also used to treat Hepatitis B in addition to HIV (Farnan et al. 2012).

**Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

A third generation of reverse transcriptase inhibitors, the objective of NNRTs is the same as other NRTIs which is to terminate the growing cDNA chain of the retrovirus. However, it does so without involving nucleosides (Farnan et al. 2012). Therefore this family of drugs is named *nonnucleoside* reverse transcriptase inhibitors.

**Protease Inhibitors (PIs)**

PIs inhibit the activity of protease, an enzyme necessary to assemble new viral particles at the late stage of the HIV life cycle (13). PIs have proven effective in combination with AZT and other nucleoside analogs (Kindt et al. 2007).

The HAART strategy is to combine one PI with two nucleoside analogs in attempt to thwart viral mutation issues. Benefits of HAART include lowered plasma viral loads to not detectable by current methods and re-establishing normal load function in infected individuals (Kindt et al. 2007). HAART has been successful in increasing the longevity of individuals infected with HIV and is characterized as changing the effect of
the disease from “fatal” to “chronic.” Disadvantages of HAART include maintaining a regimented schedule of administration of a large number of pills (Kindt et al. 2007).

**Immune Modulators**

The strategy of using immune modulators in ART is to build up the immune system and restore it to normal function. Recombinant Interleukin-2 (Il-2) is used in conjunction with HAART. Disadvantages include the injectable administration, low tolerance by patients, and toxicity (Kindt et al. 2007).

**Fusion Inhibitors**

Fusion inhibitors are used in ART at the earliest stage of infection when the virus attaches to the host cell. Enfuvirtide (Fuzeon, T-20) is an envelope fusion viral peptide used in ART (Kindt et al. 2007).

**Integrase Strand Transfer Inhibitors**

Integrase inhibitors are used to terminate the HIV life cycle by inhibiting the essential HIV replication enzyme, integrase. This form of ART was developed as an alternative to PIs and NNRTIs where drug resistance thwarted their effect (Kindt et al. 2007; Farnan et al. 2012).

**Virus Entry Inhibitors**

Virus entry inhibitors were designed to prevent HIV from entering host cells. Presently, Maraviroc and T-20 are used in ART. Recent developments in virus entry inhibitors include a new viral entry inhibitor, VIRIP. VIRIP is a 20-peptide fragment of Alpha\textsubscript{1}-antitrypsin which is a natural, abundant circulating serine protease inhibitor. VIRIP is marketed as an “anchoring inhibitor” because it prevents the gp41 fusion
peptide of HIV from inserting itself into the host cell membrane thereby blocking fusion of the virion envelope with the host cell membrane (Forssmann et al. 2010). Naturally occurring in the body, Alpha₁-antitrypsin was found to inhibit not only HIV infection but also production of the virus within the cells (Shapiro et al. 2001).

**HIV and Aging**

The benefits of cART, HAART and other newly derived ART therapies have resulted in people living longer with HIV and able to participate in the work force. This presents occupational health issues and as well as issues of corporate social responsibility that are being addressed by some industries worldwide.

The prevention and management of infectious diseases, and in particular, HIV infection, has been an area of increasing focus of the oil and gas industry. HIV infection is highly prevalent in many of the regions where oil and gas production occurs, for example, Kazakhstan, Nigeria, and China. With the introduction of antiretroviral therapy, people living with HIV are living longer and able to participate in the exploration and production work force. Recent epidemiological studies indicate that age-related illnesses are more common in HIV-positive (HIV⁺) individuals than in age-matched HIV-negative (HIV⁻) individuals. Together with the typical age-related illnesses of older people, challenging workplace issues are foreseeable (Battalora et al. 2012).

Among long-term survivors of HIV infection, increased risk of bone, heart, cognitive diseases and certain malignancies have been described. Correlations exist between bone health in HIV-infected persons and increased risk of fragility fractures. Additionally, cardiovascular disease and neurocognitive deficits are recognized as occurring prematurely in HIV⁺ individuals. Further, it is suggested that long-term
antiretroviral therapy may result in medication toxicity. Such degenerative illnesses have wide impact on health and the working environment during exploration and production operations including reduced productivity, reduction in labor pool experience, and increased safety risks in transporting, lifting, and equipment operation. Outcomes like these result in additional project and health costs that are ultimately paid by the operator, contractor, stakeholder and the community (Battalora et al. 2012).

A need exists to translate the relevance of recent epidemiological findings based on cohort studies to the oil and gas industry. The direct impact of these findings on health and the working environment, personal safety, health safety and environment (HSE) management are not entirely prospective and many of them are currently manifested today. From this education, a socially responsible discussion including objectives for timely preparation for workplace issues resulting from HIV and aging, both premature and chronological aging may develop. This discussion must involve not only the operator, but also the contractor, stakeholder and the community (Battalora et al. 2012).

**References Cited**


CERNER Corporation (Cerner) and its employees are contracted by the U.S. Centers for Disease Control and Prevention (CDC) to store and analyze data collected by the CDC as part of the HIV Outpatient Study (HOPS) and the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study). Cerner’s Worldwide Headquarters are located at 2800 Rockcreek Parkway North, Kansas City, MO 64117 (phone: +1-816-221-1024). Carl Armon, PhD, Biostatistician, was contracted by Cerner to perform the statistical analyses for the HOPS and SUN Study. His Curriculum Vitae is located at the end of this appendix.

Descriptive data summaries, box plots, and univariate and multivariable Cox proportional hazards analyses were performed using statistical analysis system (SAS) version 9.3 (SAS Institute, Cary, NC). Yates corrected chi-square tests were performed using StatCalc (EpiInfo 2002 revision 2; Centers for Disease Control and Prevention, Atlanta, GA).

Statistical methods used in this thesis are briefly described below based on the references cited within the description. Simplified, non-reviewed summaries may be found using internet search engines including Wikipedia.

1. Yates corrected chi-square ($\chi^2$) test: Definition from Porta M. A Dictionary of Epidemiology. Fifth ed. New York, New York: Oxford University Press; 2008: “. . . test based on comparison of a test statistic to a chi-square distribution; used to detect whether two or more population distributions differ from one another; usually involve counts of data and may involve comparison of samples from the distribution under study or the comparison of a sample to a theoretically expected distribution.” (Porta 2008).
2. Cochran-Armitage trend test:
test used “. . . when one variable has two levels and the other variable is ordinal. The
two-level variable represents the response, and the other represents an explanatory
variable with ordered levels. The null hypothesis is the hypothesis of no trend, which
means that the binomial proportion is the same for all levels of the explanatory variable.”
(Cochran Armitage Trend Test, SAS 2014).

3. Cox proportional hazards model:
Definition from Porta M. A Dictionary of Epidemiology. Fifth ed. New York, New York:
Oxford University Press; 2008:
“. . . a statistical model in survival analysis that asserts that the effect of the study
factors on the hazard rate in the study population is multiplicative and does not change
over time.” (Porta 2008).
Definition from Vittinghoff E, Glidden, D.V., Shigoski, S.C., McCulloch, C.E. Regression
Methods in Biostatistics. Second ed. New York: Springer; 2012:
“. . . tool for assessing the relationship of multiple predictors to a right-censored, time-to-
event outcome.” (Vittinghoff et al. 2012).

4. Kruskal-Wallis test:
Definition from Zar JH. Biostatistical Analysis. Fourth ed. Upper Saddle River, NJ:
Prentice Hall, Inc.; 1999:
“. . . a non-parametric method for testing differences among groups. Significant results
indicate that at least one of the samples is different from the other samples. The test is
also used when the examined groups are of unequal size (different number of
participants). It is similar to the Wilkoxon rank sum test.” (Zar 1999).
Additional information from Rumsey C. Statistics for Dummies II. Hoboken, NJ: Wiley
Publishing, Inc.; 2009:
“The test does not identify where the differences occur or how many differences actually
occur.” (Rumsey 2009).

5. Jonckheere-Terpstra test:
“... a non parametric test for ordered differences among classes. It tests the null
hypothesis that the distribution of the response variable does not differ among classes.
It is preferred to tests of more general class difference alternatives, such as the Kruskal-
Wallis test.” (Jonckheere-Terpstra Test, SAS 2014).
6. Wilkoxon rank sum test:  
“... a non-parametric statistical hypothesis test used when comparing two related samples, matched samples, or repeated measurements on a single sample to assess whether their population mean ranks differ (i.e. it is a paired difference test).” (Rumsey 2009).

“. . . used to determine which population is different in the same way.” (Vittinghoff et al. 2012).

References Cited


Curriculum Vitae of Carl Armon PhD (Biostatistician)

BIOGRAPHICAL SKETCH

NAME
Carl Armon

POSITION TITLE
Biostatistician

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR CONFERRED</th>
<th>FIELD OF STUDY</th>
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<td>University of Pennsylvania, Philadelphia, PA</td>
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<tr>
<td>University of Colorado, Boulder, CO</td>
<td>B.S.</td>
<td>1981</td>
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<td>University of Colorado Health Sciences Center, Denver, CO</td>
<td>M.S.</td>
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<tr>
<td>University of Colorado Health Sciences Center, Aurora, CO</td>
<td>Ph.D.</td>
<td>2009</td>
<td>Clinical</td>
</tr>
<tr>
<td>Science</td>
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RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

A. Positions and Honors.

PROFESSIONAL EXPERIENCE:

2001-present: Biostatistician, under subcontract with Cerner Corporation, Vienna, VA and Centers for Disease Control, Atlanta, GA, to provide statistical analysis of the HIV Outpatient Study (HOPS) database.

2002-present: Research Associate, Department of Epidemiology, Children’s Hospital Colorado, Aurora, CO

Honors

Outstanding Ph.D. Student, Clinical Science Clinical Investigation Track, University of Colorado Health Sciences Center, 2006.

Nomination for Centers for Disease Control and Prevention 2010 Charles C. Shepard Science Award for manuscript "The association of HIV susceptibility testing with survival among HIV-infected patients receiving antiretroviral therapy: A cohort study".

B. Publications.


**Selected Abstracts:**


Posters:


HIV+ persons with cancer: HOPS during the HAART era. 18th Conference on Retroviruses and Opportunistic Infections, Boston, February 27- March 2, 2011.


Presentations:


APPENDIX C

HOPS AND SUN STUDY CONSENTS

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

The following information is being presented to help you decide whether or not you want to participate in a research study. Please read it carefully. If there is anything you do not understand, ask the doctor.

Study Title: “The HIV Outpatient Study (HOPS)”

Study Site:

Principal Investigator:

Address:

Phone:

Study Sponsor: Centers for Disease Control and Prevention (CDC) and Cerner Corporation

PURPOSE: You are being invited to participate in this research study because you are a patient at our clinic and you are HIV-positive. Our clinic works collaboratively with the Centers for Disease Control and Prevention (CDC) and Cerner Corporation. Cerner collects information on patients with HIV infection from medical clinics in the United States for a research study to better understand HIV disease and treatments. Data gathered by Cerner are shared with the CDC. The data may also be used for other purposes permitted by law, including comparative data analysis and the development, marketing and distribution of products and services.

We are asking you to allow us to use information gathered as a result of your treatment at this clinic. Your information will be included in the Cerner's database with data from over 9,000 HIV-positive patients seen at several clinics around the country. This database has already been existence for many years; ________________________ has participated since _____.

PROCEDURE: Data for this project will be gathered from your medical record; this will not require any effort from you. The database includes demographic information, diagnoses, laboratory results, symptoms, treatments, and hospitalizations. Information in the database is handled with the same strict confidentiality as your medical record.

In addition we may occasionally ask you to participate in surveys or questionnaires on various topics. These may include personal questions about sex, drug use, medication
adherence, or other topics. These surveys or questionnaires may be done on paper, by computer, or by an automated telephone system. You may refuse to participate in these special studies and still be in the main study.

This study will not require extra office visits or extra lab tests. It will cost you nothing to be in this study.

**RISKS:** There are no known health risks to you from participating in this study. There is a risk of loss of confidentiality, meaning that information collected about you could become known to others outside of the study. To minimize the risk of this happening your data in the database is identified only by a code number.

The additional surveys or questionnaires that you may be asked to participate in may include questions about sexual practices, illegal drug use, or similar topics. Although these surveys are confidential, questions about these topics may cause some discomfort or anxiety.

**BENEFITS:** There is no direct benefit to you from participation in this study. The information gathered in this study, however, may result in a better understanding of HIV disease and treatments, which may ultimately benefit persons with HIV infection.

**CONFIDENTIALITY:** Your personal identifying information (including your name, date of birth, and possibly your medical record number) will be entered and kept in a confidential and secure database, separately from your medical information. Your personal identifying information cannot be seen by anyone outside of this clinic. Cerner and CDC study staff will see your medical information in the database only with your secure HOPS study participant number, not your name.

Your medical records and the consent form you sign may be inspected by authorized research investigators or the CDC to make sure the study follows federal and state regulations. From time to time, Cerner or CDC staff may review your medical records and survey data to check that your information in the database is correct. Because of this need, we cannot guarantee absolute confidentiality. However, CDC and Cerner staff are held to the same rules of confidentiality as office and study staff.

If the results of this research are published in a medical journal or presented at a conference they will not include your name or any other information that may identify you.

**PAYMENT FOR STUDY PARTICIPATION:** You will not be paid to participate in this study.

**VOLUNTEERING TO BE PART OF THIS RESEARCH STUDY:** Your participation in this study is voluntary. You may refuse to participate or you may quit at any time. If you decide to stop taking part in this study, tell the study doctor and your data will stop being
added to the study database. Any of your information already in the database at the time you quit the study may be still used for research.

If you stop participating in this study, this will not affect your medical care, benefits to which you are otherwise entitled, or ability to take part in future research studies.

**TERMINATION:** We do not know when this study will end. It will go on until it is stopped for some reason, or until funds are gone. The investigator or the sponsor may terminate your participation in this study without your consent.

**QUESTIONS AND CONTACTS:**

If you have any questions or problems related to this research you may call __________________, Investigator, at ______________________.

If you have questions about your rights as a person who is taking part in a research study, you may contact a member of the CDC’s Human Research Protection at 1-800-584-8814.

**CONSENT STATEMENT**

By signing this form, I confirm that

- I have fully read (or someone has read and explained to me) this informed consent form describing a research study.
- I was given the opportunity ask questions and my questions have been answered to my satisfaction.
- I understand the risks and benefits, and I freely give my consent to participate in the research project outlined in this form.
- I understand that I am not giving up any of my legal rights.
- I have been offered a copy of this informed consent form, which is mine to keep.

*___________________________  ______________________________  
Signature of Participant                   Printed Name of Participant                      Date

___________________________     ______________________________
Signature of Witness                          Printed Name of Witness                                 Date

(if appropriate)
INVESTIGATOR STATEMENT:

The subject signing this consent form has had the study fully and carefully explained to him or her. I hereby certify that, to the best of my knowledge, the subject signing this consent form understands the nature, demands, risks and benefits involved in participating in this study.

_________________________________________     ______________________________
Signature of Investigator                              Printed Name of Investigator                         Date

_________________________________________     ______________________________          _______
Signature of Person Obtaining Consent       Printed Name                                                Date
If Other than Investigator

The research project/study and informed consent form were reviewed and approved by the CDC Human Research Protection Institutional Review Board. The board may be contacted at 1-800-584-8814.
DENVER INFECTIOUS DISEASE CONSULTANTS, P.L.L.C.
KENNETH S. GREENBERG, D.O., PHARM. D.
BENJAMIN YOUNG, M.D., Ph.D.
JOHN HAMMER, M.D.

4545 East Ninth Avenue, Suite 120
Denver, Colorado 80220
303-393-8050

STUDY TO UNDERSTAND
THE NATURAL HISTORY OF HIV AND AIDS
IN THE ERA OF EFFECTIVE THERAPY
(The ‘SUN’ Study)

APPENDIX 1

INFORMED CONSENT FORM
TO PARTICIPATE IN SUN STUDY

Version 3.1
Flesch-Kinkaid Score: 8.2

Page 1 of 13
STUDY TO UNDERSTAND THE NATURAL HISTORY OF HIV AND AIDS
IN THE ERA OF EFFECTIVE THERAPY
(The SUN Study)

PATIENT INFORMATION AND CONSENT FORM

Physician Investigator/Study Doctor: 

Study Site: 4545 E. 9th Avenue
Suite 120
Denver, CO 80220

PURPOSE

Why are we doing this study?

The Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN Study) is a research study. We want to learn more about the effects that treatment for HIV infection is having on some people. We want to learn more about the diseases people with HIV infection develop now that they are living longer. We also want to learn how to help people with HIV from giving HIV to someone else. We are asking you to volunteer for this research study. If you are in this study you will help us find out more about these problems and how to prevent and treat them.

Who is doing this study?

The study is being done by:
1. The U.S. Centers for Disease Control and Prevention (CDC)
2. Cerner Corporation (a data management company1)
3. Health care clinics throughout the United States, including the study site where you are being asked to enroll.

CDC is in charge of overseeing the study. Cerner Corporation is in charge of managing the data collected during the study. Each study site is responsible for examining and collecting data from study participants.

1 Cerner Corporation will collect, organize, and store the data for the SUN Study.

Page 2 of 13

Initials ________________________
Date ________________________
How long will the study last?

This study will last for at least 5 years. We will continue collecting data at each scheduled study visit (every 6 months). The date when the study will end is not known but may be years from now. We will notify you when the study concludes and we will no longer collect data about you.

PROCEDURES

What am I being asked to do?

You will be asked to come to the clinic for a physical exam, an interview and lab tests about every 6 months. You will receive advice about ways to help you maintain safer sexual practices. We also are asking for consent to review your medical records.

Physical exam:

At each physical exam we will examine your body, measure the size of your body, and take your blood pressure. We will insert two to four small swabs a few inches into your rectum to collect cells to test for viruses and sexually transmitted diseases (STDs). We will also swab your throat to test for STDs. If you are a woman, a pelvic exam will be done at least once a year and a Pap smear to test for cancer and for viruses.

Interview:

At each visit you will be asked to fill out an interview. The interview will ask some questions about your medical history, sexual activity, drug and alcohol use, and mental and emotional health. The interview may change a little each time you take it. We want you to feel at ease answering the interview questions honestly. You will be given the interview on a computer. You will wear headphones so that only you can hear the questions. You will be asked to answer the questions alone and in private. Your answers will be stored in the computer in a way that no one taking care of you will be able to find out what you said. Your answers will help us know how HIV is affecting your health and your well-being. You do not have to answer any questions you do not want to. Someone will be nearby in case you have questions about the interview or are upset by any of the questions.

Urine samples:

At each visit we will test your urine to learn how your kidneys are functioning. We will also test your urine to learn if you have sexually transmitted infections such as gonorrhea or chlamydia.
Vaginal swabs:

If you are a woman, we will ask you to swab your vagina so that we can look for certain infections. This swab will be small and soft.

Rectal swabs:

We will insert two to four small swabs a few inches into your rectum to collect cells to test for viruses and sexually transmitted diseases (STDs). We will also look at these cells for changes caused by the virus called human papillomavirus (HPV).

Throat swab:

We will swab your throat to look for certain STDs.

Blood draws:

At each visit, we may draw up to 10 tablespoons of blood from your arm (this is equal to about 150 cc’s). Most of the time we will draw about 4 tablespoons of blood (about 6 tubes). We will use this blood to learn about how your body is working and to see if you have had some other infections, such as viral hepatitis (Hepatitis A, B and C) and syphilis. A list of the tests that we plan to do will be given to you today. Some tests will only be done once, while other tests may be done at every visit.

Samples of your blood and urine will be stored at a special lab at CDC². This lab will keep your samples safe and secure for testing during the study. No one will be able to tell that these blood and urine samples came from you. The samples stored at this lab will not have any data written on them that could identify you. They will not have records stored with them that could identify you. These samples will only be used for research related to this study. Your specimens will only be kept until the study ends. After the study ends they will be destroyed unless you let us keep them for future research that is not part of this study (see Consent for Specimen Banking and Future Research below).

Other specimens:

Other samples that are collected from you during the study (such as the urine and the anal/vaginal swabs) may also be stored at the same special lab for future testing. We are asking your consent to let us do testing on these samples in the future. Like your blood and urine, no one will be able to tell that these samples came from you. The samples stored at this lab will not have any data written on them that could identify you. They will not have records stored with them that could identify you. Your specimens will only be kept until the study ends. After the

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² 1 standard blood draw tube collects approximately 10 cubic centimeters (cc’s) of blood; 1 tablespoon is about 15 cc’s (1 ounce = 30 cc’s = 2 tablespoons = 6 teaspoons).

² CDC Specimen Management Facility
study ends they will be destroyed unless you let us keep them for future research that is not part of this study (see Consent for Specimen Banking and Future Research).

Additional specimen testing:

During the course of SUN Study the study investigators may do additional tests. These tests may be on your blood, urine or other specimens. These tests may include tests that are not in the protocol because they were not known at the time your blood, urine, and other specimens were collected. These tests may include genetic testing that may have no direct impact on your health. The genetic testing we plan to do is called "HLA typing". HLA typing is used most often to match organs and tissues for human transplants, such as kidneys and hearts. In some cases, people with certain HLA types are more likely to get some diseases. We want to learn if people with HIV are more likely to develop some problems because of their HLA type. All future testing not specified in this protocol will only be done to better understand how to diagnose and treat HIV infection, to better understand how treatment of HIV affects people, and to better understand any other health problems that may affect persons with HIV infection. If we do more genetic tests during the study period, your doctor will tell you about them at your next routine visit.

X-rays:

For this study we will take some x-rays. These x-rays will help us learn about the health of your heart and bones and to study the fat in your body. We may or may not perform on you all of the x-ray tests that are listed in the protocol. At most, we would do these tests once a year. If you did all the x-ray tests in the protocol, then in one year the amount of x-rays will be about the same as the amount of natural background radiation you would be exposed to outdoors over 8-9 months.

Ultrasound:

For this study we will examine the artery in your neck with ultrasound. This test will help us learn about the health of this blood vessel. At most, we would do this test once a year. Ultrasound is a form of sound waves that will not harm you. We will also take your blood pressure during this test.

We will also examine your heart with ultrasound. This test will help us learn about the size and function of your heart. At most, we would do this test once a year. To examine the arteries in your neck a small probe is moved back and forth on your skin. The same thing is done to look at your heart. The test does not hurt.

Electrocardiogram (EKG):

For this study we may perform an electrocardiogram. This test is also called an EKG and will help us learn about the health of your heart. We may or may not do this test. At most, we
would do this test once a year. An EKG is an electrical recording of your heart and will not harm you.

**Neurocognitive testing:**

At least once a year you will be asked to take a 30-minute computerized test. This test measures your memory and other cognitive abilities.

**Medical records:**

While you are in the study, we need to know about the health care you get. We need to make sure that we find out when you have a problem caused by HIV or related to having HIV. We also need to know when you have a problem related to a bad effect caused by treatment for HIV. We are asking for your consent to let us look at all of your medical records while you are in the study. This includes records of care you receive at places other than this clinic. We will collect information about your health that relates to HIV infection. This information is very important. It helps researchers learn about all the ways that HIV affects people's health. If you are taking medicine to treat HIV now, or were taking such medicines before joining the study, we are asking you to let us look at all of your old medical records since the time when you started taking these medicines.

We are also asking you to let us study any samples that are collected from you as part of your medical care while you are in the study. This includes samples taken from you at places other than this clinic. If you have taken or are now taking medicine for HIV, we are also asking your consent to test samples that were collected since you started this treatment.

Please tell your study doctor if you are worried about sharing your medical records or test samples. There may be ways to limit access to some records or samples. If the research staff cannot satisfy your concerns, it would be best not to enroll in the study.

**What happens to the data you gather from me?**

Cerner Corporation will collect the data gathered from you at the clinic where you are enrolled. Your data will be put into one database with data from patients at all the other clinics around the country. This database will cover many years of care. This database will not have any personal data that could allow another person to identify that it came from you. Cerner Corporation will manage this database. Cerner Corporation will share the data with the CDC and the study sites. We are asking you to allow us to use the data gathered from you during the study, including the data in your medical records that we review.

**Compensation:**

You will be given money for the time you agree to take part in this study. A $50.00 American Express Gift Cheque will be given at the first scheduled study visit and annually thereafter. The study will pay only for the exams and tests that are not part of the standard care.
given to persons infected with HIV. The study will not pay for any care you need that results from the findings of any of these tests. The study will also not pay for any care you need for problems that are caused by one of these tests (see Risks, below).

CONFIDENTIALITY

How will you protect my privacy?

We will do everything we can to protect your privacy to the extent allowable by law.

All data gathered from you during the study will be handled confidentially. We will use the same level of strict confidence that is used to manage your medical record. Just like your doctor would do, we will report any medical conditions we diagnose that the law where you live requires us to report. To find out what must be reported where you live, call your local health department.

You will be given a unique study number. Only the researchers at the site where you are enrolled will know who you are and which study number belongs to you. The records linking your study number to you will be kept in locked files in a locked room. Only people involved with the study at the site where you are enrolled will have access to these data. All data gathered from you that are given to Cerner Corporation will not contain any data about you that would let someone find out who you are. It will not be possible for researchers at CDC and at the other study sites to find out who you are. It will not be possible for the doctors who will read your x-rays or ultrasound tests will to find out who you are. No names, no social security numbers, no medical record numbers, no addresses, and no zip codes will be put into the database.

Someone from Cerner Corporation will visit the study site where you are enrolled from time to time. This person will make sure that the data added into the database are correct. This person may need to check your study chart or medical files and could therefore find out who you are. This person will not take any personal data from your chart or file that could identify you out of the clinic. They will not share data about who you are with anyone else from Cerner Corporation, the CDC, or any of the other study sites.

All stored specimens will be kept confidential. Access to specimens we collect from you will be limited to the study’s investigators and lab personnel. No other person (including your relatives or doctors that may treat you but who are not investigators in this study) will have access to the stored samples without your written consent. These persons will not have access to information about them without your written consent. Your specimens will be stored in a building that is secure. Records about your specimens that are kept in computers will be stored securely. Your specimens will not be stored together with information that could let someone know that they came from you. Your specimens will be labeled with a unique code; your name will not be written on any specimens.

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* Because public health reporting requirements vary at each study site, we cannot be more specific in the consent form.
Only the SUN study researchers and the staff they designate to work on SUN Study may read records which have your name on them. In addition, HCA-HealthONE IRB and the FDA have the right to inspect your records. Reports based on this study or on future studies will not identify you by name. None of the data gathered about you will be given to employers. None of the research data gathered about you will be given to insurance companies or other third parties not directly involved in the study. Stored samples will not be sold to third parties for research.

We have gotten a Certificate of Confidentiality (CoC) from the U.S. government for this study. The CoC protects you and any information about you that we learn during this study. We do not have to tell anyone that you are in the study. We do not have to tell anyone anything about you. We do not have to tell anyone who you are or that you are in the study even if a court orders us to or sends us a subpoena. The CoC is valid in any federal, state, or any other local court.

There are three times when the CoC does not apply. In these three cases we will have to give information about you to proper authorities:

1. We suspect or know you are abusing a child.
2. We suspect or know you intend to hurt yourself or hurt other people.
3. You have an infection that we must report to the state health department. We will give you a list of these infections if you ask for it. You may also call the health department at 303-692-2700 for this list.

A CoC does not stop you from telling other people that you are in this study. It does not stop you from telling other people what we learn about you during this study. You are free to tell anyone you wish anything about what you are doing in this study and what we learn about you. If you want the study doctor to tell someone else that you are in this study, then you must give written permission. The study doctor must do what you wish. The same is true if you want the study doctor to tell what we learn about you during the study to an insurer, employer, or anyone else. The study doctor cannot hold back this information because of the CoC. As long as you give written permission, the study doctor must respect your wishes to give out information about you. This means that you must actively protect your privacy. You must also make sure that if you tell anyone you are in this study, that they will protect your privacy. The same is true if you ask the study doctor to give someone else information we learn about you during the study.

The U.S. government is paying for this study. Some federal agencies monitor projects that the government pays for. For instance, they make sure that federal money is not wasted or stolen. Other agencies, such as the Food and Drug Administration (FDA), make sure people in studies that the government pays for are not harmed. If these agencies ask for information about this study, then we must give it to them. This might include information that you are in the study or information that we learn about you during the study. If we give information about you to another federal agency for any reason, that agency must protect your privacy.

**RISKS**
How could this study harm me?

Drawing blood from your vein may cause local pain, swelling, bleeding, bruising, light-headedness, or rarely, an infection at the site of the needle stick.

Placing swabs in your throat, anus, or vagina may cause mild discomfort or local pain.

Repeated x-rays can damage cells. The risks from the x-rays you will receive in this study are very small. If you are a woman, we will check your urine to see if you are pregnant before any x-ray. If you are pregnant, you will not be x-rayed.

Ultrasound is not harmful to your health.

None of the tests done in this study will include any cutting or surgery.

There is a very small chance that some of the tests for sexually transmitted diseases may come back positive, even though you have no infection. These results would still be reported to public health authorities if required by the law where you are enrolled.

Some of the tests done on your blood or other samples in the future may include looking at your genes (your DNA and RNA). Some tests may also look at the genes of the HIV (the HIV’s DNA and RNA) that is in your blood or other samples. We will only do this kind of testing to learn about problems that affect people infected with HIV. For instance, studies to learn how your immune system responds to the virus and studies to learn why some people get bad effects from the treatment of HIV and other do not.

What will happen if you find a health problem during the study?

If one of the tests done as part of the study show that you have a health problem, the researchers will make sure you are informed of the problem. They will also refer you to a health care provider for proper follow-up and treatment. You may need to have extra tests done. The study will not pay for the cost of any extra tests or treatments that are needed as a result of a health problem found as part of the study.

What will happen if I am physically harmed as a result of taking part in this study?

If you are physically harmed from an exam or test done as part of this study, there are no plans to compensate you or pay for medical costs resulting from this injury that are not covered by your insurance plan. If you are injured the researchers will refer you to a health care provider for proper follow-up and treatment. Neither CDC, Cerner Corporation, HCA-HealthONE IRB, nor any of the researchers at any of the sites or researchers reading your x-rays or ultrasound tests will take responsibility for such an injury. Taking part in the study does not prevent you from seeking such payment if you think you have been hurt.
BENEFITS

How could this study help me?

By taking part in this study, you will help us learn more about HIV and how HIV and the treatments for HIV affect people. This knowledge may help other people infected with HIV.

You may find out about a health problem you did not know you had.

You will get some tests that are not done usually for persons infected with HIV. If you request, we will share the results directly with you. If you request, we will give the results from these tests to your health care provider and put them in your regular medical records.

If you agree to be in this study, the cost of your health care will not change.

How could I get the same benefits without being in the study?

Some of the tests done as a part of the SUN Study are not a part of routine care for people with HIV infection². We will give you a list of the tests for this study. This list will show you which tests are not considered routine. You could still get your routine health care through your provider and could discuss your interest in any special non-routine tests with her or him.

PATIENTS RIGHTS

What are my rights?

As a research study patient, you have the right to ask questions. You should not agree to be in this study until all your questions have been answered. You have the right to withdraw from this study at any time. If you choose to withdraw from this study, your care will not change.

The testing of your blood and other samples from your body that takes place during the study may help to make new lab tests. This testing may lead to the discovery of new medicines, or other products or services that could make a profit. You will not receive any profit or any other financial gains from such research.

When the study is over, all the specimens from you that remain in storage will be destroyed. You may choose to allow us to keep your stored specimens for future research that is not part of this study (see Specimen Banking below).

If you have questions about your rights as a member in this research study, please call the office of CDC’s Deputy Associate Director for Science at 1-800-584-8814. Please leave a short

² Non-routine care is defined as either an experimental procedure or a procedure not recommended or discussed in the most current versions of accepted HIV care guideline documents.
message with your name and phone number. Say that you are calling about CDC protocol # 3979. Someone will return your call as soon as possible.

You may also call Dr. John Hammer at 303-393-8050 if you have any questions or problems about this research study, if you feel that you have been harmed in this study, or if you want to withdraw from this study. In addition, you may contact Robert Rifkin, M.D., HCA-HealthONE IRB Chairman, @ 303-584-2300 for information on your rights as a research patient.

Could I be removed from the study against my wishes?

Your study doctor can stop you from being in the study at any time if:

1. You miss two or more study visits and we cannot reach you by phone or mail.
2. You are unable to complete any testing in the study.

If you become pregnant during the study, then you will be stopped from being in the study until you are not pregnant. If you are put in prison or jail during the study, then you will be stopped from being in the study until you are out of jail or prison. When you are no longer pregnant or out of jail or prison, you can then schedule a study visit to start back in the study.
CONSENT

I, __________________________,
have read this consent form. I have been given the chance to review the study protocol for the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (The SUN Study). I consent to take part as a member in this study in keeping with the terms laid out in this consent form.

I authorize the study researchers (which include CDC and Cerner Corporation) to review and collect data from my medical records while I am enrolled in this study. If I have been treated in the past with, or am now taking, medicines called antiretrovirals I authorize the study researchers and Cerner Corporation to review my medical records from the time that I started taking these medicines to the present.

I authorize using the data gathered from me to learn more about how to diagnose and treat HIV infection. I authorize using these data to better understand how treatment of HIV affects people. I also authorize using these data to better understand any other health problems that may affect persons living with HIV infection.

Specimens taken from me may be tested for other purposes not specified in the SUN Study protocol. Such testing will only be used during this study to better understand how to diagnose and treat HIV infection, to better understand how treatment of HIV affects people, and to better understand any other health problems that may affect persons living with HIV infection. If this testing leads to a product or service that is profitable, I will not receive any profits or other financial gains from this research.

I have been given the chance to ask questions. I am content with the answers that I got. I know that I will be given a copy of this consent form. I know that I may withdraw from this study at any time. I know that withdrawing will not affect my care. I have been given the name and number of a contact person for questions, concerns, or to call if I wish to withdraw.

By signing this form I have not waived any of the legal rights that I otherwise would have as a patient or a member in a research study.

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I authorize that the results of any exams and testing done during the study that are not part of routine medical care may be released to my health care provider and be put in my regular medical records. These tests include the special x-ray and ultrasound exams, and the neurocognitive tests. This authorization does not include my responses on the computerized interview I take every six months; these responses will not be shared with my health care provider.

___ Yes, release these test results to my health care provider and put them in my regular medical chart

___ No, do not release these test results to my health care provider or put them in my regular medical chart

In the future the study researchers may need to get in touch with me about issues related to the study. If I am unable to make informed decisions for myself as a result of disability, mental incapacity, or death I assign the following person to act as my proxy to make decisions for me. This person may only respond for me about future issues related to this study; he or she may not change any of my prior requests or consents.

Name of proxy: __________________________________________

Address of proxy: __________________________________________

City State Zip code

Phone number of proxy: __________________________________________

___ I do not designate a proxy for future contact related to this study.

Patient’s Name ____________________________ Patient’s Signature ____________________________ Date __________

Physician/Investigator’s Name ____________________________ Physician/Investigator’s Signature ____________________________ Date __________

Witness Name ____________________________ Witness Signature ____________________________ Date __________
DENVER INFECTIOUS DISEASE CONSULTANTS, P.L.L.C.
KENNETH S. GREENBERG, D.O., PHARM. D.
BENJAMIN YOUNG, M.D., Ph.D.
JOHN HAMMER, M.D.

4545 East Ninth Avenue, Suite 120
Denver, Colorado 80220
303-393-8050

Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN Study)

Authorization for Use or Disclosure of Protected Health Information

Pursuant to 45 CFR §164.508 and the Health Insurance Portability and Accountability Act, I, hereby authorize HCA-HealthONE and/or the Principal Investigator and Co-Investigators named below and their administrative and clinical staff to use or disclose the protected health information ("PHI") described below to the persons or entities and for the purposes set forth below:

1. The Principal Investigator and Co-Investigators who are authorized to rely upon this authorization are:
   Kenneth S. Greenberg, D.O., Pharm.D., Benjamin Young, M.D., Ph.D., John Hammer, M.D.

2. The PHI which I authorize to be used or disclosed are described as follows:
   • All medical information, which pertains to or identifies me and is created or maintained by HCA-HealthONE IRB or the Principal Investigator and Co-Investigators in connection with the research study identified below in Section 4.

3. The entity or entities, person(s) to receive the PHI identified above are:
   • HCA-HealthONE IRB
   • The Principal Investigator and Co-Investigators identified above.
   • The Research Sponsor identified herein: U.S. Centers for Disease Control and Prevention (CDC).
   • Other (describe): Staff and subcontractors of Cerner Corporation, Staff and subcontractors of Denver Infectious Disease Consultants, P.L.L.C.

4. The PHI may be used or disclosed for the following purposes:
   • Medical research conducted by the Principal Investigator and Co-Investigators or HCA-HealthONE IRB pursuant to the research study identified herein, including follow up studies, creation of a research database or research depository.

5. This authorization shall be and remain in force and effect as follows:
   • This authorization shall expire upon your election to withdraw from the research study.

6. I understand that I have the right to revoke this authorization, in writing, at any time by sending such written revocation to the Principal Investigator or Co-Investigators who are listed in item "1" above. In addition, I may also copy the revocation to HCA-HealthONE IRB's Privacy Officer. I understand that a revocation will not be effective to the extent that HealthONE Alliance has already used or disclosed the PHI described above in reliance on this authorization. I also understand that a revocation will not be effective if this authorization was obtained as a condition of obtaining insurance coverage and the insurer has a legal right to contest a claim under the policy or the policy itself.

Version: March 2004
7. I understand that information used or disclosed pursuant to this authorization may be disclosed by the recipient and may no longer be protected by federal law.

8. I understand that my receipt of medical research-related treatment is conditioned on my authorization of the use or disclosure of PHI for medical research as requested above. If I refuse to give, or revoke or withdraw my authorization, I understand that I will cease to participate in this research study and I will be unable to receive medical research-related treatment from the providers participating in this research study.

9. By my signature below, I acknowledge that I have received a copy of this authorization to use or disclose PHI.

Date: ________________________

______________________________
Signature of Patient or Personal Representative

______________________________
Authority of Personal Representative to sign
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Subject: RE: from Linda Battalora - permission to include BMD/Fractures and FRAX abstract/poster material in PhD dissertation

Date: Monday, April 7, 2014 at 6:14:49 AM Mountain Daylight Time

From: Buchacz, Kate (CDC/OID/NCHHSTP)

To: Linda Battalora

Dear Linda –

You have my and the CDC’s permission to include the materials you specified below in your Ph.D. dissertation.

Thank you for taking the lead on these research projects and the excellent collaboration.

Kate Buchacz, PhD
Epidemiologist
Division of HIV AIDS Prevention, CDC
1600 Clifton Road NE, MS E-45
Atlanta, GA 30333
Phone: 404-639-5167
acu7@cdc.gov

From: Linda Battalora [mailto:lbattalo@mines.edu]
Sent: Sunday, April 06, 2014 4:23 PM
To: Buchacz, Kate (CDC/OID/NCHHSTP)

Subject: from Linda Battalora - permission to include BMD/Fractures and FRAX abstract/poster material in PhD dissertation

Importance: High

Hello Kate -

I hope you are well!
I am writing to request your permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in my PhD dissertation.
If you would kindly respond in the affirmative to this request as soon as possible, I would greatly appreciate it.
My thesis and permissions are due to the CSM Graduate Office on Monday, April 7. Your email affirmation will be included in the section designated Permissions.

Thank you!

Linda

Linda A. Battalora, B.S., M.S., J.D.
Teaching Associate Professor
Colorado School of Mines
Petroleum Engineering Department
1500 Illinois Street, MZ 319
Golden, Colorado 80401
United States of America
Subject: RE: from Linda Battalora - permission to include BMD/Fractures and FRAX abstract/poster material in PhD dissertation

Date: Monday, April 7, 2014 at 7:06:17 AM Mountain Daylight Time

From: Brooks, John T. (CDC/OID/NCHHSTP)

To: Linda Battalora

Linda,

You have my permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in your PhD dissertation. Congratulations!

-john

John T. Brooks, M.D.
Leader, HIV Epidemiology Research Team
Division of HIV/AIDS Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
Office of Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Road NE, Mailstop E-45
Atlanta, GA 30329-4018
phone: 404-639-3894
fax: 404-639-6127
email: zud4@cdc.gov

From: Linda Battalora [mailto:lbattalo@mines.edu]
Sent: Sunday, April 06, 2014 4:18 PM
To: Brooks, John T. (CDC/OID/NCHHSTP)
Subject: from Linda Battalora - permission to include BMD/Fractures and FRAX abstract/poster material in PhD dissertation
Importance: High

Hello John -

I hope you are well!
I am writing to request your permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in my PhD dissertation.
If you would kindly respond in the affirmative to this request as soon as possible, I would greatly appreciate it.
My thesis and permissions are due to the CSM Graduate Office on Monday, April 7. Your email affirmation will be included in the section designated Permissions.

Thank you!
Linda

Linda A. Battalora, B.S., M.S., J.D.
Teaching Associate Professor
Colorado School of Mines
Petroleum Engineering Department
1500 Illinois Street, MZ 319
Golden, Colorado 80401
United States of America
Subject: RE: from Linda Battalora - permission to include BMD/Fractures and FRAX abstract/poster material in PhD dissertation

Date: Monday, April 7, 2014 at 7:36:37 AM Mountain Daylight Time

From: Patel, Pragna (CDC/CGH/DGHP)

To: Linda Battalora

Yes, of course. I give you permission to use the BMD/fractures and FRAX data for your thesis.

Pragna

From: Linda Battalora [mailto:lbattalo@mines.edu]
Sent: Sunday, April 06, 2014 4:20 PM
To: Patel, Pragna (CDC/CGH/DGHP)

Subject: from Linda Battalora - permission to include BMD/Fractures and FRAX abstract/poster material in PhD dissertation

Importance: High

Hello Pragna -

I hope you are well!  
I am writing to request your permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in my PhD dissertation.  
If you would kindly respond in the affirmative to this request as soon as possible, I would greatly appreciate it.  
My thesis and permissions are due to the CSM Graduate Office on Monday, April 7. Your email affirmation will be included in the section designated Permissions.

Thank you!

Linda

Linda A. Battalora, B.S., M.S., J.D.  
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Colorado School of Mines  
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Geo-Environmental-Microbiology (G.E.M.) Laboratory  
APEX Family Medicine/Research
Subject: RE: from Linda Battalora - permission to include BMD/Fractures and FRAX abstract/poster material in PhD dissertation
Date: Monday, April 7, 2014 at 7:16:05 AM Mountain Daylight Time
From: Bush, Tim (CDC/OID/NCHHSTP)
To: Linda Battalora

Linda,
This sounds fine to me. Good luck with your thesis.
Tim

From: Linda Battalora [mailto:lbattalor@mines.edu]
Sent: Sunday, April 06, 2014 4:21 PM
To: Bush, Tim (CDC/OID/NCHHSTP)
Subject: from Linda Battalora - permission to include BMD/Fractures and FRAX abstract/poster material in PhD dissertation
Importance: High

Hello Tim -

I hope you are well!
I am writing to request your permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in my PhD dissertation. If you would kindly respond in the affirmative to this request as soon as possible, I would greatly appreciate it. My thesis and permissions are due to the CSM Graduate Office on Monday, April 7. Your email affirmation will be included in the section designated Permissions.

Thank you!
Linda

Linda A. Battalora, B.S., M.S., J.D.
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Geo-Environmental-Microbiology (G.E.M.) Laboratory
APEX Family Medicine/Research
Subject: Re: from Linda Battalora - permission to use BMD/fractures and FRAX abstract/poster material in PhD dissertation

Date: Sunday, April 6, 2014 at 3:19:05 PM Mountain Daylight Time

From: Joan S Chmiel
To: Linda Battalora

Linda,
This is ok with me.
Joan

Sent from my iPhone

On Apr 6, 2014, at 8:42 AM, "Linda Battalora" <lbattalo@mines.edu> wrote:

Dear Joan -

I hope you are well!
I am writing to request your permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in my PhD dissertation.
If you would kindly respond in the affirmative to this request as soon as possible, I would greatly appreciate it.
My thesis and permissions are due to the CSM Graduate Office on Monday, April 7.
Thank you!
Linda

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APEX Family Medicine/Research
Subject: RE: from Linda Battalora - permission to use BMD/Fractures and FRAX abstract/poster material in PhD dissertation

Date: Sunday, April 6, 2014 at 2:13:34 PM Mountain Daylight Time

From: Wood, Kathy
To: Linda Battalora
Priority: High

Linda
You have my permission to include this material in your PhD dissertation/thesis.
Kathy Wood

Sent from my Android phone using TouchDown (www.nitrodesk.com)

-----Original Message-----
From: Linda Battalora [lbattalo@mines.edu]
Received: Sunday, 06 Apr 2014, 9:45am
To: Wood, Kathy [KWOOD@CERNER.COM]
Subject: from Linda Battalora - permission to use BMD/Fractures and FRAX abstract/poster material in PhD dissertation

Dear Kathy -

I hope you are well!
I am writing to request your permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in my PhD dissertation.
If you would kindly respond in the affirmative to this request as soon as possible, I would greatly appreciate it.
My thesis and permissions are due to the CSM Graduate Office on Monday, April 7.

Thank you!
Linda

Linda A. Battalora, B.S., M.S., J.D.
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Subject: Re: from Linda Battalora - permission to use BMD/fractures and FRAX abstract/poster material in PhD dissertation

Date: Sunday, April 6, 2014 at 11:22:14 AM Mountain Daylight Time

From: Carl Armon
To: Linda Battalora

Hello Linda,

I eagerly give my permission for you to include the BMD/fractures and FRAX abstract/poster material, of which I am a co-author, in your PhD dissertation.

Regards,
Carl Armon, PhD

On 4/6/2014 7:43 AM, Linda Battalora wrote:

Dear Carl -
I hope you are well!
I am writing to request your permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in my PhD dissertation.
If you would kindly respond in the affirmative to this request as soon as possible, I would greatly appreciate it.
My thesis and permissions are due to the CSM Graduate Office on Monday, April 7.

Thank you!
Linda

Linda A. Battalora, B.S., M.S., J.D.
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APEX Family Medicine/Research
On Apr 6, 2014, at 7:40 AM, Linda Battalora <lbattalo@mines.edu> wrote:

Dear John -
I hope you are well!
I am writing to request your permission, as one of multiple co-authors on the BMD/fractures and FRAX abstract/poster material, to include this material in my PhD dissertation.
If you would kindly respond in the affirmative to this request as soon as possible, I would greatly appreciate it.
My thesis and permissions are due to the CSM Graduate Office on Monday, April 7.
Thank you!
Linda

Linda A. Battalora, B.S., M.S., J.D.
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Subject: RE: Permission to include CIDR paper and BMD/Fractures and FRAX material in dissertation - Linda Battalora

Date: Monday, April 7, 2014 at 9:33:57 AM Mountain Daylight Time

From: Edgar Turner Overton

To: Linda Battalora

Dear Linda,

Congratulations on the successful defense of your dissertation!

Please consider this email as affirmation of my permission to use both of the following items in your dissertation:

Paper (Bones, Fractures, Antiretroviral Therapy, and HIV) in Clinical Infectious Disease Reports
BMD/fractures and FRAX presented at recent conferences.

Good luck finalizing everything.
Talk soon,

Turner

Turner Overton, M.D.
Division of Infectious Diseases
University of Alabama at Birmingham
together@uab.edu
ph: (205) 934-5191
fax: (205) 975-6027

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---

From: Linda Battalora [mailto:lbattalo@mines.edu]
Sent: Saturday, April 05, 2014 8:32 PM
To: Edgar Turner Overton
Subject: Permission to include CIDR paper and BMD/Fractures and FRAX material in dissertation - Linda Battalora
Importance: High

Hello Turner -

I hope you are well. I successfully defended my dissertation last week, and diligently working on thesis editing. The manuscript is due to the Graduate Office on Monday, April 7.

As we discussed a while ago, I am including our paper, Bone, Fractures, Antiretroviral Therapy and HIV, published in Clinical Infectious Disease Reports in the dissertation as a chapter.

Would you respond to this email as soon as possible stating that I have your permission to do so? I will include it in the Permissions section of the dissertation.

I requested and already received permission to include the paper from the Publisher.

Also, if you would state in your email reply that I have your permission to include the BMD/fractures and FRAX co-authored material in my dissertation too, that would be helpful.
I am emailing each of the other co-authors on that material as well.

Thank you! Linda

Linda A. Battalora, B.S., M.S., J.D.
Teaching Associate Professor
Colorado School of Mines
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SPEI Denver Section Board
Unconventional Natural Gas and Oil Institute (UNGI)
Geo-Environmental-Microbiology (G.E.M.) Laboratory
APEX Family Medicine/Research
Subject: RE: Request for Permission to Include Chapter 46 HIV and Bone Health from Fundamentals of HIV Medicine in PhD Thesis
Date: Tuesday, March 25, 2014 at 8:25:35 AM Mountain Daylight Time
From: Amber McCracken
To: Linda Battalora
CC: Bruce Packett
Category: DISSERTATION

Linda – you have our permission to include Chapter 46 in your thesis. The citation looks fine and we appreciate you including that for proper attribution. If you need any additional information from me, please let me know.

Thank you,

~Amber McCracken

From: Linda Battalora [mailto:lbattalo@mines.edu]
Sent: Monday, March 24, 2014 5:54 PM
To: Amber McCracken
Subject: Request for Permission to Include Chapter 46 HIV and Bone Health from Fundamentals of HIV Medicine in PhD Thesis
Importance: High

Dear Amber:

I am writing to request permission to include Chapter 46. HIV and Bone Health of Fundamentals of HIV Medicine, 2012 ed. in my doctoral thesis at Colorado School of Mines, Golden, Colorado 80401. I am the primary researcher and author. Benjamin Young is a co-author and corresponding author.

Below is the citation for Chapter 46:


I will be submitting my thesis very soon. Therefore, time is of the essence for your reply.

Thank you for your assistance,

Linda

Linda A. Battalora, B.S., M.S., J.D.
Teaching Associate Professor
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United States of America
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Fax: (303) 273-3189

Faculty Advisor, CSM SPEI Student Chapter
SPEI HSSE-SR Advisory Board
SPEI International HSE Conference, Health Subcommittee
Dear Linda,

Thank you for your prompt reply. That is perfect.

Please keep in touch.

Best regards,
Joy Deng
WJA Editorial Board
www.scirp.org/journal/wja

From: Linda Battalora <lbattalo@mines.edu>
Sent: Wednesday, March 26, 2014 11:36
To: wja
Subject: Confirmation of WJA Permission to include Journal Article in PhD Thesis

Dear Joy – Thank you very much!
Below is how the reference will appear, beneath the Chapter number:

CHAPTER 3

CHANGES IN BONE MINERAL DENSITY THROUGH 96 WEEKS IN ANTIRETROVIRAL-NAÏVE HIV-1 INFECTED PATIENTS RECEIVING ABACAVIR/LAMIVUDINE AND Raltegravir IN THE SHIELD TRIAL


Linda Battalora, Amy Thomas, Brian Wine, Belinda Ha, Benjamin Young

Best regards,
Linda

Linda A. Battalora, B.S., M.S., J.D.
Teaching Associate Professor
Colorado School of Mines
Petroleum Engineering Department
1500 Illinois Street, MZ 319
Golden, Colorado 80401
United States of America
E-mail: LBattalo@mines.edu
Phone: (303) 273-3603
Fax: (303) 273-3189
From: wja <wja@scirp.org>
Date: Tuesday, March 25, 2014 at 9:31 PM
To: Linda Battalora <lbattalo@mines.edu>
Subject: RE: Confirmation of WJA Permission to include Journal Article in PhD Thesis

Dear Linda,

Thank you for your reply again. Yes, you can add it to your doctoral thesis but you have to make it as a reference where it comes from.

Please keep in touch.

Best regards,
Joy Deng
WJA Editorial Board
www.scirp.org/journal/wja

From: Linda Battalora <lbattalo@mines.edu>
Sent: Tuesday, March 25, 2014 21:25
To: wja
Subject: Confirmation of WJA Permission to include Journal Article in PhD Thesis

Dear Joy,

Thank you for your email. To confirm, I will include my WJA article as a chapter in my doctoral thesis.
Kindly confirm once again that I have permission to do this.
Your email confirmation will be included in my Dissertation in the section titled “Permissions.” Thank you! Linda
Title of my Article:


Changes in Bone Mineral Density through 96 Weeks in Antiretroviral-Naïve HIV-1 Infected
Patients Receiving Abacavir/Lamivudine and Raltegravir in the SHIELD Trial
Linda Battalora, Amy Thomas, Brian Wine, Belinda Ha, Benjamin Young

Linda A. Battalora, B.S., M.S., J.D.
Teaching Associate Professor
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United States of America
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SPEI Denver Section Board
Unconventional Natural Gas and Oil Institute (UNGI)
Geo-Environmental-Microbiology (G.E.M.) Laboratory
APEX Family Medicine/Research

From: wja <wja@scirp.org>
Date: Tuesday, March 25, 2014 at 2:38 AM
To: Linda Battalora <lbattalo@mines.edu>
Subject: RE: Request Permission to include Journal Article in PhD dissertation

Dear Author,

Thank you for your email. You can use this article as a reference.

Please keep in touch.

Best regards,
Joy Deng
WJA Editorial Board
www.scirp.org/journal/wja

From: service <service@oalib.com>
Sent: Tuesday, March 25, 2014 8:37
To: wja
Subject: Fwd: Request Permission to include Journal Article in PhD dissertation
Subject: RE: Permission to include SHIELD paper in dissertation - Linda Battalora
Date: Monday, April 7, 2014 at 7:27:26 PM Mountain Daylight Time
From: Belinda Ha
To: Linda Battalora

Dear Linda,

This is not a problem. If you include the citation or reference, it should be fine.

Thanks for asking.

Belinda

From: Linda Battalora [mailto:lbattalo@mines.edu]
Sent: Saturday, April 05, 2014 9:12 PM
To: Belinda Ha; Brian Wine; Amy Thomas
Subject: Permission to include SHIELD paper in dissertation - Linda Battalora
Importance: High

Dear Belinda, Dear Amy, Dear Brian -

I am requesting your permission to include the paper, Changes in Bone Mineral Density Through 96 Weeks in Antiretroviral-Naive HIV-1 Infected Patients Receiving Abacavir/Lamivudine and Raltegravir in the SHIELD Trial, in my PhD dissertation. I already have permission from the publisher, World Journal of Aids, to include it.

Since Ben is my Committee Co-advisor, he has implicitly given permission and is not included on this email.

Please reply to this email as soon as possible and state that you give me your permission to include the paper.

My dissertation is due on Monday, April 7 to the graduate office. Your prompt reply is appreciated.

Thank you! Linda

Linda A. Battalora, B.S., M.S., J.D.
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Faculty Advisor, CSM SPEI Student Chapter
SPEI HSSE-SR Advisory Board
SPEI International HSE Conference, Health Subcommittee
SPEI ATCE, HSE Subcommittee
SPEI Denver Section Board
Unconventional Natural Gas and Oil Institute (UNGI)
Geo-Environmental-Microbiology (G.E.M.) Laboratory
APEX Family Medicine/Research
Subject: Re: Permission to include SHIELD paper in dissertation - Linda Battalora
Date: Saturday, April 5, 2014 at 8:43:16 PM Mountain Daylight Time
From: Amy Thomas
To: Linda Battalora

Yes of course!

Amy

On Apr 5, 2014, at 7:11 PM, "Linda Battalora" <lbattalo@mines.edu> wrote:

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