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Aging with HIV in the United States: Trends and Impact of Hospital Stays on Inpatient Resource Utilization, and Costs of Care, 2003-2015

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DEDICATION

To my elder brother, Nure Alam Siddique (Jewel), for his sacrifice to educate younger siblings and constant inspiration to seek the true meaning of education.

To my ex-sister-in-law, Tania Sabnam, for teaching me the aesthetic values of education and the necessity of modesty in life.

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ABSTRACT

Background:

Due to advances in Antiretroviral Therapy (ART), people living with HIV (PLWH) live longer in the United States. Aging prolongs exposure to HIV and antiretroviral drugs, which could lead to an elevated risk of developing multiple age-related comorbidities [HIV Associated Non-AIDS (HANA) conditions], earlier for PLWH. Higher comorbidity burdens among older PLWH may require greater use of inpatient care, i.e., higher hospitalization, inpatient resource utilization, and costs. This study examined the trends and characteristics of comorbidities, resource utilization, and costs of hospital stays with HIV (HSWH) compared to hospital stays without HIV (HSWOH). We also assessed trends for resource utilization and costs for hospital stays with major HANA conditions.

Methods:

Thirteen years of pooled data of Health Care Utilization Project (HCUP) National Inpatient Sample (NIS) data, 2003 through 2015, were analyzed to describe the trends. Among a total of 98,754,786 inpatient discharges, 69,633,686 inpatient discharges were analyzed. We excluded hospital stays for patients less than 18 years old, neonatal, pregnancy, and same-day discharge from our analysis. The primary outcomes of this study were the number of procedures, length of stay, and inpatient costs. Total hospital charges were converted to costs using hospital-wide cost-to-charge ratios provided by HCUP from accounting reports of the Center for Medicare and Medicaid Services. The key independent variables were age, and hospital stays with HIV. Using SAS 9.4, univariate, bivariate, and

multivariable survey-weighted analyses were conducted using sampling weights to measure national estimates. Multivariable regression analyses using a generalized linear model (GLM) framework were conducted to determine predictors of inpatient resource utilization and costs, controlling for the patient- and hospital-level characteristics. The study results were interpreted using significance level at $P<0.01$, 99% confidence intervals (CI), and clinical relevance of the associations.

Results:

Over the study period, the proportions of HSWH remained stable (0.81%), but the proportions of HSWH among the older increased gradually. The mean age difference between HSWH and HSWOH reduced substantially. Hospitalization rates decreased from 105 to 89 per 100,000 U.S. population over the years, while the rates for the older population aged 55-64 and 65+ years increased substantially. Overall, HSWH had fewer HANA conditions than hospital stays without HIV (HSWOH). The proportions of cardiovascular disease (CVD) and cancer increased disproportionately over time among HSWH; CVD and liver disease increased among aged 65+ years, and CVD and cancer increased among aged 50-64 years.

The median number of procedures for HSWH was consistently lower than that for HSWOH, but it increased disproportionately among older HSWH over time. While the overall length of stay and costs for HSWH was consistently higher than that for HSWOH, the differences narrowed down over the study period. The differences in inpatient resource use and costs between HSWH and HSWOH also decreased for hospital stays with major HANA conditions. Multivariable analyses showed that the procedure use was lower for HSWH. Inpatient LOS and costs were significantly higher among HSWH and older.

Conclusions:

Consistent with the aging, higher HSWH and HANA comorbidities were observed among older PLWH during hospital stays, which suggest future increased hospital resource utilization and costs for HSWH. Our study finding confirms our hypothesis of increased length of stays and costs during HSWH and utilization of procedures among older HSWH. As PLWH age, a close investigation of surgical procedures and comorbidities requiring longer inpatient stays and higher costs is needed to prepare U.S. inpatient departments for future HSWH.

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LIST OF ABBREVIATIONS

ACA …… Affordable Care Act

ADAP …… Aids Drug Assistance Program

AHRQ …… Healthcare Research And Quality

AIDS ……..…… Acquired Immune Deficiency Syndrome

ART …… Antiretroviral Therapy

cART ……..…… Combination Antiretroviral Therapy

CBO ……..… Community-Based Organization

CCS …….. Clinical Classification Software

CD4 ……..… Cluster of Differentiation 4

CDC …… Center For Disease Control And Prevention

CHC …….. Community Health Center

CPI-M ……..… Consumer Price Index- Medical Care

CVD …… Cardiovascular Disease

DUA ……..… Data User Agreement

EBV ……..… Epstein-Barr Virus

EIS …… Early Intervention Services

EMA ……..… Eligible Metropolitan Area

FDA …… Food and Drug Administration

FQHC …… Federally Qualified Health Center

HAART …… Highly Active Antiretroviral Treatment

HANA ……..…… HIV Associated non-AIDS

HAND ……..… HIV-Associated Neurocognitive Disorder

HBV . ……..… Hepatitis B Virus

HCUP ……..…… Healthcare Cost And Utilization Project

HCV …… Hepatitis C Virus

HHS ……..… Department of Health And Human Services

HIV ……..… Human Immunodeficiency Virus

HPV ……..… Human Papilloma Virus

HRQoL …… Health-related Quality of Life

HRSA …… Health Resource & Services Administration

HSWH ……..…… Hospital Stay With HIV

HSWOH ……..… Hospital Stay Without HIV

ICD-9-CM ……..…..……. International Classification of Diseases, 9th Edition, Clinical Modifications

INSTI ……..…… Integrase Inhibitor

KSHV/HHV-8 ……..… Kaposi's-Sarcoma Associated Herpes Virus

LOS ……..… Length Of Stay

MCO ……...…… Managed Care Organization

MSM ……..… Men Sex with Men

NIS …… National Inpatient Sample

NOMCAR …… Not Missing Completely At Random

PEP ……..…… Post-Exposure Prophylaxis

PHC ……...…… Personal Health Care

PI ……...… Protease Inhibitors

PLWH ……...… People Living with HIV

PPI ……..… Producer Price Index

PrEP ……...… Pre-Exposure Prophylaxis

PWID ……...… People Who Inject Drugs

STR …… Single-Tablet Regimen

TGA ……...… Transitional Grant Area

U.S. …… United States

UNAIDS …….…… Joint United Nations Program on HIV/AIDS

VA …….…… Veteran Affairs

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

In 39 years since Human Immunodeficiency Virus (HIV) infection first appeared as an infectious disease, it has become a manageable chronic condition due to the advancement of highly active antiretroviral treatment (HAART). In the United States, more than 1 million people are currently living with HIV. One in seven of the people living with HIV (PLWH) are unaware of their infection, and every year about 40 thousand people become newly infected with HIV (HIV.gov, 2018). From 2012 to 2016, while the annual number of new HIV diagnoses remained stable in the United States, the number of newly diagnosed PLWH increased among subpopulations like young gay and bisexual men (Center for Disease Control and Prevention, 2016a). New HIV diagnoses among people aged 50 years or older decreased significantly from 25% of total new diagnoses in 2006 (Jacobson, 2011) to 17% in 2016 (Center for Disease Control and Prevention, 2018). Currently, almost half of all PLWH are aged 50 years or older (Center for Disease Control and Prevention, 2018), and this proportion will rise to more than 70% by 2030 (Wing, 2017). The widespread availability of effective antiretroviral therapy (ART) to suppress HIV viral load helps PLWH live longer. Hence, HIV-related deaths are decreasing worldwide. Also, the number of older PLWH are increasing in the United States as the population age. This shift in aging brings new prevention and care challenges for the

healthcare system, due to HIV's transformation from a fatal illness to a manageable but complex chronic medical condition.

There is a debate about whether HIV accelerates the aging process or acts as an additional risk factor, which increases the likelihood of developing chronic conditions among PLWH (Pathai, Bajillan, Landay, & High, 2013; Solomon, O'Brien, Wilkins, & Gervais, 2014). Whatever the case, the development of geriatric conditions, such as comorbidities, frailty, poorer cognitive functioning, depression, and other mental illness, may be hastened with advanced aging (Center for Disease Control and Prevention, 2018; Heslin & Elixhauser, 2006; HIV.gov, 2017). The prevalence of chronic diseases, commonly described as HIV Associated Non-AIDS (HANA) conditions, such as cardiovascular diseases, cancer, osteoporosis, liver disease, renal disease, and neurocognitive decline, are increasingly common among PLWH with long-standing HIV infection (High et al., 2012; Pathai et al., 2013; United States Senate, 2013). With the high prevalence of physical and mental health comorbidities and lack of social supports, aging with HIV may create higher health care demand, including increased hospital inpatient care in the United States (Matthew Harris et al., 2015). Increasing comorbidities among older PLWH may require greater use of inpatient care, which leads to higher resource utilization and hospital costs (H. Krentz & Gill, 2015; Zingmond, Arfer, Gildner, & Leibowitz, 2017). The ongoing age shift is also important because older PLWH are at increased risk for readmission, prolonged hospitalizations (Yehia et al., 2010), and of remaining underdiagnosed (Blaylock & Wortmann, 2015; Sankar, Nevedal, Neufeld, Berry, & Luborsky, 2011). Moreover, age-related comorbidities may appear as more severe for PLWH aging with HIV even on ART compared to others (Gras et al., 2007). Therefore, it

is vital to explore how existing health care infrastructure can meet the increasing demand for clinical and non-clinical services for this growing aging population.

1.2 Statement of the Problems

With the advent of highly active antiretroviral treatment (HAART), the incidence of AIDS-defining illnesses and HIV-related mortality has reduced significantly (High et al., 2012). These successes, combined with a growing aging population (45% of the PLWH were aged 50 or older in 2015), bring new prevention and treatment challenges for HIV care (United States Senate, 2013). HANA conditions, like cardiovascular disease, cancer, osteoporosis, liver disease, renal disease, and neurocognitive decline, are common among PLWH with long-standing HIV infection (High et al., 2012; Pathai et al., 2013; United States Senate, 2013). Multiple projections suggest that the demand for health care services by older adults will rise considerably in the coming decades due to long-term ART toxicities and multiple comorbidities.

While it is difficult to determine whether HIV accelerates the aging process, or is merely an additional risk factor for chronic conditions, research shows the development of geriatric clinical conditions is hastened with advanced aging (High et al., 2012; Pathai et al., 2013). HIV induced chronic immune activation and inflammation is referred to as a factor of accelerated or early aging, and that leads to PLWH developing multiple comorbidities at a younger age than the general population (Ahn et al., 2019; Desai & Landay, 2010; Guardigni & Montano, 2018). High prevalence of physical and mental health comorbidities and lack of social supports significantly affect the quality of life of PLWH, which leads to higher health care demand, including increased hospital inpatient care in the United States. Studies show that PLWH aged 50 years have higher

hospitalization rates and length of stay (LOS) compared to younger PLWH in the United States (S. A. Berry, Fleishman, Moore, & Gebo, 2012; Fleishman et al., 2005; Tadros, Shaver, Davis, & Davidov, 2012). Also, the overall cost of HIV management has increased in recent years, and it is projected to increase further as PLWH are living longer with more HANA conditions (Ward et al., 2020).

Therefore, the rapid increase in the number of PLWH aging with HIV in the United States may have important implications for the demand and the availability of inpatient resources. Also, other demand pressures could affect infrastructure, patient-management, and hospital-based long-term care treatment outcomes. However, it remains unclear whether the existing health care infrastructure can meet increasing specialized demand for clinical and non-clinical services for the aging HIV population (High et al., 2012).

1.3 Significance of the Study

Assessing the changing patterns of hospital admissions, comorbidity burdens, resource utilization, and inpatient costs of PLWH during hospital stays is essential to planning for future inpatient care resource demand posed by the aging PLWH. However, there is a lack of research addressing the complicated relationship of age, comorbidities, and outcomes of the patients during hospital stays with HIV diagnosis in the United States. Few studies have investigated hospital resource utilization and costs with the aging of PLWH compared to non-PLWH using U.S. national inpatient data. To our knowledge, studies focusing on age-related medical conditions using the national-level inpatient data are scarce. This study adds to the literature and the field by examining and describing HANA comorbidities associated with the aging of patients during hospital stays, using thirteen years of national inpatient sample (NIS) data (2003-2015). Studying recent trends

of the patient and facility-level factors, inpatient resource utilization, and costs associated with HIV hospital stays are important. Hospital inpatient cost analysis is critical in HIV and aging research for optimizing scarce resource allocation by both public and private payers.

The purpose of this study is to examine trends and characteristics of inpatient stays, resource utilization, and costs during hospital stays with HIV compared to hospital stays without HIV, and across patients' age. This study hypothesized that the aging of PLWH is associated with increased hospital admission and a higher presence of HANA conditions among older HIV patients compared to non-HIV patients during their inpatient stays. This study also hypothesized that the comorbidity burdens of older patients are associated with increased resource utilization and costs of care during their hospital stays than their non-HIV counterparts.

1.4 Research Questions

Question 1. What are the differences in characteristics and comorbidities between hospital stays with HIV and hospital stays without HIV, from 2003 to 2015?

Question 2. What are the age-specific trends in HANA comorbidities, resource utilization, and costs of hospital stays with HIV and hospital stays without HIV, from 2003-2015?

Question 3. What are the variations in inpatient resource utilization and costs of care between hospital stays with HIV and hospital stays without HIV by age of the patients?

Question 4. What are the variations in inpatient resource utilization and costs of care between hospital stays with HIV and hospital stays without HIV by age of the patients hospitalized with select major HANA conditions?

1.5 Research Objectives

The overall goal of this study is to describe, compare, and examine the patient- and hospital-level characteristics, comorbidity burdens, inpatient resources utilization, and costs of hospital stays with HIV diagnosis compared to that with non-HIV diagnoses, from 2003 through 2015. The specific aims and hypotheses have been arranged based on related publications and are described below.

Paper 1

Paper 1 is a descriptive study which focuses on the specific aims:

Aim 1. Describe the overall and age-specific rates of hospital stays with HIV in the United States, 2003 to 2015.

Null hypothesis (H_0): The rates of hospital stays with HIV did not change over the study period.

Alternative hypothesis (H_1): The rates of HIV hospitalization decreased over the study period.

Aim 2. Compare the changes in the patient- and hospital-level characteristics between hospital stays with HIV and hospital stays without HIV, 2003 to 2015.

H_0: There were no changes in the patient- and hospital-level characteristics between hospital stays with HIV and hospital stays without HIV over the study period.

H_1: There were changes in the patient and hospital-level characteristics between hospital stays with HIV and hospital stays without HIV over the study period.

Aim 3. Describe the changes in the top primary diagnoses and procedures of hospital stays with HIV compared to that of hospital stays without HIV over the years, 2003 to 2015.

H_0: There were no changes in the top primary diagnoses between hospital stays with HIV and hospital stays without HIV over the years.

H_1: Hospital stays with HIV had higher proportions of age-related conditions in the primary diagnoses than hospital stays without HIV over the years.

Aim 4. Describe the prevalence of major HANA comorbidities during hospital stays with HIV compared to that during hospital stays without HIV, 2003 to 2015.

H_0: There were no differences in the proportions of major HANA conditions between hospital stays with HIV and hospital stays without HIV over the years.

H_1: Hospital stays with HIV had higher proportions of major HANA conditions than hospital stays without HIV over the years.

Aim 5. Examine the HANA comorbidity patterns across the different age groups during hospital stays with HIV compared to that during hospital stays without HIV, 2003 to 2015.

H_0: There were no differences in the age-specific proportions of HANA conditions between hospital stays with HIV and hospital stays without HIV over the years.

H_1: Hospital stays with HIV had higher proportions of HANA conditions among older patients than hospital stays without HIV over the years.

Paper 2

Paper 2 focuses on the resource utilization, and costs of hospital stays with HIV compared to that of hospital stays without HIV in the United States for the select major HANA condition(s). This paper compares yearly trends of inpatient resource utilization (number of procedures and LOS) and costs of care between these two types of hospital stays. Moreover, it discusses variations in resource utilization and costs across different age groups. The specific aims are:

Aim 1. Describe the differences in inpatient resource utilization (number of procedures and LOS) and costs between hospital stays with HIV and hospital stays without HIV over the years, 2003 to 2015.

H_0: There were no changes in resource utilization and costs between hospital stays with HIV and hospital stays without HIV over the years.

H_1: Hospital stays with HIV had higher resource utilization and costs than hospital stays without HIV over the years.

Aim 2. Estimate the variations in inpatient resource utilization (number of procedures and LOS) and costs between hospital stays with HIV and hospital stays without HIV over the years for patients hospitalized with select major HANA conditions, 2003 to 2015.

H_0: There were no changes in resource utilization and costs between hospital stays with HIV and hospital stays without HIV over the years for patients hospitalized with select major HANA conditions.

H_1: Hospital stays with HIV had higher resource utilization and costs than hospital stays without HIV over the years for patients hospitalized with select major HANA conditions.

Aim 3. Compare the inpatient resource utilization, and costs between hospital stays with HIV and hospital stays without HIV across different age groups of the patients, 2003 to 2015.

H_0: There were no changes in the age-specific resource utilization and costs between hospital stays with HIV and hospital stays without HIV over the years.

H_1: Hospital stays with HIV had higher resource utilization and costs than hospital stays without HIV over the years with the increasing age of the patients.

Aim 4. Assess the association of inpatient resource utilization and costs with the HIV and age of the patients during hospital stays, controlling for patient and facility-level factors.

H_0: There is no association of inpatient resource utilization and costs with the HIV and age of the patients during hospital stays, controlling for patient and facility-level factors

H_1: There are significant associations of inpatient resource utilization and costs with the HIV and age of the patients during hospital stays, controlling for patient and facility-level factors.

Aim 5. Examine the effect of HIV and patients' age on resource utilization and costs of care during hospital stays with the select major HANA conditions, controlling for patients' demographic and facility-level factors.

H_0: There are no effects of HIV and age on inpatient resource utilization and costs during hospital stays, controlling for patient and facility-level factors.

H_1: There are significant effects of HIV and age on inpatient resource utilization and costs during hospital stays, controlling for patient and facility-level factors.

CHAPTER 2

LITERATURE REVIEW

2.1 Aging in the United States

The United States' population pyramid (Figure 2.1) clearly shows that a large portion of the American population is aging (U.S. Census Bureau, 2019) due to the post-World War II baby boomers because babies born in between 1946 to 1964 are currently at least 55 years old. A rapid change in age structure may have significant social and economic consequences, including a major impact on the organization and delivery of health care (Wiener & Tilly, 2002). With aging, multiple chronic health conditions appear, which sometimes turn into disabilities requiring long-term care services, such as home health, nursing homes, personal care, and congregate housing (Wiener & Tilly, 2002). Multiple projections suggest that the demand for health care services by older adults will rise considerably in the coming decades. This additional demand will create immense pressure on the healthcare workforce to deliver those services (Institute of Medicine, 2008). Thus, priority should be given to strengthening care delivery for co-occurring chronic conditions through the widespread adoption of evidence-based practices targeting older adults in the areas of disease prevention, long-term care, palliative care, and effective care management (Rowe, Fulmer, & Fried, 2016).

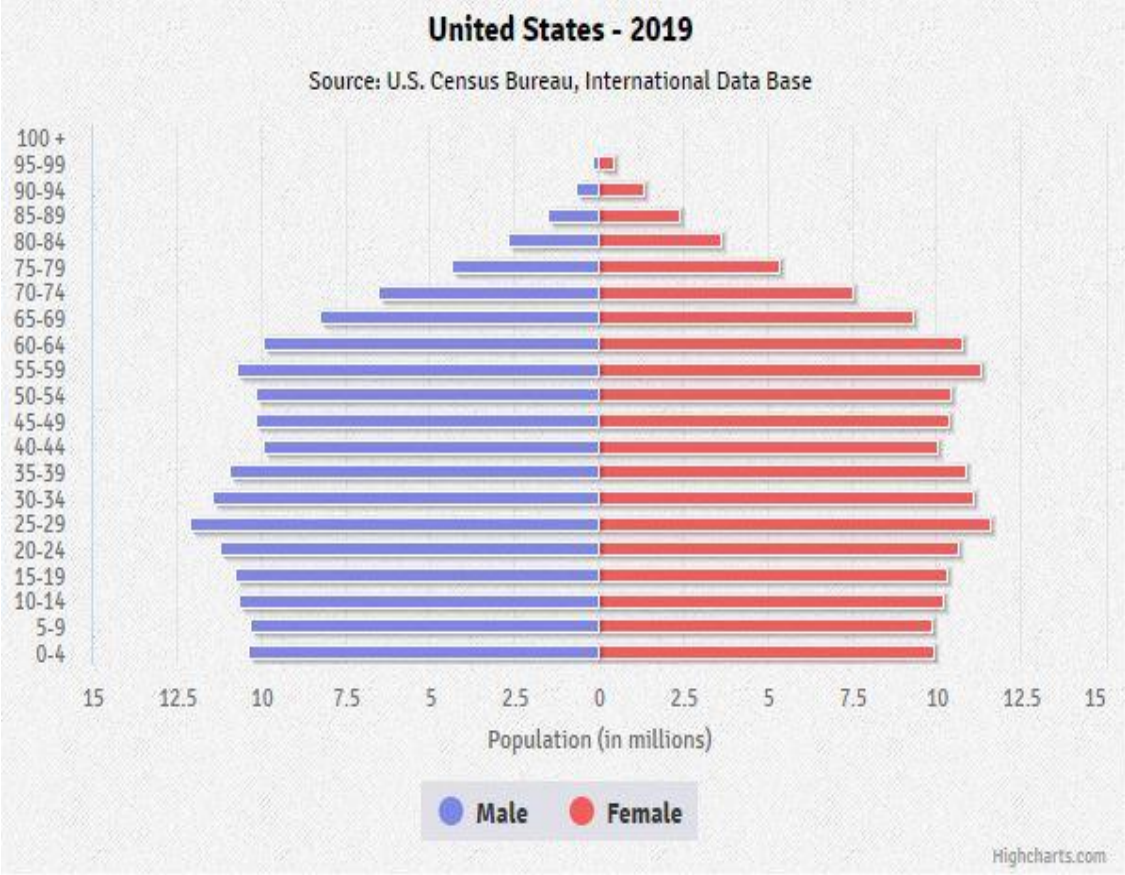


Figure 2. 1 Population pyramid of the United States, 2019.

2.2 HIV Infection in the United States

More than 1 million people are living with HIV (PLWH) today in the United States. One in seven PLWH is unaware of their infection, and every year about 40 thousand people become newly infected with HIV (HIV.gov, 2018). In 2018, a total of 37,832 people received an HIV diagnosis in the United States and six dependent areas, and the annual number of new HIV diagnoses decreased by 9 percent from 2010 to 2017 (Center for Disease Control and Prevention, 2019a). New HIV infections (HIV incidence) refers to the estimated number of people who are newly infected with HIV during a year, which is different from the number of people diagnosed with HIV during a year. HIV can be diagnosed through blood or saliva testing in multiple ways, such as antigen/antibody tests,

antibody tests, or nucleic acid tests (NATs). The stage of HIV infection (early, acute, and chronic infection and AIDS) can be determined by measuring CD4 T Cell count, viral load (HIV RNA), and drug resistance tests. AIDS is the late stage of HIV infection that occurs when the body's immune system is severely damaged due to the destruction of white blood cells. HIV infection is identified as AIDS (stage 3) when PLWH have fewer than 200 CD4 cells per cubic millimeter of blood (<200 cells/mm^3), or having one or more opportunistic infections regardless of their CD4 counts (Castro et al., 1993). In 2018, a total of 17,032 PLWH were diagnosed with AIDS in the United States and six dependent areas. Since the beginning of the HIV epidemic, more than 700,000 people have died of HIV/AIDS in the United States, and nearly 15,000 people die each year from AIDS (Center for Disease Control and Prevention, 2016b).

The HIV/AIDS epidemic has seen dramatic shifts since its first cases were identified in 1981. Today, a previously fatal infection has become a manageable chronic condition due to the advancement of HIV/AIDS treatment. The advent of combination antiretroviral therapy (cART) prevents HIV from growing inside the body and keeps the virus at a very low level or 'suppressed' (HIV.gov, 2019b). The viral load (HIV RNA) tests are done to check the status of HIV after diagnosis and to monitor the success of HIV treatments. Viral suppression, which keeps the immune system working and prevents illness, is measured as a viral load test result of fewer than 200 copies/mL at the most recent viral load tests (Centers for Disease Control and Prevention, 2019). PLWH on ART can achieve viral suppression with reduced risk of transmitting HIV to their HIV-negative sexual partners (Centers for Disease Control Prevention, 2018a). Therefore, ART is recommended for all PLWH irrespective of how long they have had the virus or how

healthy they are (Center for Disease Control and Prevention, 2019d). According to the CDC, an estimated 62% of persons with diagnosed HIV in the United States were virally suppressed in 2016 (Center for Disease Control and Prevention, 2019d).

Despite these successes, while the number of newly diagnosed PLWH fell by 19% between 2005 to 2014, the prevalence of HIV infection has increased among some subpopulations like young gay and bisexual men (Center for Disease Control and Prevention, 2016a). The increased HIV incidence among gay and bisexual men might be explained by the lower access to diagnosis, care, retention, and viral suppression due to societal barriers like stigma and discrimination. Thus, the progress regarding the outcomes of advanced HIV treatment and prevention strategies remain uneven for all PLWH. Apart from curbing HIV incidence and mortality, the quality of life of the PLWH, including physical and emotional well-being, social support system, and life roles, has emerged as a critical issue. Because, despite achieving virological and immunological stability, PLWH have a significantly lower health-related quality of life (HRQoL) than do the general population (Miners et al., 2014). A study showed that asymptomatic PLWH men have worse perceived physical health when symptomatic PLWH have worse perceived mental and physical health than their non-PLWH counterparts (Bing et al., 2000). A review study noted that "existing data suggest that physical manifestations, ART, psychological well-being, social support systems, coping strategies, spiritual well-being, and psychiatric comorbidities are important predictors of quality of life in the HIV population (Basavaraj, Navya, & Rashmi, 2010)."

2.3 Demographics of PLWH in the United States

An estimated 1.1 million people in the United States were living with HIV at the end of 2016, however, about 14% of them do not know their HIV status and so need testing (Centers for Disease Control and Prevention, 2018a). According to the Center for Disease Control and Prevention (CDC), an estimated 54.6% of young PLWH aged 13-24 years living with HIV remain unaware of their infection. More than half of the total PLWH were older than 50 years, with the largest percentage increase in rates of PLWH by persons aged 65 years and older in 2016 (Centers for Disease Control and Prevention, 2018a). About 67% of PLWH have received some HIV care, 49% retained in care, and 53% were virally suppressed in 2016 (Centers for Disease Control and Prevention, 2018a).

Literature shows that about 38% of new infections were transmitted by individuals unaware of their HIV infection; whereas, 42% newly infected PLWH got HIV from PLWH aware of their infection but not in care and 20% from those receiving care but not virally suppressed (Li, Purcell, Sansom, Hayes, & Hall, 2019). The annual number of new HIV diagnoses has remained stable in the United States in the last several years, however, newly diagnosed HIV cases have increased among subpopulations like young gay and bisexual men (Center for Disease Control and Prevention, 2016a).

African Americans and Hispanics/Latinos are disproportionately affected by HIV. In 2017, African Americans and Hispanics/Latinos accounted for 43% and 26% of new HIV diagnoses, when they are 13% and 18% of the U.S. population (Centers for Disease Control and Prevention, 2018a). Survival after an AIDS diagnosis is lower for African Americans than for other racial/ethnic groups. African Americans accounted for 43% of deaths among PLWH in 2016 (Centers for Disease Control and Prevention, 2018a).

Although HIV has been reported in all U.S. states, the District of Columbia, and U.S. dependent areas, the HIV epidemic is not evenly distributed across the U.S. regions. The South accounted for about half of new HIV diagnoses, while nearly two-thirds (64%) of PLWH live in only ten U.S. states. These states are Florida, California, Texas, New York, Georgia, North Carolina, Illinois, New Jersey, Pennsylvania, and Louisiana (Centers for Disease Control and Prevention, 2018a). However, rates of new HIV diagnoses per 100,000 population are higher in District of Columbia (53.6), Georgia (30.0), Florida (26.6), Louisiana (26.6), Maryland (20.2), Nevada (19.7), Texas (19.0), Mississippi (17.3), South Carolina (16.9), and New York (16.4) (Centers for Disease Control and Prevention, 2018a). The overall rate of HIV incidence among women decreased by 21% from 2010 to 2015; however, the rate of HIV diagnoses is higher among women of color. African American women accounted for 59% of new diagnoses among women (Centers for Disease Control and Prevention, 2018a). Adolescents and young adults continue to be at high risk; 56% of new HIV diagnoses in 2017 are aged 35 years or less. Among young and gay or bisexual men, minorities have particularly been affected more by the HIV epidemic in the United States (Centers for Disease Control Prevention, 2018b).

2.4 Risk of HIV Transmission

HIV is mainly spread by having sex or sharing syringes and other injection equipment with someone already infected with HIV. HIV infection is known as a sexually transmitted disease because sexual contact is identified as the major risk factor for HIV transmission. Primarily, risky behaviors like having vaginal or anal sex without using a condom and sharing needles or syringes, play a significant role in HIV transmission in the United States. Substance use may contribute to these risks indirectly because alcohol and

other drugs can lower one's inhibitions and make him/her less likely to use condoms. People who inject drugs (PWID) are at high risk of getting HIV if they share needles, syringes, or other drug-injection equipment (e.g., cookers) with others. Receiving blood transfusions, blood products, or organ/tissue transplants that are HIV contaminated, eating food that has been pre-chewed by a PLWH, being bitten by a PLWH, and contact between broken skin, wounds, or mucous membranes and HIV-infected blood can be other potential routes of HIV transmission. However, these are the relatively rare cases of HIV transmission in the United States. Certain cultural and societal factors can also act as risk factors in HIV transmission (Edwards & Collins Jr, 2014). These factors include poverty, lack of education, racial/ethnic or gender discrimination, geographic location, lack of access to care, homophobia, and stigma (Gupta, Parkhurst, Ogden, Aggleton, & Mahal, 2008; Ordóñez & Marconi, 2012).

HIV transmission patterns have shifted over time; most of the newly diagnosed HIV cases (66%) occurred through male-to-male sexual contact in 2017 (Centers for Disease Control and Prevention, 2018a). Although HIV transmission through heterosexual contact is declined in recent years; the current proportion of heterosexual transmission - 24% of new diagnoses in 2017- is much higher than the proportion at the beginning of the epidemic (Centers for Disease Control and Prevention, 2018a; Centers for Disease Control Prevention, 2018b). HIV diagnoses attributable to injection drug use that accounted for 6% of new diagnoses in 2017 have also decreased in recent years. Almost half of these new HIV diagnoses occurred among gay and bisexual men with a history of injection drug use (Centers for Disease Control and Prevention, 2018a).

Pre-exposure prophylaxis (PrEP) is highly useful to prevent HIV transmission. PrEP is one tablet (Truvada), which is a combination of two antiretrovirals (tenofovir/emtricitabine), taken every day by any person at high risk of acquiring HIV (Huynh & Gulick, 2018). Similarly, post-exposure prophylaxis (PEP) plays a vital role to prevent HIV transmission among individual who has already exposed to a confirmed or suspicious HIV positive body secretion of semen, vaginal fluid, or blood. The CDC recommends screening all patients for PrEP use, especially young MSM, sexually active heterosexuals, and injection drug users (Huynh & Gulick, 2018).

Mother-to-child transmission during pregnancy, birth, or breastfeeding is a less common mode of HIV transmission. Although the risk can be high if a mother is living with HIV and not taking ART, testing all pregnant women for HIV and start HIV treatment promptly may reduce the risk of babies born with HIV substantially. Medication therapy for both mother and child during pregnancy, childbirth, and the postnatal period has contributed to the decline in mother-to-child transmission rate to less than 1% (Huynh & Gulick, 2018). In this regard, formula feeding is a good alternative to breast milk that eliminates the risk of HIV transmission from mother to child through breastfeeding. Due to increased testing efforts among pregnant women and ART, perinatal HIV transmission has declined significantly in the United States (Centers for Disease Control and Prevention, 2018b).

2.5 Current Treatment of HIV Infection

The treatment of HIV disease depends on the stage of the disease and the presence of any concurrent opportunistic infections. ART is the principal method for preventing immune deterioration caused by HIV infection. Successful long-term ART results in a

gradual recovery of CD4 cell counts and an improvement of immune responses that prevent chances of other opportunistic infections. As a result, ART has substantially reduced AIDS-related morbidity and mortality and improved long-term outcomes for PLWH. Also, ART plays a crucial role in preventing HIV transmission when it started early. According to the CDC, PLWH who take ART daily as prescribed, and keep an undetectable viral load have 'effectively no risk' of sexually transmitting HIV to their HIV-negative partners (HIV.gov, 2019b). When HIV viral load is so low that it does not show up in a standard laboratory test (< 50 copies HIV RNA per mL), it is called undetectable viral load. However, there are many PLWH who are not diagnosed with HIV, not in HIV medical care (defined as viral load/CD4 test every 6 months, or on ART), or have viral load under control (Centers for Disease Control and Prevention, 2018b).

Current HIV treatment guidelines recommend a rapid start (treatment sooner after diagnosis). A person's initial HIV regimen generally includes three HIV medicines from at least two different HIV drug classes (U.S. Food and Drug Administration, 2018). The most common drug classes include single-tablet regimens (STRs), Integrase Inhibitors (INSTIs), Protease Inhibitors (P.I.s), and Nucleoside Reverse Transcriptase Inhibitors. Detailed lists of U.S. Food and Drug Administration (FDA) approved HIV medicines are discussed elsewhere (U.S. Food and Drug Administration, 2018). In the United States, physicians prescribe ART based on the recommendation of the U.S. Department of Health and Human Services (HHS) HIV/AIDS medical practice guidelines.

2.6 The '90-90-90' HIV Treatment Targets

The Joint United Nations Program on HIV/AIDS (UNAIDS) set 90-90-90 goals in 2013 that 90% of all PLWH know their HIV status, 90% of all diagnosed HIV receive

sustained ART, and 90% of all receiving ART have viral suppression by 2020 (Joint United Nations Programme on HIV/AIDS, 2014). In the United States, 86% of all PLWH are diagnosed, yet a large proportion of these diagnosed PLWH are not in treatment and did not achieve the desired level of viral suppression. The CDC reported that 64% of all PLWH (74% of all diagnosed) received care but only 49% retained in care (58% of all diagnosed), and only 53% of all PLWH (62% of all received ART) were virally suppressed in 2016 (Figure 2.2) (Bradley et al., 2014; Center for Disease Control and Prevention, 2019d). Beyond the viral suppression of HIV, researchers suggest a concept of the 'fourth 90' to the testing and treatment target- ensure that 90% of people with viral load suppression have a good health-related quality of life (HRQoL) (Guaraldi, Milic, & Wu, 2019). Some researchers explained it from the perspective of aging, i.e., ensuring healthy aging for PLWH since a large portion of PLWH are now in advanced age that makes them prone to the elevated risk of multiple comorbidities (Harris, Rabkin, & El-Sadr, 2018; Lazarus et al., 2016).

2.7 Health Care Delivery and Financing for PLWH

The U.S. health care system is facing enormous challenges with HIV care management since HIV is a noncurable infection, and there are a growing number of PLWH due to increased lifespan and new HIV infection every year. HIV requires long-term and expensive medical management and support services, heavily reliant on prescription drugs. The central challenges for policymakers are how to ensure adequate resources to fight HIV/AIDS and how to adapt public policies and programs with the changes in the demographic profile of the HIV epidemic in the United States (Health Policy

Institute, 2003). The U.S. health care system supports PLWH to engage and keep them into the care through the following programs.

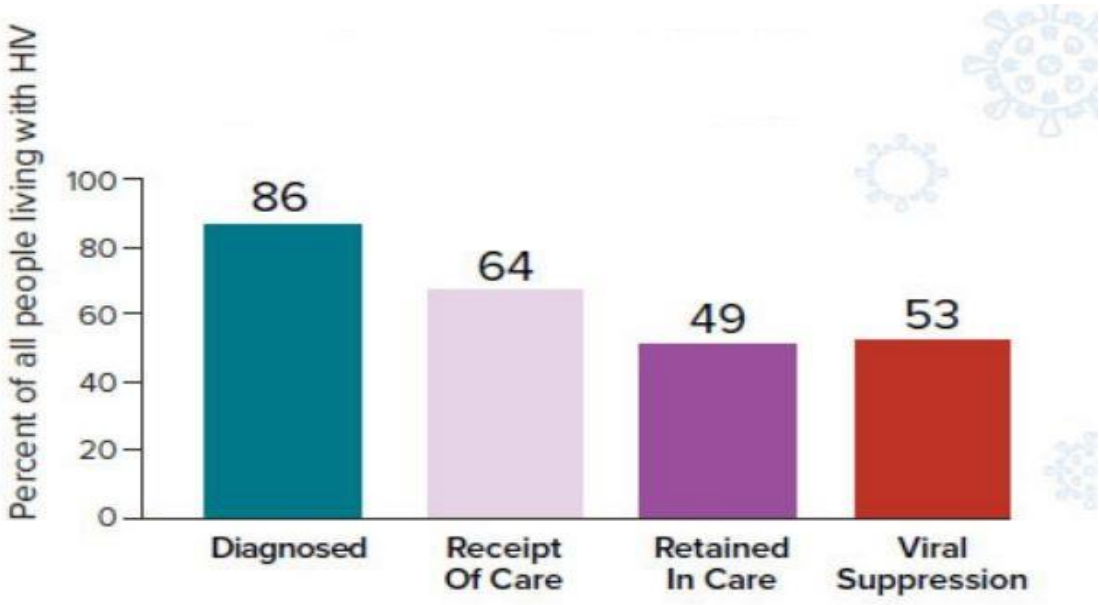


Figure 2. 2 Estimated percentage of PLWH, by outcome along the HIV care continuum in the United States, 2016 (Center for Disease Control and Prevention, 2019d).

2.7.1 Ryan White Program

The Ryan White HIV/AIDS program, which is administered by the Health Resource & Services Administration (HRSA), provides a comprehensive system of HIV primary medical care, essential support services, and medications for more than half a million low-income diagnosed PLWH each year (Health Resources and Services Administration, 2019). Uninsured and underinsured PLWH can get HIV medical care, access to medications, case management, substance abuse, oral health, mental health, and other support services they need through this program (Institute of Medicine, 2011). The program funds states, cities/counties, and local community-based organizations to provide care and treatment services to PLWH to improve health outcomes and reduce HIV transmission among hard-to-reach populations. Hospital-based clinics provide medical

care to almost half of the medical clients, when publicly-funded community health centers (CHCs), other community-based organizations (CBOs), and health departments provide medical care to the rest of the clients at Ryan White-funded sites (Institute of Medicine, 2011). Other providers of HIV medical care services include private doctors' office, day treatment programs, home care programs, skilled nursing facilities, and correctional facilities. Ryan White HIV/AIDS program is divided into five parts, following from the authorizing legislation (Health Resources and Services Administration, 2019).

Part A: Part A of the Ryan White HIV/AIDS Treatment Extension Act of 2009 provides assistance to Eligible Metropolitan Areas (EMAs) and Transitional Grant Areas (TGAs) that are most severely impacted by the HIV epidemic. EMAs with 2,000+ reported AIDS cases and TGAs with 1,000-1,999 reported AIDS cases in the past 5 years and must have a population of at least 50,000 are eligible to receive the funds. Two-thirds of funds are distributed by a formula based on the area's share of living HIV (non-AIDS and AIDS) cases, and the remainder is distributed via competitive supplemental grants based on "demonstrated need."

Part B: Part B of the Ryan White HIV/AIDS Treatment Extension Act of 2009 provides grants to States and Territories to improve the quality, availability, and organization of HIV health care and support services. Recipients include all 50 states, the District of Columbia, Puerto Rico, the U.S. Virgin Islands, and the six U.S. Pacific territories/associated jurisdictions. Also, Part B includes grants for the AIDS Drug Assistance Program (ADAP).

Part C: Part C of the Ryan White HIV/AIDS Program provides grant funding to local community-based organizations to support outpatient ambulatory health service and

support services through Early Intervention Services (EIS) program grants. Part C also funds planning grants, which help organizations more effectively deliver HIV care and services through Capacity Development grants.

Part D: Ryan White HIV/AIDS Program Part D grant funds public and private organizations to provide family-centered and community-based services to children, youth, and women living with HIV and their families, including outreach, prevention, primary and specialty medical care, and psychosocial services. The recipients are local, community-based organizations seeking to enhance their response to the HIV epidemic in their area through providing family-centered primary medical care and support services when payments for such services are unavailable from other sources. Part D also supports activities to improve access to clinical trials and research for these populations.

Part F: Part F of the Ryan White HIV/AIDS Program provides funds to support clinician training, technical assistance, and the development of innovative models of care to improve health outcomes and reduce HIV transmission. These programs include the Special Projects of National Significance Program, AIDS education and Training Centers Program, The Dental Programs, and Minority AIDS Initiative.

Since 1990, the Ryan White HIV/AIDS program has been playing a vital role in the United States' public health response to HIV epidemic. The program serves as an important source of ongoing access to HIV medication that enable PLWH to achieve close to normal life expectancy by maintaining a very low viral load. For example, 86% of Ryan White clients were virally suppressed in 2017, exceeding the national average of 60% (Health Resources and Services Administration, 2019). Low-income people diagnosed with HIV or AIDS can get primary medical care, essential support services, and

medications through HRSA's Ryan White HIV/AIDS program when they do not have health insurance or their insurance does not pay for the care. Some pharmaceutical companies provide medications to low-income PLWH who have no insurance or prescription drug coverage (Center for Disease Control and Prevention, 2020b). Affordable Care Act (ACA) safeguards PLWH from dropping or denying coverage because of the pre-existing condition, imposing lifetime caps, and canceling coverage due to mistakes made on an application. ACA helps people access quality, affordable coverage through the health insurance marketplaces, and through providing financial assistance for people with low and middle incomes in the form of tax credits. Moreover, ACA contributes to cover more people by expanding Medicaid eligibility and lowering prescription drug costs for Medicare recipients, which enable some PLWH to get engaged with HIV care (HIV.gov, 2019a). Finally, the Social Security Administration offers disability benefits for PLWH who are unable to work (Center for Disease Control and Prevention, 2020b).

2.7.2 Medicare

Medicare, the federal health insurance program for people age 65 and older and younger adults with permanent disabilities, is an important source of health coverage for PLWH because there are a growing number of elderly with HIV due to increased lifespan. Most PLWH on Medicare are under age 65 years because many PLWH do qualify for it due to their disability. About one-quarter of PLWH in care get their health insurance through Medicare, and it is now the single largest source of federal financing for HIV care and treatment (Bradley et al., 2014). In 2016, Medicare spending on HIV totaled $10 billion, which is 51% of federal spending on HIV care, and it has increased over time in recent years due to the addition of Medicare Part D prescription drug benefit (Kaiser

Family Foundation, 2016). Medicare provides broad coverage of many basic health care services, including hospital care, physician services, and prescription drugs. Among services covered by Medicare, some vital services are expanded coverage for HIV testing, prescription drug, and facial wasting (lipoatrophy) treatments (Kaiser Family Foundation, 2016). The majority of PLWH under Medicare are dually eligible for Medicare and Medicaid and receive low-income subsidies from Part D.

2.7.3 Medicaid

It is the largest public health insurance program in the United States, jointly financed by the federal and state governments, which has played a critical role in HIV care since the epidemic began. Currently, it is covering 73 million low-income individuals (13% of the overall population), whereas 42% of them are with HIV (Kaiser Family Foundation, 2019). The role of Medicaid has grown over time since PLWH are living longer, new infections continue to occur, and the program was expanded under the ACA. The number of PLWH enrolled in Medicaid has increased in recent years due to ACA's Medicaid expansion, which facilitates PLWH beneficiaries to gain broad health care coverage. The majority of the Medicaid beneficiaries with HIV (65% in 2013) qualify for coverage through a disability status (Kaiser Family Foundation, 2019). Medicaid covers a wide range of services, including inpatient and outpatient hospital, physician and nurse, laboratory, nursing facility, dental care, prescription drugs services, which are paid fee-for-service basis, through capitated managed care organizations (MCOs), or through a combination of these (Kaiser Family Foundation, 2019).

2.7.4 Department of Veteran Affairs

The Department of Veteran Affairs (V.A.) is the largest single provider of HIV medical care to PLWH in the United States, serving over 31,000 Veterans with HIV across the country in 2018 (Department of Veteran Affairs, 2019). The VA is committed to ensuring the HIV care continuum from testing and diagnosis to linkage to care, and treatment and prevention. The VA provides comprehensive care to veterans with complex care needs and prevalent comorbidities. Veterans with service-connected disabilities, including HIV, are eligible for compensation benefits regarding health care.

2.7.5 Federally Qualified Health Centers

Federally Qualified Health Centers (FQHCs) are community-based health care providers that receive funds from the HRSA Health Center Program to provide primary care services to high need communities that are designated as a medically underserved area or population. FQHCs include community health centers, migrant health centers, healthcare for homeless, and public housing primary care programs. These health centers emphasize coordinated and comprehensive primary health care services as well as supportive services, including education, translation, and transportation that promote access to health care. FQHCs play a vital role in ending the HIV epidemic by serving as a key point of entry for people undiagnosed with HIV. In 2018, more than 191,000 patients living with HIV received medical care services at those health centers, including many sites co-funded by the Ryan White HIV/AIDS program (Helath Resources and Services Administration, 2019).

2.8 HIV and Aging in the United States

The increasing availability of potent ART has allowed many PLWH to live longer, particularly those who initiate ART therapy at early disease stages. Due to the success of combination antiretroviral drug treatments, PLWH can expect to live a near-normal lifespan compared to non-PLWH. Different studies show that PLWH have a similar life expectancy to the general population if they are diagnosed early, have good access to care, and adhere to their HIV treatment (National Institute of Allergy and Infectious Diseases, 2018; Pebody, 2018). However, even with the availability of effective ART after HIV being diagnosed, differences in access to care, comorbidities, and substance use can widen the survival gap; for example, tobacco use accounts for up to 8 years of potential life lost (Marcus et al., 2016). As a result of the success in gaining a higher life expectancy, PLWH are living longer, thus aging with HIV. Currently, almost half of all PLWH are aged 50 or older (Center for Disease Control and Prevention, 2018), with this proportion projected to rise to more than 70% by 2030 (Wing, 2017). The good news is that the rate of new HIV diagnoses among the people aged 50 or older decreased significantly from 25% of total new diagnoses in 2006 (Jacobson, 2011) to 17% in 2016 (Center for Disease Control and Prevention, 2018). Irrespective of HIV status, the older the population, the higher the onset of age-related health conditions, which will create a higher demand for health care services in the United States in the upcoming decades (Institute of Medicine, 2008). The interaction of HIV with the process of aging and aging-related comorbidities are expected as the virus consistently activate the immune cells that make the individuals susceptible to inflammation-induced diseases and diminishes their capacity to fight some diseases (Fauci, Hodes, & Whitescarver, 2010). Brooks et al. summarized this interaction in their review

paper by stating, “apart from the expected contribution of normal aging, 3 additional sets of factors contribute to risk, to varying degrees and often in complex interplay (Brooks, Buchacz, Gebo, & Mermin, 2012): (1) factors associated directly with chronic HIV infection including viral replication and attendant inflammation, (2) toxicities and other complications of treatment with antiretroviral agents, and (3) host-related factors that are especially prevalent among HIV-infected adults, including certain coinfections (e.g., human papillomavirus, hepatitis B); and lifestyle factors (e.g., alcohol and tobacco use, obesity).”

2.9 The Burden of Multiple Comorbidities among Older PLWH

PLWH with higher viral load and weaker immune systems are susceptible to numerous infectious and noninfectious diseases. The clinical conditions of the older PLWH get complicated due to coinfection with some other virus, like Human Papilloma Virus (HPV), Kaposi's-sarcoma Associated Herpes Virus (KSHV/HHV-8), Epstein-Barr Virus (EBV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) (Hille, Webster-Cyriaque, Palefski, & Raab-Traub, 2002; Peters et al., 2012; Pinzone, Berretta, Cacopardo, & Nunnari, 2015).

Since PLWH are now living longer, age-related chronic conditions have increasingly become significant health concerns despite suppression of HIV viral load to clinically undetectable levels. Age confers higher vulnerability towards more rapidly advancing HIV disease, including a higher risk of HIV-induced neurocognitive disorders, AIDS-defining illness, and mortality, suggested to be caused by a variety of factors not limited to delayed diagnosis, immune senescence, and differential response to combination

ART (Rodriguez-Penney et al., 2013). Thus, PLWH receiving ART suffer chronic conditions just like non-PLWH, alongside HIV infection and its treatment.

Aligned with the aging process, the longer exposure of the older PLWH to both HIV and antiretroviral drugs may increase the risk of illness, including cardiovascular, liver, kidney, bone, lung disease, and certain cancer not associated with HIV infection (Gallant, Hsue, Shreay, & Meyer, 2017; Guaraldi et al., 2011; Schouten et al., 2014). Studies found a higher prevalence of multi-morbidity among HIV patients than in the general population (Guaraldi et al., 2011; Maciel, Klück, Durand, & Sprinz, 2018; Rodriguez-Penney et al., 2013). Despite complete viral suppression and immune recovery, PLWH are more vulnerable to poor health than the non-PLWH (High et al., 2012). The vulnerability is characterized by a higher risk of some common age-related health problems, even after adjusting established risk factors, including cardiovascular disease, metabolic disorders, hepatic and renal diseases, a certain type of cancers, and age-associated immunologic changes and chronic inflammation (Deeks, 2011; Fitch et al., 2013; Guaraldi et al., 2011).

2.10 HIV, Polypharmacy, and Aging

The prevalence of polypharmacy that is commonly defined as concurrent taking 5 or more medications is higher among PLWH compared to the non-PLWH. This is because PLWH are susceptible to multiple comorbidities and reliant on prescription drugs, and they need to continue the medication until death. After initiation of antiretroviral treatment, that typically requires PLWH to take three medications, many non- antiretroviral medications are prescribed to address symptoms, side effects, and to treat or prevent comorbid diseases (Edelman, Rentsch, & Justice, 2020). Also, the increasing number of comorbidities lead

PLWH to a higher burden of other non-antiretroviral oral medications, enhanced risk of side effects, and elevated risk of drug-drug interactions. PLWH are more susceptible to medication side effects, because of interaction between antiretroviral medications and commonly prescribed non-antiretroviral medications, and increased physiologic frailty of PLWH (Edelman et al., 2020; Hughes, Tseng, & Cooper, 2015).

Since PLWH develop various chronic diseases at a higher rate than non-PLWH as they age, they are more likely to be exposed to polypharmacy at younger ages, because aging PLWH increasingly require more non-antiretroviral medications to treat chronic age-related comorbidities (H. B. Krentz, Cosman, Lee, Ming, & Gill, 2012; Ware et al., 2018). An estimated 15 to 39% of PLWH are exposed to polypharmacy (Guaraldi et al., 2018; Justice et al., 2018; Ware et al., 2018), with higher rates observed in resource-rich settings and among older persons (Livio & Marzolini, 2019). Another study showed that older men living with HIV take a median of 13 medications, including medications for HIV infection (Greene, Steinman, McNicholl, & Valcour, 2014). The risks of polypharmacy include increased adverse drug events, organ system injury, hospitalization, decreased medication adherence, and mortality (Greene et al., 2014).

2.11 HIV Infection to Accelerate and/or Accentuate Aging

Multi-morbidity is common among PLWH in the United States that occurs at an earlier age than that in HIV-uninfected participants. The prevalence of noninfectious comorbidities among ART-experienced PLWH was anticipated to be similar among non-PLWH who were 10 years older (Guaraldi et al., 2011). Thus, a critical question is whether HIV infection is accelerating aging through the common mechanism of aging or acting as an additional risk factor for comorbidity development in conjugation with traditional risk

factors. One study suggested that the answer is organ and disease-specific; when some processes appear to be accelerated due to HIV, many illnesses are likely to be accentuated rather than accelerated (Pathai et al., 2013). HIV induced chronic immune activation and inflammation are referred to as factors of accelerated or early aging, while PLWH develops multiple comorbidities at a younger age than the general population (Ahn et al., 2019; Desai & Landay, 2010; Guardigni & Montano, 2018). Besides, the trend toward a stronger association between age and noninfectious disease burden among PLWH might support premature or accelerated aging in HIV (Guaraldi et al., 2011; Schouten et al., 2014). Lopez-Otin el al. discussed the multiple biological mechanisms of aging, some of which may affect HIV-positive individuals at higher rates, including genetic instability, telomere shortening, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). Additional research is suggested to generate a more in-depth understanding regarding the mutual impacts of HIV infection and aging to develop and implement effective preventive measures for safe antiretroviral therapy among older PLWH (Sharma & Singh, 2016).

2.12 The Vulnerability of the Older PLWH

The impact of HIV infection and its treatment on the aging of PLWH may cause premature aging and the development of multiple HANA conditions. The cumulative burden of these complications reduces a person's ability to compensate and respond to many events, which jointly results in the onset of 'frailty' (Deeks, 2011; Justice, 2010). Frailty is a pathologic aging syndrome, which indicates vulnerability to diverse adverse health outcomes such as treatment toxicity, functional decline, hospitalization, surgical

complications, and death (Desquilbet et al., 2009; High et al., 2012). Studies showed the frailty-related phenotype was prevalent among PLWH at a younger age than those non-PLWH, especially in more-advanced HIV infection (Desquilbet et al., 2009; Piggott et al., 2013), because HIV infection may synergistically interact with age to contribute to functional decline (Morgan et al., 2012).

'HIV Stigma' is a critical issue for older PLWH, because it involves prejudice, discounting, discrediting, discriminating, and isolation from family and friends due to illness (Center for Disease Control and Prevention, 2019b; Gay Men's Health Crisis Inc, 2010). It greatly affects the quality of life, self-image, and mental health and may prevent them from seeking HIV care and disclosing HIV status (Cahill & Valadéz, 2013; Gay Men's Health Crisis Inc, 2010). Moreover, health care providers often do not order HIV testing for older people because of bias about reduced exposure to risky behavior (Gay Men's Health Crisis Inc, 2010). Besides, older people may mistake HIV symptoms as usual aging symptoms. Thus, older people are more likely than younger to have late-stage HIV infection at the time of diagnosis. This leads to starting treatment late and possibly suffering from more immune-system damage (Gay Men's Health Crisis Inc, 2010).

The increasing population of older PLWH also face psychological challenges regarding social engagement and interaction, adequacy of informal social supports and caregiving resources, and utilization of community-based services to meet their growing needs (High et al., 2012). The stigma associated with HIV and homosexuality interacts with age-related stigma to exacerbate stress and affect the quality of life and mental health of older PLWH. Besides, lack of social supports and networks leaves older PLWH with

fewer resources, making them more vulnerable in terms of depression, bereavement, mental health, and substance use in their later stages of life (Cahill & Valadéz, 2013).

Also, as PLWH age, the general progression of HIV infection may create symptoms that are not specific to HIV-associated diseases during end-of-life care, including fatigue, pain, insomnia, decreased libido/hypogonadism, reduced memory and concentration (HIV-associated neurocognitive disorder (HAND), depression, and distorted body image. Palliative care can play a vital role in addressing these suffering and maximize function and quality of life for PLWH, and for patients with HIV disease who are nearing the end of life (Simms, Higginson, & Harding, 2012). Therefore, HIV prevention strategies need to incorporate a comprehensive set of issues, such as non-communicable diseases, mental health disorders, pain management and palliative care, and stigma and discrimination (Lazarus et al., 2016).

2.13 Impact of Aging PLWH on U.S. Health Care System

With the additional risks of comorbidity, weak cognitive functioning, frailty, poor mental health, and provider or society level stigma, the aging of the PLWH may place enormous demands on the health care and social service systems. Some of these demands will reflect the needs created by the general aging population, yet some were specific to the needs of older PLWH, which may include a large number of racial and ethnic minorities and people with low incomes (Gay Men's Health Crisis Inc, 2010).

Due to the aging of PLWH, there would be far more demand than the supply of healthcare industry in the future, especially the demand for both clinical and non-clinical health care workers. With aging, multiple chronic conditions appear, which sometimes turns into disabilities requiring long-term care services, such as home health, nursing

homes, personal care, and congregate housing (Wiener & Tilly, 2002). Multiple projections suggest that the demand for health care services for older adults will rise considerably in the coming decades, which will create immense pressure on the health care workforce to deliver those services (Institute of Medicine, 2008). Staff at long-term care facilities, nursing homes, personal care, congregate housing, and senior centers should be trained to support the unique experiences and needs of PLWH to ensure culturally competent and non-discriminatory care (Gay Men's Health Crisis Inc, 2010). However, due to social isolation, many older PLWH are disconnected from traditional informal support networks, thus rely heavily on formal care providers, like the emergency department, hospital outpatient, and inpatient department (Shippy & Karpiak, 2005).

2.14 Challenges for U.S. Health Care System

However, effective HIV care delivery and management largely depend on the capacity of health care systems, such as hospital infrastructure and the number of health care providers focusing on managing PLWH. Infectious disease specialists, advanced practice registered nurses, physician assistants, and primary care physicians are responsible for providing a vast majority of medical care for PLWH (Institute of Medicine, 2011). Registered nurses, dentists, pharmacists, and social workers are among a large number of other providers necessary to provide quality HIV/AIDS care in a variety of settings. With the changing pattern of the HIV epidemic, the U.S. health care system requires the broader skills of primary care physicians, nurses, and physician assistants to address the comorbidities of PLWH to manage HIV the epidemic successfully. However, the projections indicate that the supply of HIV providers is not keeping up with the demand for HIV care. Also, cuts in funding and available positions that support HIV programs,

such as in health departments, are reflective of lacking in the health care system's capacity to provide care for a growing number of PLWH in the United States (Institute of Medicine, 2011). The AAMC Center for Workforce Studies projects a shortage of 45,000 primary care physicians by 2020 (Colleges, 2010). Retirement of the health care workforce who got trained in HIV/AIDS care management during the beginning of the HIV epidemic is another challenge for the health care system (Institute of Medicine, 2011).

Another hospital-level challenge is reaching HIV care to the rural areas in the United States because resources for HIV prevention and care are concentrated in urban areas (Schafer et al., 2017). However, studies showed that the HIV epidemic has migrated from primarily urban centers to more rural locales (Iyer, 2015; M Vyavaharkar, Glover, Leonhirth, & Probst, 2013). The rural residence also reported lower rates of HIV testing, delayed HIV diagnosis, later adoption of HAART, and higher HIV-related mortality (Lahey et al., 2007; Ohl et al., 2013; Ohl et al., 2010; Weis, Liese, Hussey, Gibson, & Duffus, 2010). Additionally, rural residents with HIV may face challenges with stigma, social isolation, long-distance to care, limited transportation, and lack of access to providers with HIV experts (Reif et al., 2014; Sutton, Anthony, Vila, McLellan-Lemal, & Weidle, 2010; Medha Vyavaharkar, Moneyham, Murdaugh, & Tavakoli, 2012). Rural residents with HIV may face additional challenges in engagement and retention in HIV care due to the closure of hospitals in rural counties. More than 42 rural hospitals went out of business between 2005 to 2009 due to recession, and the trend has been accelerating since 2010; there were 72 hospital closures between 2010 to 2016 (Wishner, Solleveld, Rudowitz, Paradise, & Antonisse, 2016).

2.15 Aging of PLWH and Hospital Inpatient Care

With the high prevalence of physical and mental health comorbidities and lack of social supports, aging with HIV may create higher health care demand, including increased hospital inpatient care in the United States (Matthew Harris et al., 2015). Increasing comorbidities among older PLWH require greater use of inpatient care, which leads to higher resource utilization and hospital costs (H. Krentz & Gill, 2015; Zingmond et al., 2017). PLWH with multiple comorbidities may need more frequent hospital admission or extended hospital stay in their later age. There are a growing number of older PLWH in the United States due to age-shift. This ongoing age-shift is important because older PLWH are at increased risk for readmission, prolonged hospitalizations (Yehia et al., 2010), and of remaining underdiagnosed (Blaylock & Wortmann, 2015; Sankar et al., 2011). Moreover, age-related comorbidities may be more severe for PLWH aging with HIV even on ART compared to others (Gras et al., 2007). Therefore, it is crucial to explore how existing health care infrastructure can meet the increasing demand for clinical and non-clinical services for this growing population.

2.16 Current Trends for Hospitalizations with HIV Infection

Declining hospitalizations rates were observed shortly after the widespread availability of HAART in the United States. Hospital stays with principal HIV diagnosis has decreased between 2006 and 2013; however, trends in hospital stays were volatile for HIV as secondary diagnosis over the same period (Heslin & Elixhauser, 2016). The rate of hospitalizations that included both principal or secondary diagnosis decreased for all groups under the age of 55 years, but increased for patients aged 55 years or over, between 2006 and 2013 (Heslin & Elixhauser, 2016). Thus, it is evident that while overall

hospitalization is decreasing due to HIV infection, there is a growing number of older PLWH getting admitted into the hospital, which may create additional pressure on hospital inpatient care delivery. Decreasing trends of hospitalization were found in other studies as well (Buchacz et al., 2008; Zhao, Encinosa, & Hellinger, 2007). However, some studies suggested stable or increasing rates of hospitalization (Fleishman & Hellinger, 2003; Gebo, Diener-West, & Moore, 2001; H. Krentz, Dean, & Gill, 2006). The potential causes for this lack of continued decline in hospitalization rates include aging of PLWH, toxicity from long-term antiretroviral use, development of chronic and organ disease, development of multi-drug resistant viruses, and high prevalence of substance use (Crum-Cianflone et al., 2010).

2.17 Resource Utilization of PLWH in the United States

Although the introduction of HAART has substantially reduced hospitalization among PLWH in past several decades (S. Berry, Fleishman, Moore, & Gebo, 2016; Buchacz et al., 2008; Crum-Cianflone et al., 2010; Heslin & Elixhauser, 2016), hospitalizations are still reported to be elevated among PLWH compared to individuals hospitalized with non-HIV (Bachhuber & Southern, 2014; Shih, Chen, Rothman, & Hsieh, 2011). Besides, longer duration of hospital stays is more common among the PLWH compared to their non-infected counterparts (Akgün et al., 2013; Pearce et al., 2012). A recent study showed that symptomatic PLWH have a considerably longer duration of stay in the hospital than non-PLWH when asymptomatic PLWH's length of stay is similar to non-PLWH's hospital length of stays (Rowell-Cunsolo, Liu, Shen, Britton, & Larson, 2018). Longer inpatient length of stays places a substantive burden on hospital and health

insurance systems (Shih et al., 2011) because it is typically associated with higher resource utilization for treatment (Needham et al., 2003; Papi, Pontecorvi, & Setola, 2016).

2.18 Hospital Inpatient Resource Utilization by the Older PLWH

Generally, inpatient resource utilization shows a downward trend since the introduction of HAART. Analyzing U.S. hospital records data, one study reported that annual inpatient hospitalization rates and the number of inpatient days per year decreased in the United States between 2002 to 2007, while there was no significant change in hospital length of stay per admission (Yehia et al., 2010). However, while overall hospital admission rates decreased, PLWH still experienced higher utilization of inpatient and outpatient care compared to non-PLWH (Gebo et al., 2010). The aging of HIV in the United States may pose an increasing demand for inpatient health care services, as PLWH has increased risk for readmission and prolonged hospitalizations (S. Berry et al., 2016). Expected increases in inpatient utilization due to comorbidities, and factors related to aging may reduce as new antiretroviral treatments may have the potential to reduce the need for hospitalization (Yehia et al., 2010). Since HIV requires life-long treatment, and chronic use of ART, PLWH are likely to increase health care resource utilization substantially due to long-term toxicities of ART coupled with different comorbidities (Ward et al., 2020).

Other than the direct effect of HIV infection, variations in hospital length of stays are explained by the complications, complicated perineal closures, and the tendency for males to remain hospitalized longer than females (Leeds et al., 2016). Moreover, significant variations were observed in inpatient resource utilization across the patient's age, gender, race, and insurance (Fleishman et al., 2005; Yehia et al., 2010). Geographical variations in utilization patterns exist; for example, hospitalization and inpatient length of

stays are lower in Western states compared with states in the Northeast (Gornick, 1982; Weiss & Elixhauser, 2014). Another study result indicates that inpatient cost and length of stay vary significantly across states (Hellinger, 2004).

2.19 Costs of HIV Care in the United States

Lifetime costs of HIV care depend on the disease stage at which PLWH are diagnosed, initiate care, take ART, and the extent of ART adherence and retention in care (Farnham, 2010; Hellinger, 2006). As the life expectancy of PLWH increased, the economic burden of HIV has evolved with their increasing lifespan and cumulative higher medical costs over their lifetime (Schackman et al., 2015; Sloan et al., 2012). The estimated annual costs of care for PLWH in the United States are $19,912 in 2006 U.S. dollars ($23,000 in 2010 U.S. dollars) (Gebo et al., 2010), and discounted lifetime HIV treatment costs were $367,134 in 2009 U.S. dollars ($379,668 in 2010 U.S. dollars) (Center for Disease Control and Prevention, 2019c; Schackman et al., 2006). The costs for lifetime treatment based upon the number of new diagnoses were estimated to be $16.6 billion in 2009 (Center for Disease Control and Prevention, 2019c). Increased utilization of inpatient and outpatient care and antiretroviral medications of PLWH results in high costs of HIV care, and the costs increase as patients become more immunosuppressed (Gebo et al., 2010; NORC at the University of Chicago, 2016). Cost expenditures resulted from prescription medications are the largest part of this cost burden, and studies showed that costs of prescription medications are increasing over time (NORC at the University of Chicago, 2016; Ritchwood, Bishu, & Egede, 2017; Schackman et al., 2015). Some of the HIV case costs are likely due to the treatment of comorbidities not associated with HIV, especially, the higher costs of older PLWH arise from having multiple comorbid conditions. The costs

would likely continue to increase due to non-HIV related complications, including age-related diseases such as cardiovascular disease, cerebrovascular disease, and malignancies (Gebo et al., 2010).

2.20 Hospital Inpatient Costs of the Older PLWH

There are increasing concerns about the costs associated with lifetime treatment of the HIV infection, including costs associated with accessing medical care, treating comorbid conditions, and HIV medications. Due to the availability of HAART and fewer hospitalization for AIDS-defining illnesses, previous studies have projected lower health care costs (Harling & Wood, 2007; Hellinger, 1998; Meyer-Rath et al., 2013; Shapiro et al., 1999). However, the overall cost of HIV management has increased in recent years, and it is projected to increase further as PLWH are living longer with more HANA conditions (Ward et al., 2020). Since HIV treatment is a life-long process, and PLWH needs to take ART persistently, the cost of HIV management would be increased due to long-term ART toxicities and multiple comorbidities (Ward et al., 2020). The average cost of HIV care is consistently higher for older PLWH than younger PLWH (Gebo et al., 2010); the estimated direct cost of noninfectious comorbidities for PLWH age 60 years or above is two times than those aged less than 40 years ($21,280 vs. $10,588) (Guaraldi et al., 2013). Frequent and lengthy hospitalizations are common among some PLWH, which are associated with higher personal costs and healthcare expenditure (S. A. Berry et al., 2012; Bozzette et al., 2001; Guaraldi et al., 2013). With the aging of PLWH, despite a CD4 count equivalent to those of younger patients, older patients will account for a disproportionately higher burden of care and costs (H. Krentz & Gill, 2015). The reduction of total care cost observed in the increasing CD4 count was compensated by the increase

of total care cost with increased age (Guaraldi et al., 2013). The age-shift of PLWH in the United States increases the percentage of non-communicable disease among PLWH, which eventually increases the non-communicable disease treatment cost as the proportion of the total direct cost of HIV management (Smit et al., 2017).

2.21 Theoretical Background of the Study

DesHarnais et el.'s health outcome model represents that the patient's health outcome is the combined results of patient's physiological reserve, social conditions, health conditions for which patients get admitted, and provider performance (Figure 2.3) (DesHarnais, Chesney, Wroblewski, Fleming, & McMahon Jr, 1988). They described patient's demographic characteristics (e.g., age, sex) and health conditions (e.g., health conditions, comorbid conditions) as patients' physiological reserve, and living conditions, financial situation, and the ability for self-care as patient's social condition. Moreover, they classified the reason for hospital admission (e.g., principal diagnosis, surgical prognosis) as immediate problem or illness. They also discussed provider performances (e.g., adequacy of staff, plant technical performance, interpersonal relationship) as predictors of patient's health outcome (Figure 2.3).

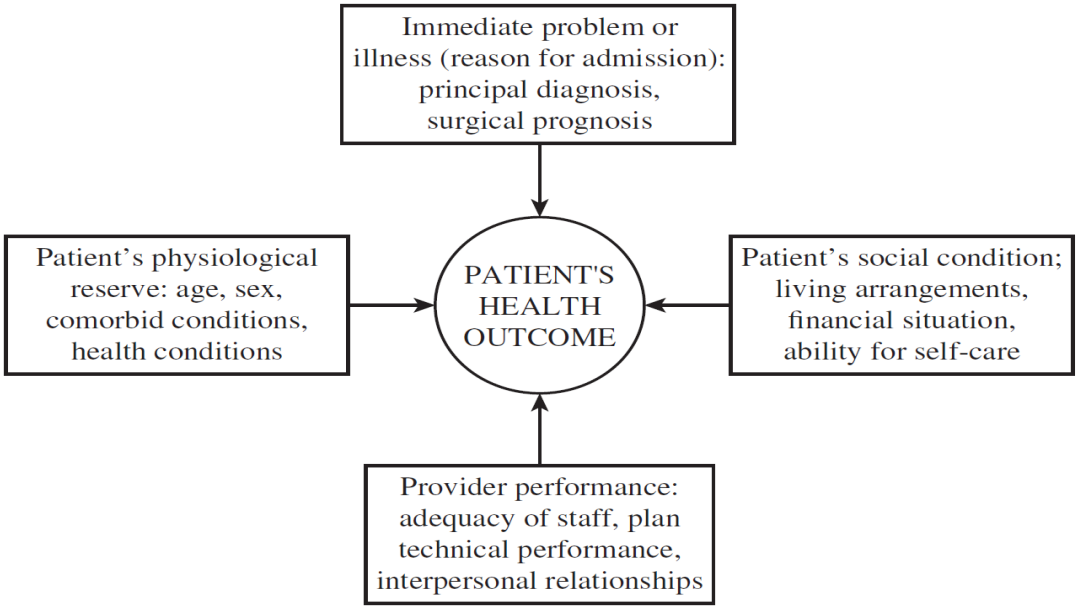


Figure 2. 3 Schematic diagram of some factors related to health outcomes (DesHarnais et al., 1988).

From the perspective of the health care system, Donabedian structure-process-outcome relationship is linear (Figure 2.4). Donabedian believed that the 'structure measures' influence 'process measures,' which in turn affect 'outcome measures.' Structure measures refer to the attributes of the service/provider, while process measures reflect the systems and processes used to deliver to produce desired outcomes (Donabedian, 2005).

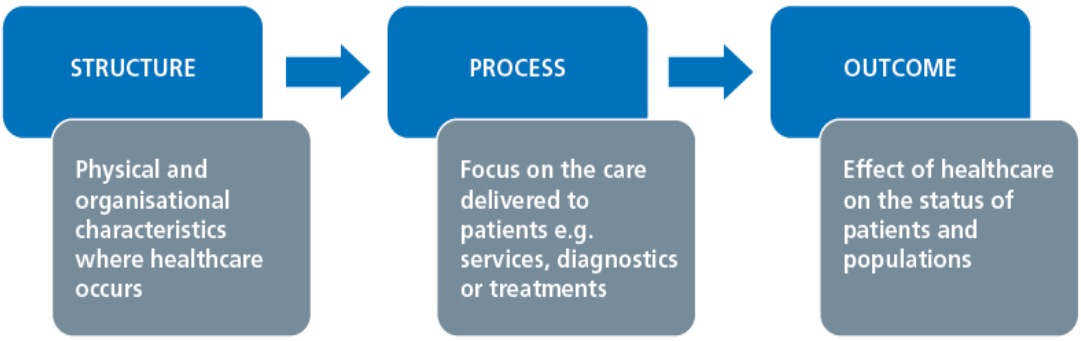


Figure 2. 4 The Donabedian model for quality of care (Donabedian, 2005).

2.22 Conceptual Framework of the Study

The conceptual framework for this study is built upon DesHarnais et el.'s health outcome model (DesHarnais et al., 1988) and modified for this study to incorporate the unidirectional relationship among aging of PLWH, comorbidities, and hospital outcomes as suggested in the literature. Inspired by the Donabedian model for quality of care (Donabedian, 2005), instead of placing patient's health outcomes in the center, the proposed framework described hospital outcomes, i.e., resource utilization and costs, as the byproduct of those linear interactions, along with patient demographics and facility-level characteristics.

Aging of PLWH: There are a growing number of older people due to the age-shift in the U.S. population who are somewhat at risk of HIV infection. Besides, the advent of HAART has substantially reduced AIDS-defining morbidity and mortality and improved the life expectancy of PLWH. Also, PLWH who take ART daily as prescribed, and keep an undetectable viral load have 'effectively no risk' of sexually transmitting HIV to their HIV-negative partners (HIV.gov, 2019b). These successes, aligned with the growing older at-risk population, led to the aging of PLWH in the United States (High et al., 2012; Pathai et al., 2013). However, the current study did not examine the interaction among early ART use, the growing at-risk older population, and the aging of PLWH. Instead, it investigates the impact of the aging PLWH on inpatient comorbidities, resource utilization, and costs compared to their non-PLWH counterparts. Development of some geriatric conditions, such as comorbidities, frailty, poorer cognitive functioning, depression, and other mental illness, might be hastened with advanced aging (Center for Disease Control and Prevention, 2018; Heslin & Elixhauser, 2006; HIV.gov, 2017).

Comorbidities: The prevalence of age-related chronic diseases such as cardiovascular diseases, cancer, osteoporosis, liver disease, renal disease, and neurocognitive decline, are increasingly common among PLWH with long-standing HIV infection (Gallant et al., 2017; High et al., 2012; Pathai et al., 2013; United States Senate, 2013). Thus, the aging of PLWH may increase the risks of multiple comorbidities during hospital stays, which may eventually direct hospital resource utilization and costs of the patients.

Hospital resource utilization and costs: Primary diagnosis and inpatient comorbidity burden determine the hospital resource utilization and costs of the patients. Patient-level characteristics such as age, gender, race/ethnicity, health insurance, location, and type of hospitalization are essential predictors of inpatient resource use and costs of care (Fleishman et al., 2005; Yehia et al., 2010). Similarly, hospital-level characteristics such as teaching status, location, ownership, regions, and size of the hospital affect inpatient resource utilization and costs (Patel et al., 2018). Besides, the length of hospital stay, number, and types of procedures used during the hospital stay largely define the inpatient costs (Okunji, Daniel, & Frough, 2016) (Figure 2.5).

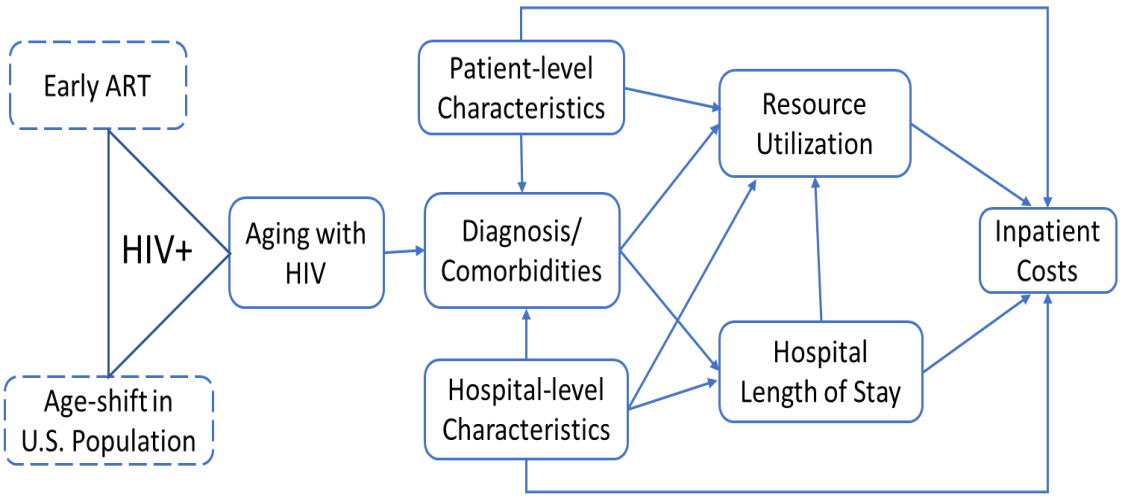


Figure 2. 5 Factors related to the patient's inpatient outcomes during the hospital stays in the United States (this study did not examine the content in the boxes with the dashed lines).

CHAPTER 3

METHODOLOGY

3.1 Data Source and Sample Description

The National (Nationwide) Inpatient Sample (NIS) data, 2003 through 2015, from Healthcare Cost and Utilization Project (HCUP), sponsored by Agency for Healthcare Research and Quality (AHRQ), were analyzed to assess comorbidity, care utilization, costs during the hospital stays in the U.S. hospital inpatient department. The NIS is the largest all-payer inpatient care database in the United States that collects approximately 20% stratified sample (more than 7 million hospital stays each year) from all discharges of U.S. community hospitals from 46 states and the District of Columbia (Agency for Healthcare Research and Quality, 2018b). Before 2012, NIS collected all discharge records from a 20% sample hospitals from each stratum; starting in 2012, NIS collects 20% discharges from all U.S. hospitals (Houchens, Ross, Elixhauser, & Jiang, 2014). The NIS includes short-term, non-Federal, general, and other community hospitals, excluding long-term care facilities, such as rehabilitation, psychiatric, and alcoholism, and chemical dependency hospitals. In the case of the NIS, the universe is all inpatient discharges from community hospitals in the United States, excluding rehabilitation hospitals beginning with 1998, and excluding long-term acute-care hospitals starting with 2012.

The unit of analysis in our study is hospital discharges from the hospital inpatient department. Discharge level weights provided with the NIS were used to produce national

estimates (Agency for Healthcare Research and Quality, 2018d). Further information about the sampling and dataset are available elsewhere (Agency for Healthcare Research and Quality, 2018b). An inpatient hospital stay is designated as HIV diagnosis if the Clinical Classification Software (CCS) code for HIV is five (5). The CCS enlisted International Classification of Diseases, 9th Edition, Clinical Modifications (ICD-9-CM) diagnosis codes into a smaller classification of clinically meaningful categories. For example, ICD-9-CM diagnosis codes for different stages of HIV (042, 0420, 0421, 0422, 0429, 0430, 0431, 0432, 0433, 0439, 0440, 0449, 07953, 27910, 27919, 79571, 7958, V08) was combined into CCS code 5, which indicates presence of HIV during hospital stays (Heslin & Elixhauser, 2006).

3.2 Inclusion and Exclusion Criteria

Hospital stays, which indicated neonatal or pregnant issues, and by younger than 18 years old, were excluded from the study. Since the HCUP shifted from ICD-9-CM to ICD-10-CM on October 1, 2015, this study excluded hospital discharges data from the fourth quarter of 2015 (October to December 2015), because the Elixhauser comorbidity index is still under development for ICD-10 coding (Hirode et al., 2020). We also excluded hospital length of stays reported as zero (LOS=0) because, in this case, patients discharged on the same day. Table 2.1 presents the total number of discharges collected in the NIS and the number of observations we analyzed each year. In paper 2, we use the subpopulation of major select HANA conditions, which are cardiovascular disease, liver disease, diabetes, cancer, and bone loss, to compare hospital resource use and costs of hospital stays.

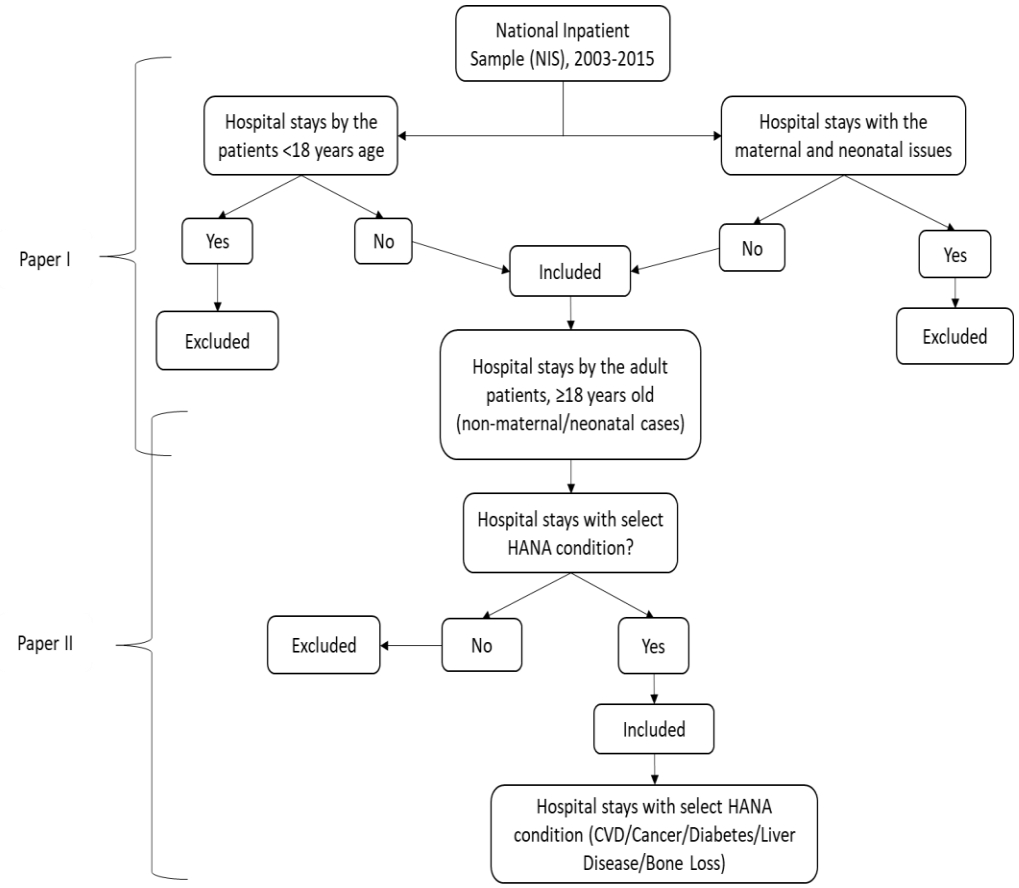


Figure 3. 1 Sample selection for the study.

Table 3. 1 Sample distribution over the years, 2003 to 2015.

Year	Total Unweighted Discharge	Sample Analyzed	Percentage
2003	7,977,728	5,551,718	69.59
2004	8,004,571	5,511,086	68.85
2005	7,995,048	5,508,807	68.90
2006	8,074,825	5,638,912	69.83
2007	8,043,415	5,516,862	68.59
2008	8,158,381	5,780,983	70.86
2009	7,810,762	5,537,613	70.90
2010	7,800,441	5,581,324	71.55
2011	8,023,590	5,840,700	72.79
2012	7,296,968	5,212,811	71.44
2013	7,119,563	5,077,899	71.32

2014	7,071,762	5,030,710	71.14
2015 (Q1-Q3)	5,377,732	3,844,261	71.48
Total	**98,754,786**	**69,633,686**	**70.51**

3.3 Study Variables

Outcome variables: The outcome variables of the study are the length of stay (number of days), the number of procedures used, and hospital inpatient costs. Total hospital charges were converted to costs using hospital-wide cost-to-charge ratios provided by HCUP from accounting reports of the Center for Medicare and Medicaid Services (Agency for Healthcare Research and Quality, 2018a). Hospital charges refer to the amount a hospital billed for the entire hospital stay, excluding professional (physician, anesthesiologist) fees. Costs reflect the actual expense incurred in the production of hospital services, including supplies, wages, and utility costs. All costs were adjusted for the inflation to the 2015 U.S. dollars using the Personal Health Care (PHC)- Hospital Care Index from the Centers for Medicare & Medicaid Services. The PHC-Hospital care index for 2015 was divided by each year's PHC index and multiplied these results with the respective year's costs to get the inflation-adjusted inpatient costs. The CMS Office of the Actuary constructs the PHC Index based on components of the Consumer Price Index-Medical care (CPI-M) and the Producer Price Index (PPI), and additional composite indices (Agency for Healthcare Research and Quality, 2019b). Moreover, various adjustments were made to make the costs variable comparable over the years suggested by the HCUP (Agency for Healthcare Research and Quality, 2019a).

Comorbidities: The Clinical Classifications Software (CCS), developed as part of the HCUP, were used to identify comorbid conditions from the discharge records. The CCS is a diagnosis and procedure categorization scheme based on the International

Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The ICD-9-CM's multitude of codes - over 14,000 diagnosis codes and 3,900 procedure codes - are collapsed into a smaller number of clinically meaningful categories that are sometimes more useful for representing descriptive statistics than are individual ICD-9-CM codes (Agency for Healthcare Research and Quality, 2017a). Elixhauser Comorbidity Software was used to describe the comorbidity burden of the patients (Agency for Healthcare Research and Quality, 2017b). Elixhauser Comorbidity Software assigns variables that identify comorbidities in hospital discharge records using the diagnosis coding of ICD-9-CM. We used a new index that produces 'a single numeric value' index score (readmission and mortality scores) that describes the comorbidity burden, and that may be more useful for multivariable analyses purpose (B. J. Moore, White, Washington, Coenen, & Elixhauser, 2017). With the help of an infectious disease domain expert and a detailed literature search, we identified five major HANA conditions based on the CCS codes, namely cardiovascular disease (CVD), cancer, diabetes, liver disease, and bone loss. A list of diseases and respective CCS codes of the specific conditions of these five major categories are described in Appendix A (Table A.1).

Resource Utilization: The total number of procedures used were counted as a function of inpatient resource utilization. Types of procedures during hospital stays were identified using ICD-9-CM procedure codes. We also describe the hospital length of stay (LOS) as a measure of resource utilization.

Patient-level Characteristics: Many studies in the area of aging collapsed 50 years and older into a single group (Krentz & Gill, 2015; Maciel et al., 2018; Vance, Mugavero, Willig, Raper, & Saag, 2011). We expanded patients' age to include more groups per

discharge as 18-34 years, 35-49 years, 50-64 years, and 65+ years, which enables us to examine trends between the traditional elderly group (65+ years) with the literature identified accelerated HIV aging group (50+ years). We also used the age variable as continuous to describe the changing likelihood of outcomes across independent variables. Also, we included patients' race/ethnicity, location, primary payer, median household income for ZIP code, admission source, and types of hospital stays.

Facility-level Characteristics: Hospital level characteristics include bed size (small, medium, large), location/teaching status (rural, urban non-teaching, urban teaching), control/ownership (public, private nonprofit/voluntary, private for-profit), region of the hospital (Northeast, Midwest, South, West), number of diagnoses, and disposition of the patients.

3.4 Ethical Considerations

Ethical considerations for using NIS data are ensured by the required HCUP Data User Agreement (DUA) training. The DUA has some requirements researchers need to follow to preserve patient rights, and that emphasized the responsibilities of the researchers while handling this dataset. HCUP Central Distributor removed all identifiable data from the NIS before releasing it to the researchers. Since NIS is non-identifiable secondary data, this study is waived from the human subject study by the University of South Carolina Institutional Review Board (#Pro00097307).

3.5 Analytical Approach

Using the analytic guidelines outlined by HCUP-NIS (Agency for Healthcare Research and Quality, 2018c), a survey-weighted analysis was conducted accounting for survey design complexity by using sampling weights (discharge weight). In trend analyses,

we used newly generated 'discharge trend weight' provided by the HCUP to adjust the NIS redesign applied in 2012 (Agency for Healthcare Research and Quality, 2015). In order to get the consistent yearly national rates, we used these new weights for 2003 to 2011, that are equivalent to normal discharge weights for 2012 and afterward. Data analysis was performed using SAS version 9.4 (Carry, NC) and Stata version 15 (StataCorp LLC, College Station, TX). The univariate, bivariate, and multivariable analyses were conducted to describe the hospital stays, examine the bivariate relationships, and determine the associations of HIV and age with the outcome variables, respectively.

Analysis for Paper 1: Since Paper 1 is a descriptive study, various univariate analyses were performed and presented using tables, charts, and graphs. First, we examined changes in patient and hospital-level characteristics of all hospital stays for the base year (2003), middle year (2009), and recent year (2015). Second, we calculated overall and age-specific hospitalization rates (per U.S. population) and described the yearly trends from 2003 to 2015. To calculate these rates, we divided the number of hospitalizations from the NIS by the number U.S. population in each age group collected from the U.S. Census Bureau (U.S. Census Bureau, 2020). We also calculated overall and age-specific hospitalization rates per PLWH by dividing the number of hospitalizations by the number of HIV cases (HIV prevalence) for each year, as reported by the CDC's HIV surveillance reports (CDC, 2020). Third, we also described yearly trends of hospital stays with HIV among all-listed diagnoses (Dx1-Dx30) and primary diagnosis only (Dx1). The formula for calculating the proportion of hospital stays with HIV (per 1,000) is:

Eqn. 1: Rate of hospital stays with HIV (per 1,000) = Number of hospital stays with HIV ÷ Total number of hospital stays×1000.

Fourth, we describe the top 20 primary diagnoses and procedures used during hospital stays for three years (2003, 2009, 2015) by HIV status. Finally, we described yearly trends of five major HANA conditions for all-listed diagnoses (Dx1-D30) and primary diagnoses (Dx1). The formula for calculating the percentage of particular HANA condition was:

Eqn. 2: Rate of particular HANA condition among hospital stays with HIV = Number of hospital stays with HANA ÷ Number of hospital stays with HIV ×100.

Eqn. 3: Rate of particular HANA condition among hospital stays without HIV = Number of hospital stays with HANA ÷ Number of hospital stays without HIV ×100.

We also report the age-specific percentages of HANA conditions and describe the trends from 2003 to 2015.

Analysis for Paper 2: Survey-weighted univariate, bivariate, and multivariable analyses were conducted using SAS version 9.4 (Carry, NC). First, we compared yearly trends of inpatient resource utilization and costs of HSWH and HSWOH. For descriptive analyses, we examined both mean and median to describe the overall patterns of resource utilization and costs. We found, means to be more sensitive to the extreme value of costs and LOS, so we reported the median values only (see Appendix B for mean charts). Second, we compared resource utilization and costs of HSWH and HSWOH across the age groups. For the descriptive purpose, we assessed the trends of differences between HSWH and HSWOH in terms of resource utilization and costs. The differences were calculated by subtracting resource utilization and costs of HSWOH from that of HSWH as shown in equation (1):

Eqn. 1: Difference in inpatient resource utilization/costs = inpatient resource utilization/costs for HSWH – inpatient resource utilization/costs for HSWOH

Third, we depicted yearly trends of differences in resource utilization and costs for hospital stays among the major five HANA conditions. Finally, multivariable modeling was performed to measure the association of the number of procedures, LOS, and costs for hospital stays with HIV and age, controlling for the patient- and hospital-level characteristics. Guided by previous studies using the NIS database (Enomoto, Gusani, Dillon, & Hollenbeak, 2014; Molloy, Martin, Moschetti, & Jevsevar, 2017; Perera, Armstrong, Sherrill, & Skrepnek, 2012; Zou et al., 2019), three Generalized Linear Models (GLMs) were fitted independently with the following outcomes: 1) number of procedures; 2) length of stay; 3) inpatient costs. These models were chosen because these three outcome variables were highly skewed and did not meet the normality assumption of the classical linear model. As the distribution of the number of procedures was observed over-dispersed (variance>mean) with numerous zeros (no procedures), a zero-inflated negative binomial regression model was fitted to determine the predictors of procedures used. Inpatient costs and length of stays were log-transformed and assessed using GLMs with gamma distribution and log link function to estimate the predictors of hospital costs and length of stays. We also ran and described these models for hospital stays with five major HANA conditions separately. To check the missing values, we reran these models keeping the missing observations considering them as 'not missing completely at random (NOMCAR),' and observed no difference with the main models. Statistical significance was assessed at alpha 0.01 due to the study's large sample size.

Model Equations:

Model for number of procedures:

Log (Number of procedures) = β_0 + β_1 HIV + β_2 Age + β_3 Female + β_4 Race/ethnicity + β_5 Primary Payer + β_6 Patient's location + β_7 Income + β_8 Weekend admission + β_9 Elective admission + β_{10} Hospital bed size + β_{11} Hospital teaching status + β_{12} Region + β_{13} Length of stay + β_{14} Comorbidity scores + β_{15} Year

Model for length of stays:

Log (Length of stay) = β_0 + β_1 HIV + β_2 Age + β_3 Female + β_4 Race/ethnicity + β_5 Primary Payer + β_6 Patient's location + β_7 Income + β_8 Weekend admission + β_9 Elective admission + β_{10} Hospital bed size + β_{11} Hospital teaching status + β_{12} Region + β_{13} Number of Procedures + β_{14} Comorbidity scores + β_{15} Year

Model for inpatient costs:

Log (Costs) = β_0 + β_1 HIV + β_2 Age + β_3 Female + β_4 Race/ethnicity + β_5 Primary Payer + β_6 Patient's location + β_7 Income + β_8 Weekend admission + β_9 Elective admission + β_{10} Hospital bed size + β_{11} Hospital teaching status + β_{12} Region + β_{13} Number of Procedures + β_{14} Length of stay + β_{15} Comorbidity scores + β_{16} Year

Given the nature of the data, it is plausible that patients hospitalized within one hospital are more similar than patients within another hospital. Also, multiple inpatient visits made by the same patients could result in correlated outcomes within the hospitals. Therefore, to accommodate these within-subject correlations and between-subject heterogeneity, generalized linear mixed modeling (GLMM) approach could be the best to incorporate hospital-level random effects. However, due to very large size of the data and complexity of survey-weighted mixed-effect modeling, it is beyond the capacity of

statistical software we used in this study (SAS 9.4 and Stata 15). To check how this limitation could affect our study results, we ran GLMMs using several smaller subsamples (10% random sample) as a sensitivity analysis and identified minimal hospital-level random effects. Considering the circumstances, we performed survey-weighted GLMs suggested by several previous peer-reviewed journal articles.

CHAPTER 4

PAPER 1: AGING WITH HIV IN THE UNITED STATES: CHANGING TRENDS OF INPATIENT STAYS AND COMORBIDITIES IN SHORT-STAY HOSPITALS, 2003 TO 2015[1]

[1] Siddiqi, K. A., Olatosi, B., Ostermann, J., Zhang, J., & Khan, M. M. To be submitted to *Journal of Acquired Immune Deficiency Syndromes*.

4.1 Abstract

Background: Due to advances in Antiretroviral Therapy (ART), people living with HIV (PLWH) live longer in the United States. Aging prolongs exposure to HIV and antiretroviral drugs, which could lead to an elevated risk of developing multiple age-related comorbidities [HIV Associated Non-AIDS (HANA) conditions], earlier for PLWH. This could also lead PLWH to have higher hospitalization with increased HANA comorbidities. Few studies have explored the aging of PLWH and its impact on hospital stays. This study examined trends for characteristics and comorbidities of hospital stays with HIV (HSWH) compared to hospital stays without HIV (HSWOH).

Methods: Thirteen years of pooled data of National Inpatient Sample (NIS) from the Health Care Utilization Project (HCUP), 2003 through 2015, were analyzed to describe the trends. We excluded hospital stays for patients less than 18 years old, neonatal, pregnancy, and same-day discharge from our analysis. Using SAS 9.4, we performed survey-weighted descriptive analyses using sampling weights provided by HCUP.

Results: Over the study period, the proportions of HSWH remained stable (0.81%), but the proportions of HSWH among the older increased gradually. The mean age difference between HSWH and HSWOH reduced substantially. Hospitalization rates decreased from 105 to 89 per 100,000 U.S. population over the years, while the rates for the older population aged 55-64 and 65+ years increased substantially. Overall, HSWH had fewer HANA conditions than hospital stays without HIV (HSWOH). The proportions of cardiovascular disease (CVD) and cancer increased disproportionately over time among HSWH; CVD and liver disease increased among aged 65+ years, and CVD and cancer increased among aged 50-64 years.

Conclusions: Consistent with the aging of PLWH, higher HSWH and HANA comorbidities were observed among older HIV patients, which suggest increased future hospital resource utilization for HSWH. Appropriate training of health care providers may be essential to managing increased health burdens of older PLWH, and associated complications during hospital stay in the United States.

Keywords: HIV, Aging, Inpatient Stay, Comorbidities, United States.

4.2 Introduction

Today, Human Immunodeficiency Virus (HIV) infection is a manageable chronic condition due to advanced highly active antiretroviral treatment (HAART). People living with HIV (PLWH) now live longer due to early diagnosis, engagement, and retention in HIV medical care (National Institute of Allergy and Infectious Diseases, 2018; Pebody, 2018). This change has resulted in life expectancy gains for PLWH, with many aging and living longer with HIV. Currently, almost half of all PLWH are 50 years or older (Center for Disease Control and Prevention, 2018). This proportion is projected to increase to 70% by 2030 (Wing, 2017). The interaction of HIV with the aging process and aging-related comorbidities is expected since the virus consistently activates immune cells that make individuals susceptible to inflammatory induced diseases and diminishes the capacity to fight other diseases (Fauci et al., 2010).

Due to increased life expectancy for PLWH, age-related chronic conditions are foremost health concerns after viral load suppression is achieved. Along with aging, prolonged exposure to both HIV and antiretroviral drugs may increase the risk of age-related chronic illnesses, commonly called HIV Associated Non-AIDS (HANA) conditions. The HANA chronic diseases include cardiovascular, liver, kidney, bone, and

lung disease and non-HIV associated cancers (Gallant et al., 2017; Guaraldi et al., 2011; Schouten et al., 2014). Studies already show a higher prevalence of multimorbidity among PLWH than in the general population (Guaraldi et al., 2011; Maciel et al., 2018; Rodriguez-Penney et al., 2013). The higher prevalence of HANA among PLWH raises the question of whether HIV infection is accelerating aging or acting as an additional risk factor for comorbidity development. While it is difficult to determine whether HIV accelerates the aging process, or is merely an additional risk factor for chronic conditions, research shows the development of geriatric clinical conditions is hastened with advanced aging (High et al., 2012; Pathai et al., 2013). A previous study showed that the rates of hospitalization with HIV diagnosis increased for the older PLWH population (Heslin & Elixhauser, 2016). With the high prevalence of physical and mental health comorbidities and lack of social supports, aging PLWH may demand increased inpatient care services in the United States (Matthew Harris et al., 2015).

Assessing and describing the changing patterns of hospitalization and comorbidity burdens of PLWH during hospital stays is essential to planning for future inpatient care resource demand posed by the aging PLWH. Gaps in the literature exist for trends and differences in characteristics and comorbidities for hospital stays with HIV (HSWH), and hospital stays without HIV (HSWOH) in the United States. To our knowledge, studies assessing the trends focused on major age-related comorbidities using nationally representative U.S. inpatient data are few. This study examines and describes the characteristics and trends of HSWH compared to HSWOH using the national inpatient sample (NIS). This study also describes comorbidity trends in HSWH compared to

HSWOH across age groups of the patients. Investigating the recent trends of HSWH and co-occurring HANA conditions is important for planning purposes.

4.3 Methods

4.3.1 Data Source and Sample

This study pooled data from the National Inpatient Sample (NIS) data, 2003 through 2015 from the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest all-payer inpatient care database that contains hospital discharge records (more than 7 million hospital stays each year) of the U.S. community hospitals in 46 states and the District of Columbia (Agency for Healthcare Research and Quality, 2018b). The NIS includes short-term, nonfederal, general, and other community hospitals. It excludes long-term care facilities, such as rehabilitation, psychiatric, alcoholism, and chemical dependency hospitals. Prior to 2012, NIS collected all discharge records from a 20% sample hospitals from each stratum; starting in 2012, NIS collects 20% discharges from all U.S. hospitals (Houchens et al., 2014). This was modified again in 2015 to reflect new ICD-10 codes. Further information about the sampling and dataset changes are available elsewhere (Agency for Healthcare Research and Quality, 2018b).

The unit of analysis in this study is hospital stay from the U.S. inpatient department. We used discharge level weights, available through the HCUP-US website, to produce nationally representative estimates (Agency for Healthcare Research and Quality, 2018d). Hospital stays, which indicated neonatal or pregnancy issues, and by younger than 18 years old, were excluded from the study. We also excluded hospital length of stays (LOS) reported as zero (LOS=0) because this indicated such patients got discharged on the same day. Since the HCUP shifted from ICD-9-CM to ICD-10-CM on October 1, 2015, this

study excluded hospital discharges data from the fourth quarter of 2015 (October to December 2015) because the Elixhauser comorbidity index is still under development for ICD-10 coding (Hirode et al., 2020).

4.3.2 Study Variables

We used the Clinical Classifications Software (CCS) developed for HCUP to identify comorbidities and procedures from hospital stays. The CCS is a diagnosis and procedure categorization scheme based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (Healthcare Cost and Utilization Project, 2017). An inpatient hospital stay was designated an HIV associated hospital stay if the CCS code for HIV is 5 (ICD-9-CM codes: 042, 0420, 0421, 0422, 0429, 0430, 0431, 0432, 0433, 0439, 0440, 0449, 07953, 27910, 27919, 79571, 7958, V08) (Heslin & Elixhauser, 2006). With the help of an infectious disease domain expert and literature search, we identified five major HANA conditions based on the CCS codes, namely cardiovascular disease (CVD), cancer, diabetes, liver disease, and bone loss. The name and CCS codes for specific conditions of these five major categories are described in Appendix A (Table A.1).

Patient-level Characteristics: Many HIV related aging studies collapsed 50 years and older into a single age group (H. Krentz & Gill, 2015; Maciel et al., 2018; Vance, Mugavero, Willig, Raper, & Saag, 2011). We expanded the patient's age to include more groups per hospital stay as 18-34 years, 35-49 years, 50-64 years, and 65+ years. We also included patients' sex, race/ethnicity, location, primary payer, and median household income by ZIP code.

Facility-level Characteristics: Hospital level characteristics examined included admission source, type of admission, the number of diagnoses, patient disposition at

discharge, bed size (small, medium, large), location/teaching status (rural, urban non-teaching, urban teaching), control/ownership (public, private non-profit/voluntary, private for-profit), and geographic region (Northeast, Midwest, South, West).

Resource Utilization: The total number of procedures used and hospital length of stay (LOS) were counted as a function of inpatient resource utilization. Types of procedures during hospital stays were identified using ICD-9-CM procedure codes. The average costs per hospital stay were also measured by converting total charges to costs using hospital-wide cost-to-charge ratios provided by HCUP from accounting reports of the Center for Medicare and Medicaid Services (Agency for Healthcare Research and Quality, 2018a). Charges and costs were adjusted for the inflation to the 2015 U.S. dollars using the Personal Health Care (PHC)- Medical Care Index from the Centers for Medicare & Medicaid Services (Agency for Healthcare Research and Quality, 2019b).

4.3.3 Ethical Statement

Ethical considerations for using NIS data are ensured by the required HCUP Data User Agreement (DUA) training. HCUP Central Distributor removed all identifiable data from the NIS before releasing it to the researchers. This study was deemed a non-human subject study by the University of South Carolina Institutional Review Board (#Pro00097307).

4.3.4 Data Analysis

Using the analytic guidelines outlined by HCUP-NIS (Agency for Healthcare Research and Quality, 2018c) (Healthcare Cost and Utilization Project, 2018b), a survey-weighted analysis was performed accounting for survey design complexity by using sampling weights (discharge weight). To adjust the NIS redesign applied in 2012, we used

newly generated 'discharge trend weight' provided by the HCUP for 2003 to 2011 to get the consistent yearly national rates (Agency for Healthcare Research and Quality, 2015). Descriptive analyses were conducted using SAS version 9.4 (Carry, NC). First, we examined changes in patient- and hospital-level characteristics of all hospital stays for the base year (2003), middle year (2009), and recent year (2015). Second, we calculated overall and age-specific hospitalization rates (per U.S. population) and described the yearly trends from 2003 to 2015. To calculate these rates, we divided the number of hospitalizations from the NIS by the number U.S. population in each age group collected from the U.S. Census Bureau (U.S. Census Bureau, 2020). We also calculated overall and age-specific hospitalization rates per PLWH by dividing the number of hospitalizations by the number of HIV cases for each year (HIV prevalence), as reported by the CDC's HIV surveillance reports (Center for Disease Control and Prevention, 2020a). Third, we also described yearly trends of hospital stays with HIV among all diagnoses (Dx1-Dx30) and principal diagnosis only (Dx1). The formula for calculating the proportion of HSWH (per 1,000) is:

Eqn. 1: Rate of HSWH (per 1,000) = Number of hospital stays with HIV ÷ Total number of hospital stays×1000.

Fourth, we described the top 20 principal diagnoses and procedures used during hospital stays for three years (2003, 2009, 2015) by HIV status. Finally, we described yearly trends of five major HANA conditions for all diagnoses (Dx1-D30) and principal diagnoses (Dx1). The formula for calculating the percentage of particular HANA condition was:

Eqn. 2: Rate of particular HANA condition among HSWH = Number of hospital stays with HANA ÷ Number of hospital stays with HIV ×100.

Eqn. 3: Rate of particular HANA condition among HSWOH = Number of hospital stays with HANA ÷ Number of hospital stays without HIV ×100.

We also report the age-specific percentages of HANA conditions and describe the trends from 2003 to 2015.

4.4 Results

Table 4.1 shows patient and hospital-level attributes of the hospital stays with- and without HIV (HSWH and HSWOH) for the baseline year (2003), middle year (2009), and final year (2015) of the study period. Some variables which were not available throughout the study period are presented in a supplement table in Appendix A (Table A.2).

4.4.1 Patient-level Characteristics of Hospital Stays

In table 4.1, the proportion for HSWH increased slightly in 2009 (0.85%) compared to baseline 2003 (0.81%) and 2015 (0.81%). The overall mean age difference between HSWH and HSWOH decreased over the study period. The change in mean age difference was 19 years (61.82 vs. 43.09) in 2003, 15 years (61.83 vs. 46.49) in 2009, and 13 years (62.25 vs. 49.17) in 2015. The proportion of HSWH for older age groups increased from 2003 to 2015 but decreased for the younger age groups. From 2003 to 2015, HSWH increased by 22.25% for ages 50-64 years and 6.52% for ages 65 or older. Males constituted the majority of HSWH, and the proportions were unchanged across most study years. Differential changes were also observed by race and ethnicity. The proportion of Whites with an HSWH increased in 2015 compared to baseline. Conversely, decreases were observed for Hispanics for 2015 compared to baseline. Overall, the percentage of HSWH for lowest-income area residents (0-25th percentile) increased slightly from 2003 to 2015. Medicare payments for HSWH increased from the baseline year 2003 (27.10%) to 34.87%

for 2015. By rurality, HSWH increased for both small metropolitan areas and rural residents (Table 4.1).

4.4.2 Hospital-level Characteristics of Hospital Stays

In table 4.1, the median number of diagnoses increased over the study period for both types of hospital stays. Overall, the proportion of discharges to long-term care (home health care, and SNF, intermediate care, and other) increased, while home discharge (routine), and death during hospital stay decreased for both types of hospital stays. The proportion of HSWH decreased in government (nonfederal) hospitals but increased in private non-profit hospitals. HSWH also decreased in rural and urban non-teaching hospitals but increased in urban teaching hospitals. HSWH in Northeast hospitals decreased from 2003 to 2015; compared to increases experienced in other regions. Compared to 2003, the proportion of hospital stays in 'small bed size' hospitals increased in 2015 for all hospital stays; but decreased in 'large bed size' hospitals.

In terms of hospital resource use, slight changes occurred in the median number of procedures used during hospital stays from 2003 to 2015. However, the median length of stay (LOS) decreased for both types of hospital stays over the study period, with the most substantial decrease observed for HSWH. The median total hospital charges per hospital stay increased for both types of hospital stays over the years from 2003 to 2015 in terms of U.S. dollars, but the increases were relatively lower among HSWH. Inpatient costs per hospital stay increased for HSWOH, while it was decreased slightly for HSWH over the study years (Table 4.1).

4.4.3 Population-based Hospitalization Rates, 2003 to 2015

Figure 4.1 presents the yearly trends of hospital inpatient stays with HIV diagnosis per 100,000 U.S. adult population by age groups, 2003 to 2015. Overall hospitalization rates decreased over time (105 to 89 per 100,000), while hospitalization rates among older age groups increased. Hospitalization rates increased from 70 to 126 hospitalizations per 100,000 among ages 55-64 years and from 17 to 42 hospitalization per 100,000 among ages 65+ years.

Figure 4.2A represents the yearly trends of the estimated prevalence of HIV cases, the total number of hospitalizations by PLWH, and rates of hospitalization among PLWH (per 100 PLWH). Figure 4.2B shows yearly trends of hospitalization rates for PLWH by age groups. In Figure 4.2A, the prevalence of HIV increased over the study period, while hospital stays decreased over time. Hospitalization rates decreased from 51 hospitalizations per 100 PLWH in 2003 to 21 hospitalizations per 100 PLWH in 2015. Figure 4.2B shows the hospitalization rate per 100 PLWH decreased among all age groups, and the decreases were a little higher among older age groups (50-64 and 65+years).

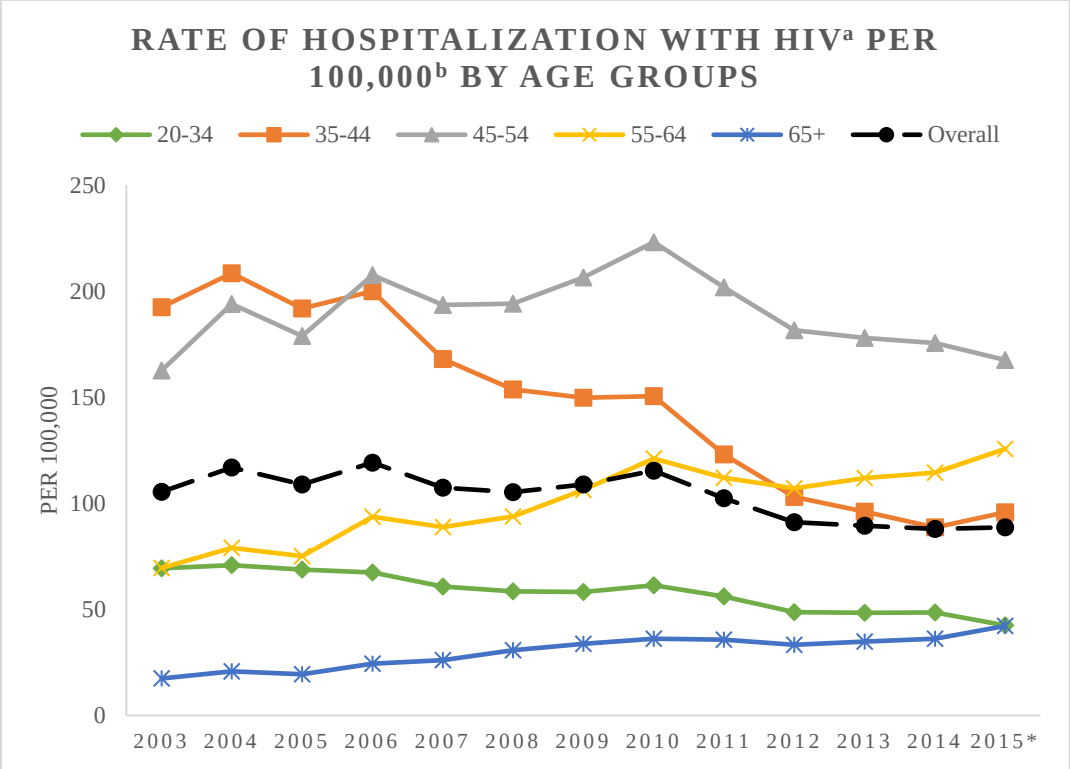


Figure 4. 1 Trends of hospital inpatient stays including HIV per 100,000 adult population by age group (years), 200 3 to 2015

*Total number of hospitalizations in 2015 is for the first three quarters (January to September), however, the approximate rates were calculated by multiplying the number of hospital stays by 4/3 to make the rates consistent with other years.

[a]Excludes hospital stays by less than 18 years old, same-day discharges (LOS=0), and that with a diagnosis code for pregnancy, labor, delivery, or neonatal cases.

[b] Source: Population estimates, U.S. Census Bureau.

Table 4. 1 Patient and hospital-level characteristics of hospital stays, 2003, 2009 and 2015.

	2003				2009			
	HIV-		HIV+		HIV-		HIV+	
Characteristics	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**
Overall	5,505,953	99.19	45,765	**0.81**	5490815	99.15	46798	**0.85**
Patient-level characteristics								
Age (years**): mean**	61.82		43.09		61.83		46.49	
Age groups								
18-35 years	557,279	10.12	10,068	21.74	549,244	9.99	7,919	16.69
36-49 years	960,111	17.39	24,864	54.53	876,843	15.95	20,529	43.97
50-64 years	1,281,050	23.23	9,683	**21.21**	1,437,936	26.14	15,981	**34.27**
65+years	2,707,513	49.26	1,150	**2.52**	2,626,792	47.92	12,086	**5.07**
Sex								
Male	2,449,236	44.61	30,368	66.41	2,521,382	45.97	31,952	68.17
Female	3,045,870	55.39	15,384	33.59	2,962,828	54.03	14,840	31.83
Race/ethnicity								
White	2,919,208	72.38	10,277	**26.32**	3,351,372	71.88	12,068	**27.93**
African American	550,959	13.43	21,367	53.73	613,423	13.22	21,835	51.11
Hispanic	393,636	9.66	6,057	**15.84**	410,878	8.79	5,776	**13.69**
Others	180,402	4.53	1,525	4.11	280,300	6.11	15,859	7.27
Median Household Income (by ZIP) [a]								
0-25th percentile	1,487,772	27.90	22,535	**50.84**	1,527,832	28.69	17,289	47.35

26th to 50th percentile (median)	1,443,833	27.03	10,677	23.80	1,440,380	26.90	8,955	24.42
51st to 75th percentile	1,345,908	24.87	7,223	16.22	1,262,138	23.61	6,350	17.34
76th to 100th percentile	1,092,732	20.20	4,048	9.14	1,100,768	20.79	3,964	10.90
Primary Payer								
Medicare	2,889,719	52.67	12,368	**27.10**	2,829,843	51.74	13,923	29.57
Medicaid	514,786	9.44	18,325	40.64	575,094	10.55	18,017	39.13
Private including HMO	1,650,985	29.94	8,052	17.67	1,536,599	27.95	7,143	15.18
Self-pay	235,008	4.25	3,721	8.09	316,757	5.77	5,172	10.88
Others (incl. No charge)	179,581	3.28	2,346	5.06	220,649	3.99	2,460	5.24
Patients' location (rurality)[b]								
Large metropolitan	2,980,732	53.96	35,173	**77.60**	2,815,152	52.81	26,687	**73.85**
Small metropolitan	1,461,439	26.18	7,386	**16.09**	1,467,281	27.18	6,986	**19.27**
Micropolitan	583,022	11.33	1,955	4.44	653,931	12.06	1,609	4.51
Rural	449,097	8.54	834	**1.87**	422,670	7.95	847	**2.37**
Hospital-level characteristics								
Weekend admission								
No	4,475,102	81.25	36,124	78.94	4,430,866	80.68	36,833	78.74
Yes	1,030,851	18.75	9,641	21.06	1,059,949	19.32	9,965	21.26
Elective admission								
Non-elective	4,041,645	73.75	40,579	88.95	4,199,449	76.75	42,158	90.31
Elective	1,443,258	26.25	5,097	11.05	1,279,180	23.25	4,538	9.69
# of Diagnoses (median)	6.43		6.98		9.25		9.59	
Disposition of patient								

Routine	3,756,366	68.37	32740	**71.63**	3,499,873	63.63	33,186	**70.90**
Transfer to short term hospital	137,019	2.53	754	1.68	128,877	2.37	812	1.74
Other transfers: SNF, intermediate care, and other	869,655	15.90	4,680	**10.21**	963,251	17.62	4,881	**10.45**
Home health care	511,715	9.37	3,171	**6.94**	703,418	12.86	3,968	**8.51**
AMA	49,899	0.91	2,312	5.11	56,715	1.05	2,461	5.36
Died in hospital	156,802	2.85	1,996	**4.38**	131,828	2.40	1,404	**2.98**
Bed size								
Small	669,941	11.55	3,535	**7.41**	687,422	12.56	4,366	**9.04**
Medium	1,441,946	25.67	11,456	25.08	1,271,362	23.85	10,852	23.47
Large	339,1421	62.78	30,774	**67.51**	3,433,043	63.60	30,662	**67.48**
Control/ownership[c]								
Government, nonfederal	Same category not available				685,391	12.73	10,668	**23.16**
Private, non-profit					3,932,248	72.74	29,356	**63.77**
Private, invest-own					774,188	14.53	5,856	13.07
Location/teaching status								
Rural	815,094	16.22	1,800	**4.31**	687,160	12.67	1,449	**3.16**
Urban non-teaching	2,417,692	42.38	14,057	**29.44**	2,316,809	43.76	12,246	**27.22**
Urban teaching	2,270,522	41.39	29,908	**66.24**	2,387,858	43.57	162,922	**69.61**
Region								
Northeast	1,127,753	20.86	15,546	**35.38**	1,074,789	20.51	16,507	**37.40**
Midwest	125,5442	23.56	4,790	10.87	1,313,733	23.80	5,718	11.88
South	221,1067	38.39	21,468	44.23	2,096,444	38.13	19,578	40.35

West	911,691	17.19	3,961	9.53	1,005,849	17.56	4,995	10.36
Hospital resource use (median)								
# of Procedures	0.41		0.38		0.45		0.33	
Length of stay (# of days)	3.0		4.09		2.90		3.66	
Total charges per hospital stay (US$)	19,049		22,697		24,423		25,733	
Costs per hospital stay (US$)	7530		8511		7,934		7,787	

(a) Since the quartile median income updates annually, the 4 quartiles vary by year. The 4 income quartiles indicates the poorest to wealthiest populations: 2003 (1-35,999; 36,000-44,999; 45,000-59,999; 60,000+), 2009 (1-39,999; 40,000-49,999; 50,000-65,999; 66,000+), 2015 (1 - 41,999; 42,000 - 51,999; 52,000 - 67,999; 68,000+).

(b) Large metropolitan areas include central counties of metro areas (>1 million) and fringe counties of metro areas (≥1 million), and small metropolitan areas contain counties in metro areas with 50,000-999,000 population. See methods section for details.

(c) Categories were dissimilar, therefore incomparable over the study periods.

[ł] This study analyzed data for quarter 1 to quarter 3 (January to September 2015), to avoid the transition in ICD codes from ICD-9-CM to ICD-10-CM effective on October 1, 2015.

Table 4. 1 Patient and hospital-level characteristics of hospital stays, 2003-2015 (continued).

	2009				2015 (Q1-Q3)[1]			
	HIV-		HIV+		HIV-		HIV+	
Characteristics	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**
Overall	5,490,815	99.15	46,798	**0.85**	3,813,082	99.19	31,179	**0.81**
Patient-level characteristics								
Age (years**): mean**	61.83		46.49		62.25		49.17	
Age groups								
18-35 years	549,244	9.99	7,919	16.69	380,277	9.97	4,672	14.98
36-49 years	876,843	15.95	20,529	43.97	510,302	13.38	10,092	32.37
50-64 years	1,437,936	26.14	15,981	**34.27**	1,047,744	27.48	13,583	**43.56**
65+years	2,626,792	47.92	12,086	**5.07**	1,874,759	49.17	2,832	**9.08**
Sex								
Male	2,521,382	45.97	31,952	68.17	1,816,785	47.65	21,046	67.51
Female	2,962,828	54.03	14,840	31.83	1,995,853	52.35	10,127	32.49
Race/ethnicity								
White	3,351,372	71.88	12,068	**27.93**	2,555,019	66.94	8,929	**29.35**
African American	613,423	13.22	21,835	51.11	542,448	14.98	16,399	53.90
Hispanic	410,878	8.79	5,776	**13.69**	331,731	9.16	3,608	**11.86**
Others	280,300	6.11	15,859	7.27	192,682	5.32	1,489	4.89
Median Household Income (by ZIP) [a]								
0-25th percentile	1,527,832	28.69	17,289	47.35	1,171,158	31.35	13,642	**52.69**

26th to 50th percentile (median)	1,440,380	26.90	8,955	24.42	931,721	24.94	5,338	20.62
51st to 75th percentile	1,262,138	23.61	6,350	17.34	892,995	23.90	4,259	16.45
76th to 100th percentile	1,100,768	20.79	3,964	10.90	740,126	19.81	2,651	10.24
Primary Payer								
Medicare	2,829,843	51.74	13,923	29.57	2,072,499	54.43	10,848	**34.87**
Medicaid	575,094	10.55	18,017	39.13	535,590	14.07	12,112	38.94
Private including HMO	1,536,599	27.95	7,143	15.18	925,120	24.30	5,145	16.54
Self-pay	316,757	5.77	5,172	10.88	149,438	3.92	1,961	6.30
Others (incl. No charge)	220,649	3.99	2,460	5.24	125,145	3.29	1,040	3.34
Patients' location (rurality)[b]								
Large metropolitan	2,815,152	52.81	26,687	**73.85**	1,998,260	52.60	18,541	**70.59**
Small metropolitan	1,467,281	27.18	6,986	**19.27**	1,148,202	30.22	5,938	**22.61**
Micropolitan	653,931	12.06	1,609	4.51	366,952	9.66	1,128	4.29
Rural	422,670	7.95	847	**2.37**	285,792	7.52	658	**2.51**
Hospital-level characteristics								
Weekend admission								
No	4,430,866	80.68	36,833	78.74	3,031,049	79.49	24,286	77.89
Yes	1,059,949	19.32	9,965	21.26	782,033	20.51	6,893	22.11
Elective admission								
Non-elective	4,199,449	76.75	42,158	90.31	3,008,362	79.18	27,939	89.84
Elective	1,279,180	23.25	4,538	9.69	791,065	20.82	3,159	10.16
# of Diagnoses (median)	9.25		9.59		12.28		13.09	
Disposition of patient								

Routine	3,499,873	63.63	33,186	**70.90**	2,262,064	59.37	21,209	**68.06**
Transfer to short term hospital	128,877	2.37	812	1.74	79,269	2.08	547	1.76
Other transfers: SNF, intermediate care, and other	963,251	17.62	4,881	**10.45**	740,064	19.42	3,794	**12.18**
Home health care	703,418	12.86	3,968	**8.51**	588,553	15.45	3,433	**11.02**
AMA	56,715	1.05	2,461	5.36	49,785	1.31	1,421	4.56
Died in hospital	131,828	2.40	1,404	**2.98**	89,970	2.36	751	**2.41**
Bed size								
Small	687,422	12.56	4,366	**9.04**	712,289	18.68	4,629	**14.85**
Medium	1,271,362	23.85	10,852	23.47	1,121,600	29.41	8,675	27.82
Large	3,433,043	63.60	30,662	**67.48**	1,979,193	51.91	17,875	**57.33**
Control/ownership[c]								
Government, nonfederal	685,391	12.73	10,668	**23.16**	455,238	11.94	5,766	**18.49**
Private, non-profit	3,932,248	72.74	29,356	**63.77**	2,773,865	72.75	21,117	**67.73**
Private, invest-own	774,188	14.53	5,856	13.07	583,979	15.32	4,296	13.78
Location/teaching status								
Rural	687,160	12.67	1,449	**3.16**	372,376	9.77	951	**3.05**
Urban non-teaching	2,316,809	43.76	12,246	**27.22**	1,054,430	27.65	5,221	**16.75**
Urban teaching	2,387,858	43.57	162,922	**69.61**	2,386,276	62.58	25,007	**80.20**
Region								
Northeast	1,074,789	20.51	16,507	**37.40**	733,871	19.25	8,726	**27.99**
Midwest	1,313,733	23.80	5,718	11.88	871,084	22.84	4,131	13.25
South	2,096,444	38.13	19,578	40.35	1,505,618	39.49	14,827	47.55

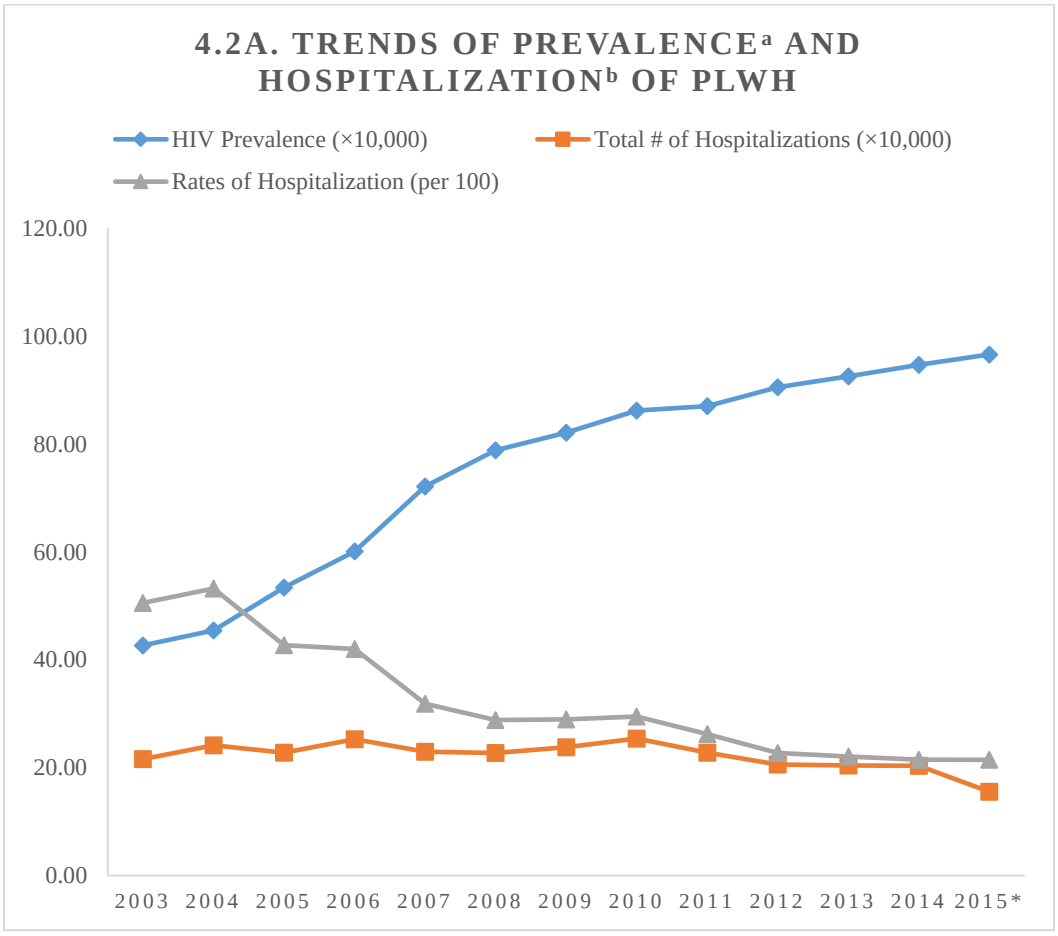
West	1,005,849	17.56	4,995	10.36	702,509	18.42	3,495	11.21
Hospital resource use (median)								
# of Procedures	0.45		0.33		0.40		0.40	
Length of stay (# of days)	2.90		3.66		2.94		3.55	
Total charges per hospital stay (US$)	24,423		25,733		31,310		31,498	
Costs per hospital stay (US$)	7,934		7,787		8,449		8,332	

(a) Since the quartile median income updates annually, the 4 quartiles vary by year. The 4 income quartiles indicates the poorest to wealthiest populations: 2003 (1-35,999; 36,000-44,999; 45,000-59,999; 60,000+), 2009 (1-39,999; 40,000-49,999; 50,000-65,999; 66,000+), 2015 (1 - 41,999; 42,000 - 51,999; 52,000 - 67,999; 68,000+).

(b) Large metropolitan areas include central counties of metro areas (>1 million) and fringe counties of metro areas (≥1 million), and small metropolitan areas contain counties in metro areas with 50,000-999,000 population. See methods section for details.

(c) Categories were dissimilar, therefore incomparable over the study periods.

[ł] This study analyzed data for quarter 1 to quarter 3 (January to September 2015), to avoid the transition in ICD codes from ICD-9-CM to ICD-10-CM effective on October 1, 2015.


4.2A. TRENDS OF PREVALENCE[a] AND HOSPITALIZATION[b] OF PLWH
HIV Prevalence (×10,000)
Total # of Hospitalizations (×10,000)
Rates of Hospitalization (per 100)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015*

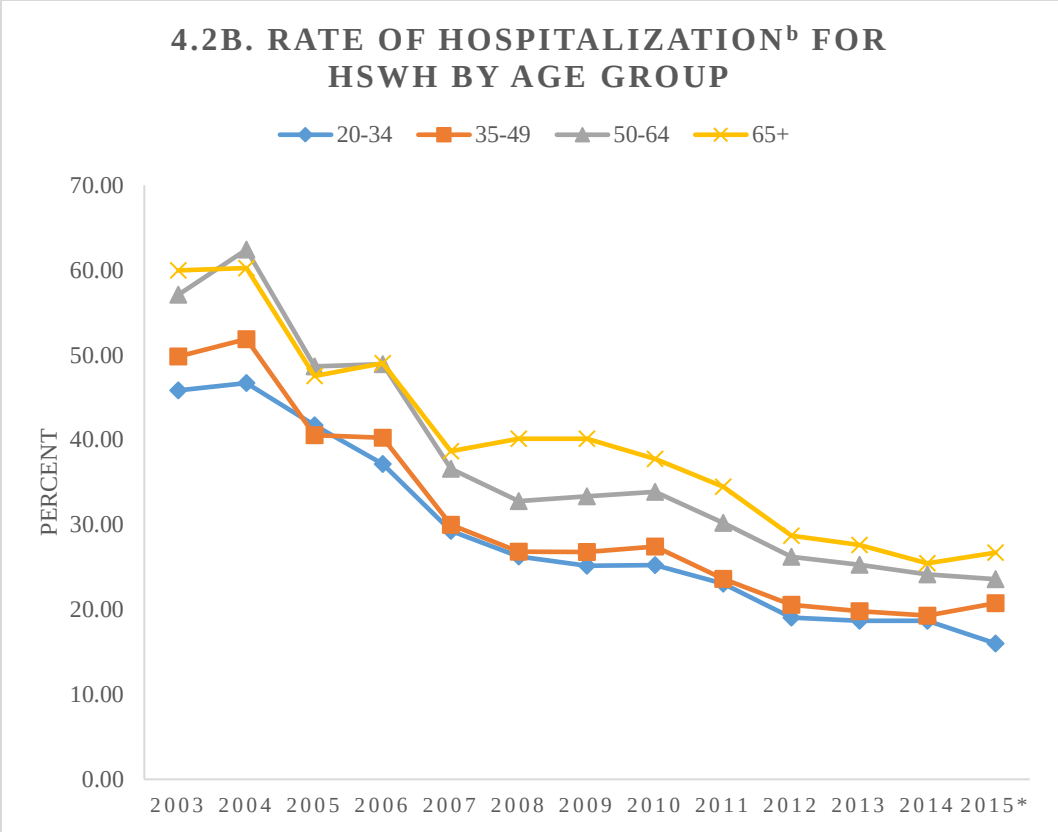


Figure 4. 2 (A) Trends of HIV prevalence (10,000), total number of hospitalization (10,000), and rates of hospitalization (per 100) for people living with HIV; (B) Hospitalization per 100 PLWH by age groups (years).

*Total number of hospitalizations in 2015 is for the first three quarters (January to September), however, the approximate rates were calculated by multiplying the number of PLWH by ¾ to make the rates consistent with other years.

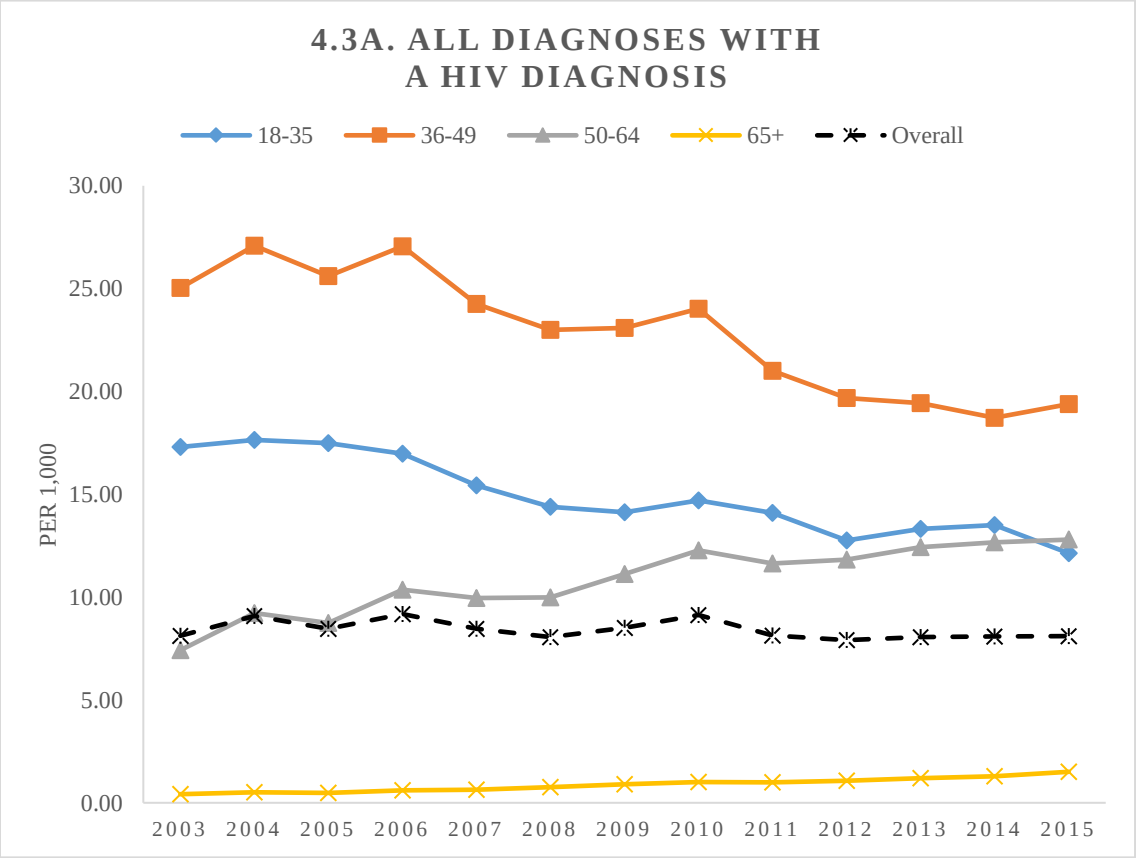
[a] Source: HIV surveillance report, vol. 16-28, Center for Disease Control and Prevention (CDC).

[b]Excludes hospital stays by less than 18 years old, same-day discharges (LOS=0), and that with a diagnosis code for pregnancy, labor, delivery, or neonatal cases.

4.4.4 Trends of Hospital Stays with HIV (HSWH)

Figure 4.3A shows the trends of age-specific HSWH (out of all hospital stays) for all diagnoses with an HIV diagnosis. Figure 4.3B represents the trends for only the principal diagnosis with an HIV diagnosis. The overall proportions of HSWH are mostly

constant, but variations exist by age. Among all diagnoses, the proportion of HSWH decreased over the study years for younger age groups (18-35 and 36-49 years) but increased for older age groups (50-64 and 65+ years). Besides, the proportions of HSWH as principal diagnosis decreased for all age groups except the elderly (65+ years), whose proportions showed slight increases over time (Figure 4.3).



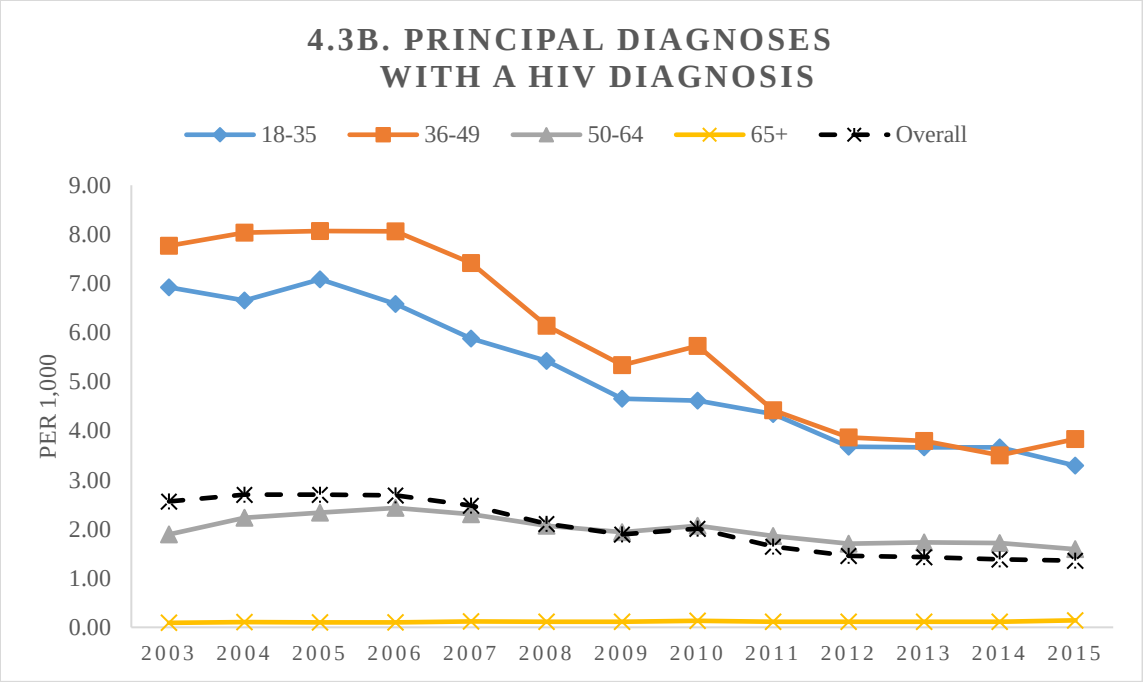


Figure 4. 3 Age-specific proportions of hospital stays with HIV diagnosis (per 1,000 hospital stays), 2003 to 2015. (A) HIV diagnosis as all diagnoses, (B) HIV as the principal diagnosis.

4.4.5 Top Principal diagnoses for Hospital Stays

Table 4.2 displays the top 20 principal diagnoses for hospitals stays in the base year (2003), middle year (2009), and the final year (2015). Chronic heart disease was the top principal diagnosis among HSWOH in 2003 and 2009 but changed to septicemia in 2015. The top principal diagnoses for HSWH was pneumonia in 2003 (8.29%) and 2009 (6.70%) and septicemia in 2015 (8.18%). The proportion of age-related chronic conditions increased over the study years for both types of hospital stays. For example, osteoarthritis increased from 2.20% (2003), 3.30% (2009) to 4.22% (2015) among HSWOH. Among HSWH, proportions for chronic conditions (acute and unspecified renal failure, congestive heart failure, diabetes, and hypertension), mental illness (schizophrenia and other psychotic disorders), and septicemia increased from 2003 to 2015. However, the proportions of

pneumonia, skin and subcutaneous tissue infections, asthma, and pancreatic disorders decreased over time. The percentage of substance-related mental disorders decreased, whereas the percentage of alcohol-related disorders increased slightly from 2003 to 2015 among HSWH (Table 4.2).

4.4.6 Top Principal Procedures Used During Hospital Stays

Table 4.3 displays the top 20 procedures for HSWH and HSWOH in the base year (2003), middle year (2009), and the final year (2015). Major procedures performed during hospital stays were slightly different for the HSWH compared with HSWOH. We observed that the percentages of hemodialysis, respiratory intubation and mechanical ventilation, and cancer chemotherapy increased over the study period among HSWH. The percentage of psychological and psychiatric evaluation and therapy increased in 2009 from 2003 but decreased in 2015. While the proportions of hip replacement (total and partial), diagnostic cardiac catheterization (coronary arteriography) were not among the top 20 procedures for HSWH in 2003, these proportions placed in the top 20 procedures in 2009 and increased in magnitude in 2015. Proportions for diagnostic bronchoscopy and biopsy of bronchus and colonoscopy decreased among HSWH over the study period (Table 4.3).

Table 4. 2 Top 20 principal diagnoses[1] for hospital stays (weighted percentage), 2003, 2009, and 2015.

2003				
Rank	**HIV-**	**%**	**HIV+**	**%**
1	Coronary atherosclerosis and other heart diseases	4.60	Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	8.29
2	Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	4.28	Affective disorders (~ mood disorder)	5.81
3	Congestive heart failure; nonhypertensive	4.18	Skin and subcutaneous tissue infections	3.80
4	Nonspecific chest pain	3.00	Substance-related mental disorders	3.09
5	Acute myocardial infarction	2.74	Pancreatic disorders (not diabetes)	2.82
6	Genitourinary incontinence procedures	2.58	Schizophrenia and related disorders	2.59
7	Arterial blood gases	2.43	Complication of device; implant or graft	2.42
8	Chronic obstructive pulmonary disease and bronchiectasis	2.30	Congestive heart failure; nonhypertensive	2.07
9	Osteoarthritis	2.20	Fluid and electrolyte disorders	2.05
10	Complication of device; implant or graft	2.11	Alcohol-related disorders	1.99
11	Acute cerebrovascular disease	2.07	Nonspecific chest pain	1.91
12	Rehabilitation care, fitting of prostheses, and adjustment of devices	1.71	Septicemia (except in labor)	1.74
13	Diabetes mellitus with complications	1.69	Asthma	1.78
14	Fluid and electrolyte disorders	1.69	Diabetes mellitus with complications	1.59
15	Arthroscopy	1.67	Epilepsy; convulsions	1.53
16	Urinary tract infections	1.63	Other liver diseases	1.48
17	Complications of surgical procedures or medical care	1.60	Anemia	1.48

18	Skin and subcutaneous tissue infections	1.56	Urinary tract infections	1.37
29	Septicemia (except in labor)	1.37	Hypertension with complications and secondary hypertension	1.34
20	Gastrointestinal hemorrhage	1.27	Acute and unspecified renal failure	1.33
2009				
	HIV-	**%**	**HIV+**	**%**
1	Congestive heart failure; nonhypertensive	3.62	Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	6.70
2	Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	3.54	Mood disorders	5.42
3	Osteoarthritis	3.30	Skin and subcutaneous tissue infections	3.99
4	Coronary atherosclerosis and other heart diseases	2.90	Substance-related disorders	3.19
5	Septicemia (except in labor)	2.85	Schizophrenia and other psychotic disorders	3.08
6	Genitourinary incontinence procedures	2.80	Septicemia (except in labor)	2.98
7	Mood disorders	2.74	Complication of device; implant or graft	2.38
8	Chronic obstructive pulmonary disease and bronchiectasis	2.58	Congestive heart failure; nonhypertensive	2.36
9	Complication of device; implant or graft	2.28	Alcohol-related disorders	2.27
10	Arterial blood gases	2.28	Nonspecific chest pain	2.12
11	Nonspecific chest pain	2.27	Acute and unspecified renal failure	2.01
12	Acute myocardial infarction	2.21	Chronic obstructive pulmonary disease and bronchiectasis	1.99
13	Skin and subcutaneous tissue infections	1.97	Asthma	1.99
14	Acute cerebrovascular disease	1.93	Fluid and electrolyte disorders	1.93
15	Urinary tract infections	1.93	Pancreatic disorders (not diabetes)	1.61

16	Diabetes mellitus with complications	1.76	Maintenance chemotherapy; radiotherapy	1.50
17	Complications of surgical procedures or medical care	1.74	Diabetes mellitus with complications	1.50
18	Arthroscopy	1.64	Epilepsy; convulsions	1.39
29	Fluid and electrolyte disorders	1.50	Urinary tract infections	1.29
20	Rehabilitation care, fitting of prostheses, and adjustment of devices	1.45	Intestinal infection	1.20
2015				
	HIV-	**%**	**HIV+**	**%**
1	Septicemia (except in labor)	6.68	Septicemia (except in labor)	8.18
2	Osteoarthritis	4.22	Mood disorders	5.66
3	Congestive heart failure; nonhypertensive	3.67	Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	4.35
4	Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	3.08	Schizophrenia and other psychotic disorders	3.20
5	Mood disorders	2.83	Skin and subcutaneous tissue infections	3.20
6	Cardiac dysrhythmias	2.57	Acute and unspecified renal failure	2.65
7	Complication of device; implant or graft	2.42	Complication of device; implant or graft	2.56
8	Acute myocardial infarction	2.38	Congestive heart failure; nonhypertensive	2.38
9	Acute cerebrovascular disease	2.38	Substance-related disorders	2.38
10	Chronic obstructive pulmonary disease and bronchiectasis	2.25	Fluid and electrolyte disorders	2.14
11	Acute and unspecified renal failure	2.09	Alcohol-related disorders	2.10

12	Skin and subcutaneous tissue infections	2.05	Chronic obstructive pulmonary disease and bronchiectasis	2.10
13	Diabetes mellitus with complications	2.05	Diabetes mellitus with complications	1.86
14	Spondylosis; intervertebral disc disorders; other back problems	2.04	Asthma	1.71
15	Urinary tract infections	1.83	Pancreatic disorders (not diabetes)	1.64
16	Complications of surgical procedures or medical care	1.68	Hypertension with complications and secondary hypertension	1.53
17	Respiratory failure; insufficiency; arrest (adult)	1.63	Acute myocardial infarction	1.49
18	Rehabilitation care; fitting of prostheses; and adjustment of devices	1.55	Complications of surgical procedures or medical care	1.46
29	Schizophrenia and other psychotic disorders	1.51	Maintenance chemotherapy; radiotherapy	1.48
20	Coronary atherosclerosis and other heart disease	1.46	Intestinal infection	1.41

[1] Principal diagnosis for hospital stays with HIV excludes HIV-infection

Formula: Percentage of a particular condition = (# of a particular disease ÷ # of total hospital stays)×100

Table 4. 3 Top 20 principal procedures during hospital stays (weighted percentages), 2003, 2009, and 2015.

2003				
Rank	**HIV-**	**%**	**HIV+**	**%**
1	Upper gastrointestinal endoscopy; biopsy	4.36	Diagnostic spinal tap	7.13
2	Percutaneous transluminal coronary angioplasty (PTCA)	4.29	Other therapeutic procedures	7.05
3	Diagnostic cardiac catheterization; coronary arteriography	4.28	Blood transfusion	6.13
4	Hysterectomy; abdominal and vaginal	3.74	Diagnostic bronchoscopy and biopsy of bronchus	5.84
5	Blood transfusion	2.95	Hemodialysis	5.76
6	Respiratory intubation and mechanical ventilation	2.88	Other vascular catheterization; not heart	5.71
7	Arthroplasty knee	2.71	Upper gastrointestinal endoscopy; biopsy	4.92
8	Other vascular catheterization; not heart	2.44	Alcohol and drug rehabilitation/detoxification	4.75
9	Cholecystectomy and common duct exploration	2.42	Respiratory intubation and mechanical ventilation	4.05
10	Hip replacement; total and partial	2.16	Colonoscopy and biopsy	1.71
11	Other therapeutic procedures	2.05	Psychological and psychiatric evaluation and therapy	1.63
12	Insertion; revision; replacement; removal of cardiac pacemaker or cardioverter/defibrillator	1.94	Incision and drainage; skin and subcutaneous tissue	1.60
13	Coronary artery bypass graft (CABG)	1.86	Abdominal paracentesis	1.57
14	Spinal fusion	1.84	Computerized axial tomography (C.T.) scan head	1.60

15	Laminectomy; excision intervertebral disc	1.77	Other respiratory therapy	1.43
16	Colonoscopy and biopsy	1.76	Bone marrow biopsy	1.33
17	Colorectal resection	1.74	Diagnostic ultrasound of heart (echocardiogram)	1.28
18	Alcohol and drug rehabilitation/detoxification	1.71	Cancer chemotherapy	1.13
29	Hemodialysis	1.67	Debridement of wound; infection or burn	1.10
20	Treatment; fracture or dislocation of hip and femur	1.60	Incision of pleura; thoracentesis; chest drainage	1.08
2009				
	HIV-	**%**	**HIV+**	**%**
1	Blood transfusion	4.29	Hemodialysis	6.88
2	Respiratory intubation and mechanical ventilation	4.20	Diagnostic spinal tap	6.37
3	Arthroplasty knee	4.01	Blood transfusion	6.36
4	Upper gastrointestinal endoscopy; biopsy	3.98	Respiratory intubation and mechanical ventilation	5.86
5	Percutaneous transluminal coronary angioplasty (PTCA)	3.77	Other vascular catheterization; not heart	5.63
6	Diagnostic cardiac catheterization; coronary arteriography	3.36	Alcohol and drug rehabilitation/detoxification	5.37
7	Other vascular catheterization; not heart	3.32	Diagnostic bronchoscopy and biopsy of bronchus	4.70
8	Hysterectomy; abdominal and vaginal	2.71	Upper gastrointestinal endoscopy; biopsy	4.71
9	Hip replacement; total and partial	2.57	Other therapeutic procedures	3.77
10	Spinal fusion	2.50	Psychological and psychiatric evaluation and therapy	2.12

11	Cholecystectomy and common duct exploration	2.31	Incision and drainage; skin and subcutaneous tissue	1.87
12	Hemodialysis	2.14	Cancer chemotherapy	1.73
13	Insertion; revision; replacement; removal of cardiac pacemaker or cardioverter/defibrillator	1.93	Colonoscopy and biopsy	1.51
14	Alcohol and drug rehabilitation/detoxification	1.88	Other therapeutic procedures; hemic and lymphatic system	1.41
15	Other therapeutic procedures	1.86	Diagnostic cardiac catheterization; coronary arteriography	1.39
16	Other OR procedures on vessels other than head and neck	1.75	Other OR procedures on vessels other than head and neck	1.36
17	Colorectal resection	1.64	Percutaneous transluminal coronary angioplasty (PTCA)	1.30
18	Diagnostic ultrasound of heart (echocardiogram)	1.57	Diagnostic ultrasound of heart (echocardiogram)	1.29
29	Treatment; fracture or dislocation of hip and femur	1.50	Abdominal paracentesis	1.20
20	Colonoscopy and biopsy	1.36	Hip replacement; total and partial	0.97
2015				
	HIV-		**HIV+**	**%**
1	Respiratory intubation and mechanical ventilation	5.90	Hemodialysis	7.33
2	Arthroplasty knee	4.93	Respiratory intubation and mechanical ventilation	6.66
3	Upper gastrointestinal endoscopy; biopsy	3.89	Diagnostic spinal tap	5.79
4	Other vascular catheterization; not heart	3.71	Other vascular catheterization; not heart	5.17
5	Blood transfusion	3.59	Blood transfusion	4.79
6	Hip replacement; total and partial	3.47	Other therapeutic procedures	4.70

7	Diagnostic cardiac catheterization; coronary arteriography	2.85	Upper gastrointestinal endoscopy; biopsy	4.56
8	Spinal fusion	2.84	Alcohol and drug rehabilitation/detoxification	3.73
9	Percutaneous transluminal coronary angioplasty (PTCA)	2.71	Diagnostic bronchoscopy and biopsy of bronchus	3.72
10	Other therapeutic procedures	2.62	Psychological and psychiatric evaluation and therapy	1.95
11	Hemodialysis	2.48	Incision and drainage; skin and subcutaneous tissue	1.87
12	Cholecystectomy and common duct exploration	2.01	Cancer chemotherapy	1.86
13	Alcohol and drug rehabilitation/detoxification	1.74	Diagnostic cardiac catheterization; coronary arteriography	1.64
14	Diagnostic ultrasound of heart (echocardiogram)	1.72	Abdominal paracentesis	1.59
15	Treatment; fracture or dislocation of hip and femur	1.71	Hip replacement; total and partial	1.53
16	Incision of pleura; thoracentesis; chest drainage	1.67	Diagnostic ultrasound of heart (echocardiogram)	1.41
17	Colorectal resection	1.59	Percutaneous transluminal coronary angioplasty (PTCA)	1.39
18	Other OR procedures on vessels other than head and neck	1.42	Other OR procedures on vessels other than head and neck	1.22
29	Abdominal paracentesis	1.28	Colonoscopy and biopsy	1.17
20	Insertion; revision; replacement; removal of cardiac pacemaker or cardioverter/defibrillator	1.27	Other respiratory therapy	1.08
Formula: Percentage of principal procedure = (# of discharges with that procedure ÷ total # of discharges with at least one procedure) ×100				

4.4.7 Major HANA Conditions during Hospital Stays, 2003 to 2015

Table 4.4 displays the yearly trends of major HANA conditions reported during hospital stays from 2003 to 2015. The proportions of all five major conditions increased gradually over the years among both types of hospital stays. However, disproportionate changes occurred for CVD and Cancer between HSWH and HSWOH. From 2003 to 2015, the proportion of CVD increased by 26.76% (37.06% to 63.82%) for HSWH, compared to an increase of 9.21% (67.33% to 76.54%) for HSWOH. The difference in proportions of hospital stays with cancer between HSWH and HSWOH reduced from 4.89% (14.07%-9.18%) in 2003 to 2.96% (18.11%-15.15%) in 2015. When we considered HANA conditions as the principal diagnosis, similar patterns were observed for all HANA conditions except CVD. The proportion of CVD increased by 3.3% for HSWH but decreased from 4.5% for HSWOH over the study period (Table 4.4).

In table 4.5, we describe yearly trends of these five major HANA conditions across age groups. The proportion of CVD increased among all age groups irrespective of the types of hospital stays; however, the increases were most substantial for older HSWH. Disproportionate increases were also observed for hospital stays with cancer among 36-49 and 50-64 years old HSWH, and for liver disease among elderly aged 65 years or more. Diabetes increased disproportionately among HSWOH for patients aged 36-49 and 50-64 years. Interestingly, disproportionate increases in liver disease were observed for younger (18-35 and 36-49 years) HSWOH. The bone loss increased over the years among all age groups for both types of hospital stays (Table 4.5).

Table 4. 4 Trends of major HANA conditions[a] during hospital stays (weighted percentage), 2003 to 2015.

All Diagnoses														
	2003		2004		2005		2006		2007		2008		2009	
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
CVD	67.33	37.06	68.05	38.36	69.41	40.65	70.83	45.15	71.16	47.06	72.12	50.55	73.07	52.50
Cancer	14.07	9.18	14.20	9.65	14.66	10.02	14.46	9.94	15.71	11.03	15.85	12.63	16.35	12.13
Diabetes	22.54	10.94	22.94	11.34	23.50	11.24	24.63	12.82	26.05	14.29	26.55	15.31	28.23	16.58
Liver Disease	7.28	25.39	7.64	25.24	7.82	25.67	7.97	25.70	7.90	27.23	8.42	27.20	9.05	28.60
Bone Loss	19.54	5.15	20.40	5.79	21.28	6.45	21.49	7.26	22.82	7.51	24.04	9.42	25.22	9.83
	2010		2011		2012		2013		2014		2015		All years	
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
CVD	73.13	54.61	74.62	58.43	74.91	59.48	75.53	60.61	75.93	61.97	76.54	63.82	72.40	51.00
Cancer	16.85	13.40	17.30	13.63	17.53	14.57	17.77	14.55	17.99	15.09	18.11	15.15	16.16	12.24
Diabetes	28.61	16.88	29.94	18.05	30.33	18.93	30.92	19.24	31.49	20.03	31.98	20.99	27.38	15.66
Liver Disease	9.36	29.93	9.85	30.35	10.26	29.90	10.66	29.61	11.31	29.73	11.64	29.35	9.09	27.91
Bone Loss	25.76	10.52	26.94	12.42	27.31	13.41	27.82	13.90	28.69	15.28	28.96	15.83	24.51	9.95
Principal diagnosis														
	2003		2004		2005		2006		2007		2008		2009	
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
CVD	23.00	7.07	22.23	6.89	21.46	6.89	22.12	7.67	20.78	7.89	20.49	8.39	20.30	8.64
Cancer	4.68	2.01	4.61	1.94	4.71	2.01	4.41	1.89	4.78	2.22	4.60	2.31	4.33	2.14
Diabetes	1.75	1.13	1.78	1.13	1.75	1.07	1.82	1.12	1.83	1.07	1.79	1.15	1.82	1.22
Liver Disease	2.43	2.36	2.42	2.18	2.39	1.86	2.37	1.82	2.13	1.67	2.17	1.80	2.21	1.96
Bone Loss	6.53	1.25	6.65	1.33	6.99	1.50	6.77	1.47	7.11	1.69	7.34	1.86	7.34	1.98

	2010		2011		2012		2013		2014		2015		All years	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
CVD	19.20	8.41	19.15	8.91	19.16	9.33	18.86	9.41	18.61	9.64	18.57	10.04	20.35	8.32
Cancer	4.43	2.52	4.29	2.28	4.20	2.47	4.16	2.47	4.08	2.40	3.95	2.18	4.41	2.21
Diabetes	1.90	1.31	1.95	1.31	1.95	1.41	2.01	1.38	2.05	1.53	2.08	1.60	1.88	1.25
Liver Disease	2.21	1.80	2.22	1.73	2.25	2.00	2.23	1.93	2.18	1.94	2.11	1.73	2.26	1.91
Bone Loss	7.62	1.96	7.52	2.22	7.68	2.20	7.98	2.52	8.22	2.68	8.10	2.63	7.35	1.91

Formula:

Percentage of a HANA condition for HSWH = (# of hospital stays with HANA ÷ # of hospital stays with HIV)×100.

Percentage of a HANA condition for HSWOH = (# of hospital stays with HANA ÷ # of hospital stays without HIV)×100.

[a] The HANA conditions are not mutually exclusive categories.

Table 4. 5 Trends of major HANA conditions [a] (all diagnoses) across age groups (weighted percentage), 2003 to 2015.

CVD														
Age (years)	**2003**		**2004**		**2005**		**2006**		**2007**		**2008**		**2009**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	18.55	23.00	19.58	24.22	20.95	26.55	22.29	30.18	23.21	30.77	24.11	30.97	25.46	33.82
36-49	41.12	34.18	42.66	34.54	43.96	36.43	46.36	40.20	47.21	42.02	48.52	45.37	50.50	46.26
50-64	68.85	54.76	69.70	55.07	70.25	57.29	72.11	60.29	72.07	61.05	72.64	64.41	73.86	64.96
65+	85.89	71.57	86.69	70.39	87.44	75.95	88.47	76.53	88.80	81.04	89.13	81.91	90.08	83.93
	2010		**2011**		**2012**		**2013**		**2014**		**2015**		**All years**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	26.07	34.93	27.17	37.77	27.84	36.29	28.63	36.44	29.54	37.14	29.86	35.92	24.72	31.53
36-49	51.21	48.45	52.55	52.08	53.45	53.11	54.37	53.58	55.10	55.20	56.03	56.37	48.89	44.22
50-64	74.11	66.67	74.96	69.78	75.36	70.14	75.68	71.20	76.10	71.99	76.79	73.72	73.31	65.64
65+	90.21	84.26	90.71	85.91	91.03	87.44	91.17	87.76	91.30	87.86	91.45	88.91	89.35	83.61
Cancer														
Age (years)	**2003**		**2004**		**2005**		**2006**		**2007**		**2008**		**2009**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	3.88	7.00	3.67	6.38	4.11	7.05	3.85	8.18	4.55	7.75	4.52	9.61	4.22	8.40
36-49	7.43	8.71	7.42	9.00	7.77	9.67	7.58	9.20	8.69	10.16	8.65	11.83	8.42	11.09
50-64	14.71	11.37	14.83	12.79	15.28	12.19	14.78	11.69	16.31	13.42	16.26	14.41	16.11	14.11
65+	18.20	19.84	18.57	18.88	18.84	19.14	18.84	16.37	20.10	19.58	20.24	19.89	21.66	20.03
	2010		**2011**		**2012**		**2013**		**2014**		**2015**		**All years**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	4.58	10.07	4.15	10.62	4.36	10.61	4.46	10.79	4.50	10.06	4.43	9.27	4.25	8.74
36-49	8.94	12.22	8.87	11.66	8.99	12.91	9.11	12.69	9.13	13.33	8.97	13.11	8.39	10.84

50-64	16.78	15.19	16.71	15.84	16.85	16.09	16.90	16.15	16.90	16.88	16.95	16.87	16.13	14.65
65+	22.23	21.25	22.84	20.76	23.25	24.40	23.48	22.67	23.89	23.24	24.02	23.91	21.15	21.29
Diabetes														
Age	**2003**		**2004**		**2005**		**2006**		**2007**		**2008**		**2009**	
(years)	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	7.38	4.03	7.76	5.47	8.25	5.26	8.73	4.96	9.56	6.87	9.77	6.90	10.50	6.59
36-49	15.09	9.34	15.80	9.35	16.39	9.24	17.39	10.39	18.53	11.11	19.05	11.72	20.52	12.72
50-64	27.29	20.35	27.65	18.75	27.94	18.40	28.87	20.44	30.15	21.84	30.32	22.76	32.04	23.59
65+	26.05	26.05	26.44	28.36	26.82	29.02	28.20	29.62	29.88	31.62	30.37	32.30	32.41	35.65
	2010		**2011**		**2012**		**2013**		**2014**		**2015**		**All years**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	10.63	7.11	11.27	8.15	11.44	8.26	11.80	8.05	12.19	7.87	12.19	7.60	10.05	6.53
36-49	21.07	13.12	22.24	14.38	22.76	15.03	23.51	14.47	24.09	14.98	24.49	16.44	19.68	11.92
50-64	32.17	23.18	33.46	23.72	33.60	24.32	34.03	24.76	34.43	25.87	35.00	25.78	31.34	22.92
65+	33.05	35.20	34.11	33.79	34.76	34.25	35.24	35.28	35.90	34.55	36.34	36.37	31.35	33.38
Liver Disease														
Age	**2003**		**2004**		**2005**		**2006**		**2007**		**2008**		**2009**	
(years)	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	7.99	17.78	8.20	20.18	8.40	18.46	8.66	18.41	8.40	19.16	9.05	17.73	9.41	19.29
36-49	10.17	27.03	10.48	25.70	10.61	26.52	10.76	25.71	10.09	26.67	10.64	27.16	10.90	27.63
50-64	9.09	30.08	9.69	29.22	10.07	31.16	10.30	31.42	10.24	34.11	10.96	33.65	11.78	35.35
65+	5.26	16.07	5.50	18.49	5.65	14.22	5.68	17.13	5.81	18.73	6.25	19.26	6.88	22.00
	2010		**2011**		**2012**		**2013**		**2014**		**2015**		**All years**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	9.54	18.48	10.24	20.29	10.44	19.07	10.88	17.71	11.35	18.98	11.63	17.96	9.49	18.76
36-49	11.24	28.59	11.75	28.97	12.16	27.37	12.57	26.73	13.12	26.88	13.71	26.85	11.24	27.0

50-64	12.22	37.60	13.00	37.10	13.55	37.30	14.02	36.98	14.68	36.47	15.04	35.74	11.90	34.80
65+	7.06	24.28	7.47	24.54	7.80	25.15	8.19	27.49	8.87	27.08	9.18	26.38	6.82	22.91

Bone Loss

Age	**2003**		**2004**		**2005**		**2006**		**2007**		**2008**		**2009**	
(years)	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	7.79	3.37	8.02	3.57	8.47	3.59	8.56	4.33	8.95	4.42	9.51	5.49	10.03	5.77
36-49	13.62	5.25	13.97	5.52	14.76	6.11	14.83	6.71	15.45	6.83	16.61	9.00	17.14	8.90
50-64	17.99	6.40	19.23	7.91	20.08	9.03	20.39	9.60	21.91	9.91	23.36	11.44	24.45	12.16
65+	24.77	7.98	25.93	9.01	26.67	11.11	26.97	12.33	28.68	12.33	29.71	14.73	31.50	15.59
	2010		**2011**		**2012**		**2013**		**2014**		**2015**		**All years**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	10.03	6.43	10.60	6.79	10.74	7.26	10.82	7.04	10.95	8.21	11.04	8.37	9.62	5.48
36-49	17.51	9.47	18.48	11.40	18.80	11.87	18.97	12.35	19.47	13.39	19.43	12.89	16.60	8.54
50-64	25.12	12.99	26.33	15.11	26.88	16.14	27.57	16.75	28.59	18.03	28.84	18.88	23.95	13.17
65+	32.32	14.94	33.13	17.94	33.61	20.60	33.99	20.44	35.02	23.11	35.25	23.94	30.43	17.16

Formula:

Percentage of a HANA condition for a particular age group, HSWH = (# of HANA diagnoses for a particular age group ÷ # of hospital stays by particular age group, HSWH)×100.

Percentage of a HANA condition for a particular age group, HSWOH = (# of HANA diagnoses for a particular age group ÷ # of hospital stays by particular age group, HSWOH)×100.

[a] The HANA conditions are not mutually exclusive categories.

4.5 Discussion

This study compared the characteristics and comorbidities for different hospital stays by the patient- and hospital-level characteristics. The study demonstrates that HIV hospitalization rates and proportions of HSWH (out of all hospital stays) elevated among older due to the increased number of older age hospital stays. Also, changing patterns of some patient-level characteristics suggest the higher presence of older patients in the U.S. inpatient department with HIV diagnosis. Finally, age-related HANA conditions, such as CVD, liver disease, and cancer disproportionately increased by age for HSWH.

Consistent with the increasing trends of the older population (U.S. Census Bureau, 2019), hospital stays by older patients increased over the study years from 2003 to 2015. The rates of HIV hospitalization also increased over this period among the older population. The finding of increasing trends for HSWH by age is supported by literature; previous studies reported increased HSWH by older patients (Crum-Cianflone et al., 2010; Heslin & Elixhauser, 2016; Zhao et al., 2007). Due to advanced ART, PLWH live longer, which may expose them to age-related complications and chronic diseases (Center for Disease Control and Prevention, 2018; Institute of Medicine, 2008). The increasing number of older PLWH may contribute to more hospital stays with HIV. Crum-Cianflone et al. commented that the aging of the HIV population may contribute to hospitalization rates among PLWH and may continue to impact these rates in the upcoming years (Crum-Cianflone et al., 2010). Moreover, factors related to aging of PLWH, including increased comorbidities, frailty, may increase the likelihood of hospitalization and longer hospital stay by the older population (Akgün et al., 2014; S. A. Berry et al., 2012; Fleishman et al., 2005; Kim et al., 2012; Smit et al., 2015; Tadros et al., 2012; Wong et al., 2018).

Declining trends of the mean age difference between the HSWH and HSWOH and increasing proportion of Medicare payments for HSWH highlight the impact of aging PLWH on U.S. inpatient department. Studies using NIS data found increasing trends of Medicare as the primary payer for HSWH (Heslin & Elixhauser, 2016; Zhao et al., 2007), and for hospital stays with other diagnoses (Asrani et al., 2018; Hirode, Saab, & Wong, 2020). Aging of PLWH and the recent addition of Medicare Part D prescription drug benefit by the ACA made Medicare the single largest source of federal financing for HIV care and treatment (Bradley et al., 2014).

The increasingly higher presence of age-related chronic diseases in the top principal diagnoses among HSWH and the disproportionate increase of these conditions may be evidence for a higher prevalence of HANA conditions during HSWH. This is consistent with previous literature which reported a higher prevalence of HANA conditions among older PLWH, including cardiovascular diseases, cancer, osteoporosis, liver disease, renal disease, and neurocognitive decline (High et al., 2012; Pathai et al., 2013; United States Senate, 2013). We observed new trends for age-related chronic conditions based on top procedures identified during HSWH. Increased proportions of hemodialysis, respiratory intubation and mechanical ventilation and cancer chemotherapy may reflect elevated rates of kidney and lung disease and cancer. The increased use of hip replacement and cardiac catheterization (coronary arteriography) procedure suggests a higher prevalence of arthritis and cardiovascular disease among HSWH. This finding is supported by a previous study that found the hip replacement and spinal surgery as the top procedure by the PLWH (King et al., 2015). Since non-AIDS related comorbidities are the most common causes of hospitalization in recent years (S. A. Berry et al., 2012; Crum-Cianflone et al., 2010),

patients require diagnostic services and surgical procedures related to the aging of HIV patients.

In contrast to previous studies that demonstrated a higher prevalence of age-related chronic diseases, such as hypertension, diabetes, stroke, cancer, cardiovascular diseases, and neurocognitive disorder, among PLWH compared to non-PLWH (Bigna, Kenne, Asangbeh, & Sibetcheu, 2018; Guaraldi et al., 2011; Mayer et al., 2018; Ruzicka, Imai, Takahashi, & Naito, 2019; Schouten et al., 2014), this study found that among five major HANA categories, only liver disease was prevalent among HSWH compared to HSWOH. This discrepancy may indicate the HSWH occurs mostly for non-HANA conditions. Besides, declining trends of HIV infections as a principal diagnosis is expected since advanced ART should relegate HIV as a principal diagnosis. Therefore, it is plausible that PLWH are hospitalized primarily with certain conditions other than HIV infection or major HANA comorbidities. Multiple studies showed that non-AIDS defining infections are the most common reason for hospital admission (S. A. Berry et al., 2012; Crowell et al., 2015; Crum-Cianflone et al., 2010; Fleming et al., 2019). However, CVD and cancer increased disproportionately over the study period among HSWH compared to HSWOH. Also, this study observed disproportionate increases in CVD, liver disease, and cancer among older HSWH in recent years. Many recent studies evident that PLWH older than 50 years of age are more likely to have HANA comorbidities (Kim et al., 2012; Nguyen & Holodniy, 2008; Schouten et al., 2014; Smit et al., 2015), and HANA associated hospital stays (S. A. Berry et al., 2012; Fleishman et al., 2005; Tadros et al., 2012; Wong et al., 2018). HIV induced chronic immune activation and inflammation is referred to as a factor of accelerated or early aging, and that leads to an elevated risk of developing multiple comorbidities as

PLWH age (Ahn et al., 2019; Desai & Landay, 2010; Guardigni & Montano, 2018). Smit et al. predict that, in the Netherlands, 84% of PLWH will have at least one chronic condition, and 28% of PLWH will have three or more chronic conditions by 2030 (Smit et al., 2015). Since the age profile of PLWH in the Netherlands is very similar to that of the United States (Smit et al., 2015; Wing, 2017), these projections may suggest a potential increase in the burden of hospital stays with HANA comorbidities in the future for the United States. Long-term use of ARV drugs, sustained HIV-associated immune activation, and chronic inflammation have been reported to be associated with a higher prevalence of multimorbidity among older PLWH (Guaraldi et al., 2011; Maciel et al., 2018; Rodriguez-Penney et al., 2013; Schouten et al., 2014; Strategies for Management of Antiretroviral Therapy Study Group, 2008).

Consistent with the HIV surveillance statistics of the United States (Bachhuber & Southern, 2014; Hess, Hu, Lansky, Mermin, & Hall, 2017), the majority of the HSWH were made by African Americans. Although HIV prevalence continues to be higher among African Americans, the proportion of HSWH by the whites increased over time, maybe because whites disproportionately represent a higher proportion of older U.S. people (Schaeffer, 2019). The decreasing trends of HSWH by patients from large metropolitan areas and the increasing trends of small metropolitan and rural areas is an important issue that needs to be investigated further to monitor the evolving HIV care needs outside of the urban setting. This may reflect the migration of the HIV epidemic from urban centers to more rural areas (Iyer, 2015; M Vyavaharkar et al., 2013). This shift indicates increasing inpatient care demand by the PLWH living in small metropolitan and rural areas. While PLWH from small metropolitan areas may have easier access to HIV care, rural PLWH

may face challenges accessing tertiary HIV care, because HIV prevention and care are concentrated in urban areas (Schafer et al., 2017).

4.6 Limitations

While this study provides a detailed picture of U.S. inpatient stays by HIV status and age of the patients, like many other studies using large claims databases, study findings should be interpreted within the context of certain limitations (Hashimoto, Brodt, Skelly, & Dettori, 2014; Sarrazin & Rosenthal, 2012). First, the unit of analysis of this study is hospital stay, so all numbers and estimates represent the records of hospital stays, and does not reflect individual-level information. NIS is not a follow-up data; thus, there may be repeat hospitalization by an individual in a year or next (in case of pooled data) with the same or different conditions. Patients with a high number of repeat hospital stays may have skewed the findings. Unfortunately, the NIS did not contain unique patient identifiers that would enable linking multiple hospitalizations by the same patient. Nevertheless, given that the main objective of this study was to describe the characteristics and comorbidity burdens of HSWH compared to HSWOH, these descriptive results still provide critical facts to inform the public health community.

Second, this study excluded hospital records that were discharged on the same day, and that indicated neonatal or pregnant issues. Thus, the results are not reflective of all U.S. hospital stays, even though this study represent all-cause U.S. hospital stays. Also, the results are not reflective of hospital stays in long-term care facilities, such as rehabilitation, psychiatric, alcoholism, and chemical dependency hospitals, because the NIS collects data from U.S. short-term U.S. community hospitals. Third, hospitalization rates of the PLWH for the year 2003 to 2007 might be underreported, because HIV prevalence data were not

reported for all 50 states in these years. Moreover, since there was no unique patient identifier in the NIS databases, we were unable to measure true hospitalization rates. A previous study showed that 31.2% of PLWH hospitalized more than once (Buchacz et al., 2008). Using a sensitivity analysis, we computed hospitalization rates considering single hospitalization by PLWH (68.8%) and observed lower hospitalization rates, but similar yearly trends across the age groups (Appendix A, Figure A.1). Finally, the accuracy of claims data depends on the quality and consistency of coding by participating hospitals. Thus, the ICD-9-CM codes we used to characterize patients' illnesses may not accurately capture the primary reasons for patient's hospitalization because hospitals use these codes primarily for billing purposes. In this study, we described the principal diagnosis as well as all-listed diagnoses that may minimize the impact of coding biases substantially.

4.7 Conclusions

This study presents a detailed snapshot of the changing patterns of hospital inpatient stays with the aging of PLWH in the United States. Policymakers, hospital administrators, and other stakeholders should consider hospital stays from two perspectives: which subpopulation of the patients shows unique attributes, and which components of the inpatient stays are most affected. For hospital stays, the increased presence of older patients with HIV and major age-related chronic conditions demonstrate the need for incorporating chronic disease management programs in inpatient care delivery. Although the hospital inpatient department is not the routine source of care for PLWH, increased HANA comorbidities for older PLWH may require greater use of inpatient care, higher resource utilization, and increased hospital costs. Studies investigating the impact of the aging of PLWH on inpatient resource utilization and costs are suggested that may unveil the real

burden of HANA comorbidities in the U.S. inpatient department. In light of the health professional shortages, hospitals may not be prepared to deal with increased demand from hospitals stays with HIV. Thus, an adequate number of HIV trained inpatient workforce and geriatric care providers should be in place for the future.

CHAPTER 5

PAPER 2: AGING WITH HIV IN THE UNITED STATES: IMPACT ON INPATIENT RESOURCE UTILIZATION AND COSTS, 2003 TO 2015[2]

[2] Siddiqi, K. A., Olatosi, B., Ostermann, J., Zhang, J., & Khan, M. M. To be submitted to *AIDS Care*.

5.1 Abstract

Background: With the aging of PLWH, the longer exposure to HIV infections and antiretroviral drugs may increase the risk of age-related chronic illnesses [HIV Associated Non-AIDS (HANA) conditions]. Higher comorbidity burdens among older PLWH may require greater use of inpatient care, i.e., higher hospital resource utilization and costs. This study examined the impact of aging PLWH on trends for inpatient resource utilization, and costs of hospital stays with HIV (HSWH) compared to hospital stays without HIV (HSWOH). We also assessed resource utilization and costs for hospital stays with major HANA conditions.

Methods: Health Care Utilization Project (HCUP) National Inpatient Sample (NIS) data, 2003 through 2015, were analyzed using SAS 9.4. We excluded hospital stays for patients less than 18 years old, neonatal, pregnancy, and same-day discharge from our analysis. Univariate, bivariate, and multivariable survey-weighted analyses were conducted using sampling weights to produce national estimates. Multivariable regression analyses using a generalized linear model (GLM) framework were conducted to determine predictors of inpatient resource utilization and costs, controlling for the patient- and hospital-level characteristics.

Results: The median number of procedures for HSWH was consistently lower than that for HSWOH, but it increased disproportionately among older HSWH over the years. While the overall length of stay and costs for HSWH were consistently higher than that for HSWOH, the differences narrowed down over the study period. The differences in inpatient resource use and costs between HSWH and HSWOH were also decreasing over the years among hospital stays with major HANA conditions. Multivariable analyses

showed that the procedure use was lower for HSWH, but it increased significantly with increased age compared to HSWOH. Inpatient LOS and costs were significantly higher among HSWH and older, but LOS and costs decreased among HSWH compared to HSWOH with the increase in age.

Conclusions: This study finding confirms our hypothesis of increased procedure utilization by age for HSWH. A close investigation of types of surgical procedures and comorbidities requiring longer inpatient stays and higher costs is needed to make the inpatient department more efficient as PLWH age in the United States.

Keywords: Aging, HIV, Inpatient, Resource Utilization, Costs, United States.

5.2 Introduction

More than 1 million people are living with HIV (PLWH) today in the United States. One in seven PLWH is unaware of their infection, and every year about 40 thousand people become newly infected with HIV (HIV.gov, 2018). Due to the effective combination of antiretroviral treatment (cART), HIV infection has become a chronic condition in recent decades. Today, PLWH may expect a normal lifespan due to early diagnosis of HIV, early linkage and retention in HIV medical care (National Institute of Allergy and Infectious Diseases, 2018; Pebody, 2018). PLWH in the United States are aging as a result of both life expectancy gains and an increase in newly acquired infections at older ages (McMillan, Krentz, Gill, & Hogan, 2018). Almost half of all PLWH are 50 years or older (Center for Disease Control and Prevention, 2018), and projected to be around 70% by 2030 (Wing, 2017). HIV induced chronic immune activation and inflammation is referred to as a factor of accelerated or early aging, and this leads to PLWH developing various comorbidities at

a younger age compared to the general population (Ahn et al., 2019; Desai & Landay, 2010; Guardigni & Montano, 2018).

With the aging of PLWH in the United States, age-related chronic conditions have become the major health concerns once the viral load suppression is achieved. The longer exposure to HIV infections and antiretroviral drugs (ARV) may increase the risk of age-related chronic illnesses, commonly called HIV Associated Non-AIDS (HANA) conditions. The HANA comorbidities include, but are not limited to cardiovascular, liver, kidney, bone, and lung disease and non-HIV associated cancers (Gallant et al., 2017; Guaraldi et al., 2011; Schouten et al., 2014). Also, older PLWH have a higher prevalence of multimorbidity than the general population (Guaraldi et al., 2011; Maciel et al., 2018; Rodriguez-Penney et al., 2013). Studies also showed that aging of PLWH hastens the development of geriatric conditions, such as comorbidities, frailty, poorer cognitive functioning, depression, and other mental illness (Center for Disease Control and Prevention, 2018; Heslin & Elixhauser, 2006; HIV.gov, 2017).

PLWH aging with HIV may place enormous demands on health care and social service systems because of the additional risks of comorbidity, weak cognitive functioning, frailty, poor mental health, provider or society level stigma, and lack of social supports (Matthew Harris et al., 2015). Studies showed that higher comorbidity burdens among older PLWH require greater use of inpatient care, i.e., higher hospital resource utilization and costs (H. Krentz & Gill, 2015; Zingmond et al., 2017). However, it is unclear whether the existing health care infrastructure and workforce are adequate to meet increasing specialized demand for clinical and non-clinical services for this growing HIV population (High et al., 2012). Assessing the changing patterns of inpatient resource utilization and

costs of PLWH during hospital stays is important to estimate future demand for inpatient care resources posed by the aging of PLWH.

It is critical to understand the changing patterns of hospital resource utilization and costs with the changing demographic structure; yet, research describing recent trends of resource utilization and costs for inpatient stays is lacking. Also, to the best of our knowledge, no studies investigated the relationship between aging of PLWH and resource utilization and costs during hospital stays using national inpatient data. This study examined the impact of aging on inpatient resource use patterns, and costs of hospital stays with and without HIV using the national inpatient sample (NIS) database. We also assessed resource utilization and costs for hospital stays with major HANA conditions. Hospital resource utilization and costs analysis is important for assessing future demand for inpatient care delivery.

5.3 Methods

5.3.1 Data Source and Sample

This study pooled the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) data, 2003 through 2015. The NIS is the largest all-payer inpatient care discharge database (more than 7 million hospital stays each year) from U.S. community hospitals in 46 states and the District of Columbia (Agency for Healthcare Research and Quality, 2018c). The NIS includes short-term, nonfederal, general, and other community hospitals. It excludes long-term care facilities, such as rehabilitation, psychiatric, alcoholism, and chemical dependency hospitals. Prior to 2012, NIS collected all discharge records from a 20% sample hospitals from each stratum; starting in 2012, NIS collects 20% discharges from all U.S. hospitals (Houchens et al., 2014). This was modified

again in 2015, to reflect new ICD-10 codes. More information about the sampling and dataset changes are available elsewhere (Agency for Healthcare Research and Quality, 2018c).

The unit of analysis in this study is hospital stay from the U.S. inpatient department. Discharge level weights, provided with the datasets, were used to produce nationally representative estimates (Agency for Healthcare Research and Quality, 2015). Hospital stays, associated with neonatal or pregnancy issues, and by younger than 18 years old, were excluded. Hospital length of stays (LOS) reported as zero (LOS=0) were also excluded since it indicated same-day discharge. Due to the shift from ICD-9-CM to ICD-10-CM on October 1, 2015, this study excluded hospital discharge data from the fourth quarter of 2015 (October to December 2015) because the Elixhauser comorbidity index remains under development for ICD-10 coding (Hirode et al., 2020).

Five subpopulations for hospital stays with five major select HANA conditions (cardiovascular disease, liver disease, diabetes, cancer, and bone loss) were also used to compare hospital resource utilization and costs for hospital stays with different comorbidities. An infectious disease domain expert and detailed literature search guided the identification of five major HANA conditions based on the Clinical Classifications Software (CCS) codes. CCS is a diagnosis and procedure categorization scheme based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (Healthcare Cost and Utilization Project, 2017). A list of diseases and respective CCS codes of the specific conditions of these five major categories are described in Appendix A (Table A.1).

5.3.2 Study Variables

Outcome Variable: The outcome variables of the study are the number of procedures used, the length of stay (number of days), and inpatient costs (U.S. Dollar). Total hospital charges were converted to costs using hospital-wide cost-to-charge ratios (CCR) provided by HCUP from accounting reports of the Centers for Medicare and Medicaid Services (Agency for Healthcare Research and Quality, 2018a). When all-payer inpatient cost-to-charge ratios (APICC) were not available, the weighted group average (GAPICC) were used as CCR, as suggested by HCUP data documentation (Agency for Healthcare Research and Quality, 2019a). Hospital charges refer to the amount a hospital billed for the entire hospital stay, excluding professional (e.g., physician) fees. Costs reflect the actual expense incurred in the production of hospital services, including supplies, wages, and utility costs. All costs were adjusted for the inflation to the 2015 U.S. dollars using the Personal Health Care (PHC) - Hospital Care Index from the Centers for Medicare & Medicaid Services (Agency for Healthcare Research and Quality, 2019b). The PHC-Hospital care index for 2015 was divided by each year's PHC index and multiplied these results with the respective year's costs to get the inflation-adjusted inpatient costs. The CMS Office of the Actuary constructs the Personal Health Care Index based on components of the Consumer Price Index- Medical care (CPI-M) and the Producer Price Index (PPI), and additional composite indices (Agency for Healthcare Research and Quality, 2019b). Moreover, costs of each stratum of the Northeast region were multiplied by some adjustment factors to minimize overestimation due to the absence of one large state (Pennsylvania) in 2004 NIS, as suggested by the HCUP data documentation (Agency for Healthcare Research and Quality, 2019a).

Key Independent Variable: The key independent variable is hospital stay status with two levels, namely hospital stay with HIV (HSWH) and hospital stay without HIV (HSWOH). An inpatient hospital stay was designated an HIV associated discharge if the CCS code for HIV is 5 (ICD-9-CM codes: 042, 0420, 0421, 0422, 0429, 0430, 0431, 0432, 0433, 0439, 0440, 0449, 07953, 27910, 27919, 79571, 7958, V08) (Heslin & Elixhauser, 2016). Patient's age during hospital stays is another key independent variable. We describe age groups as 18-34 years, 35-49 years, 50-64 years, and 65+ years. We also used age as a continuous variable to describe the changing likelihood of outcomes across independent variables.

5.3.3 Covariates of the study

Patient-level Characteristics: Patients' sex, race/ethnicity, location, primary payer, and median household income by ZIP code were included as covariates. Elixhauser Comorbidity Software was used to adjust the comorbidity burden of the patients (Agency for Healthcare Research and Quality, 2017b). We used a new index of Elixhauser Comorbidity Software that produces 'single numeric value' index scores (readmission and mortality scores) that describe the comorbidity burden, and that may be more useful for multivariable analyses purpose (B. J. Moore et al., 2017).

Hospital-level Characteristics: Hospital level characteristics examined included elective admission, weekend admission, bed size (small, medium, large), location/teaching status (rural, urban non-teaching, urban teaching), and hospital geographic region (Northeast, Midwest, South, West).

5.3.4 Ethical Statement

Ethical considerations for using NIS data are ensured by the required HCUP Data User Agreement (DUA) training. HCUP Central Distributor removed all identifiable data from the NIS before releasing it to the researchers. Since NIS is non-identifiable secondary data, this study was deemed a non-human subject study by the University of South Carolina Institutional Review Board (#Pro00097307).

5.3.5 Data Analysis

Using the analytic guidelines outlined by HCUP-NIS (Agency for Healthcare Research and Quality, 2018d), a survey-weighted analysis was performed accounting for survey design complexity by using discharge level weights. To adjust the NIS redesign applied in 2012, we used newly generated 'discharge trend weight' provided by the HCUP for 2003 to 2011 to get the consistent yearly national rates (Agency for Healthcare Research and Quality, 2015). Univariate, bivariate, and multivariable analyses were conducted using SAS version 9.4 (Carry, NC).

First, we compared yearly trends of inpatient resource utilization and costs of HSWH and HSWOH. For descriptive analyses, we examined both mean and median to describe the overall patterns of resource utilization and costs. We found, means to be more sensitive to the extreme value of costs and LOS, so we reported the median values only (see Appendix B for mean charts). Second, we compared resource utilization and costs of HSWH and HSWOH across the age groups. For the descriptive purpose, we assessed the trends of differences between HSWH and HSWOH in terms of resource utilization and costs. The differences were calculated by subtracting resource utilization and costs of HSWOH from that of HSWH as shown in equation (1):

Eqn. 1: Difference in inpatient resource utilization/costs = inpatient resource utilization/costs for HSWH – inpatient resource utilization/costs for HSWOH

Third, we depicted yearly trends of differences in resource utilization and costs for hospital stays among the major five HANA conditions. Finally, multivariable modeling was performed to measure the association of the number of procedures, LOS, and costs for hospital stays with HIV and age, controlling for the patient- and hospital-level characteristics. Guided by previous studies using the NIS database (Enomoto et al., 2014; Molloy et al., 2017; Perera et al., 2012; Zou et al., 2019), three Generalized Linear Models (GLMs) were fitted independently with the following outcomes: 1) number of procedures; 2) length of stay; 3) inpatient costs. These models were chosen because these three outcome variables were highly skewed and did not meet the normality assumption of the classical linear model. As the distribution of the number of procedures was observed over-dispersed (variance>mean) with numerous zeros (no procedures), a zero-inflated negative binomial regression model was fitted to determine the predictors of procedures used. Inpatient costs and length of stays were log-transformed and assessed using GLMs with gamma distribution and log link function to estimate the predictors of hospital costs and length of stays. We also ran and described these models for hospital stays with five major HANA conditions separately. To check the missing values, we reran these models keeping the missing observations considering them as 'not missing completely at random (NOMCAR),' and observed no difference with the main models. Statistical significance was assessed at alpha 0.01 due to the study's large sample size.

5.4 Results

5.4.1 Trends of Hospital Resource Utilization and Costs (median), 2003 to 2015

Figure 5.1 depicts the trends of resource usage during hospital stays in terms of the median number of procedures and length of stay (LOS). Although there were some variations in the median number of procedures, similar yearly trends were observed for both HSWH and HSWOH. The median number of procedures were mostly stable over time for both types of hospital stays with frequent fluctuations among HSWH. Median procedures were lower for HSWH most of the years, yet differences were diminishing over the years. The median LOS for HSWH was consistently higher than HSWOH, but the median decreased over the years (Figure 5.1).

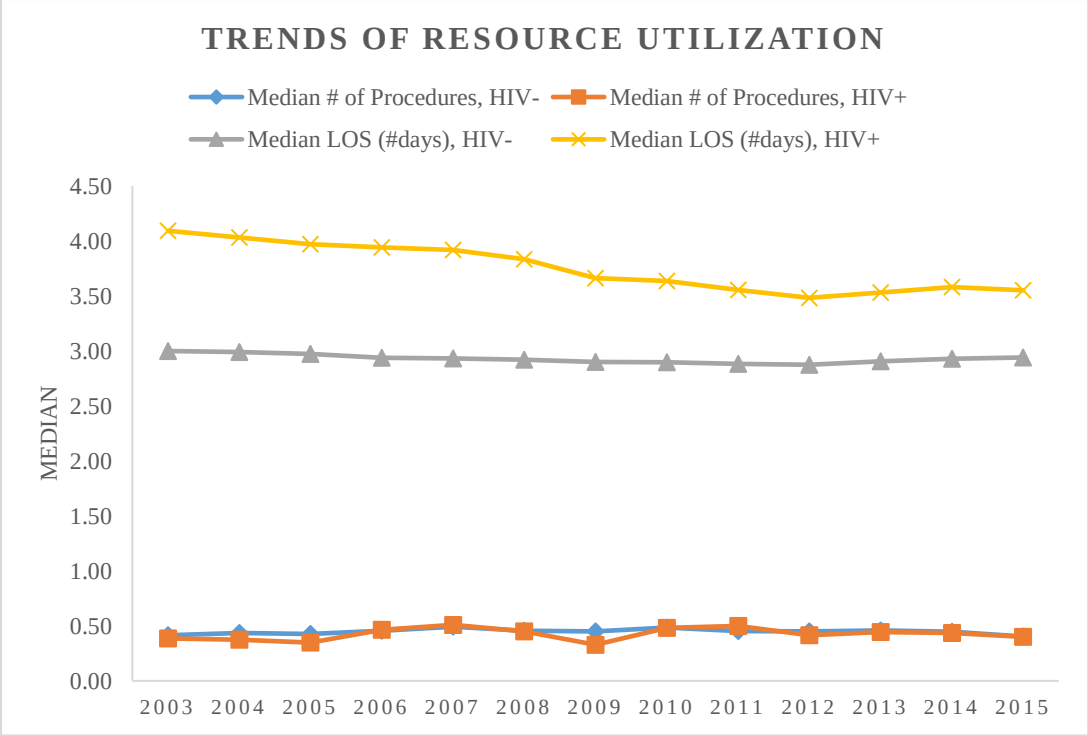


Figure 5. 1 Trends of median resource utilization during hospital stays, 2003 to 2015.

Figure 5.2 illustrates the yearly trends of median inpatient costs during hospital stays, adjusted in 2015-U.S. dollars. Regular fluctuations were observed in median costs for HSWH, which ended with a consistent increase of median costs from 2012 to 2015, while median costs consistently increased for HSWOH except for a drop in 2009. The median costs were consistently higher for HSWH at the beginning of the study period but became lower than HSWOH in 2009 and afterward (Figure 5.2).

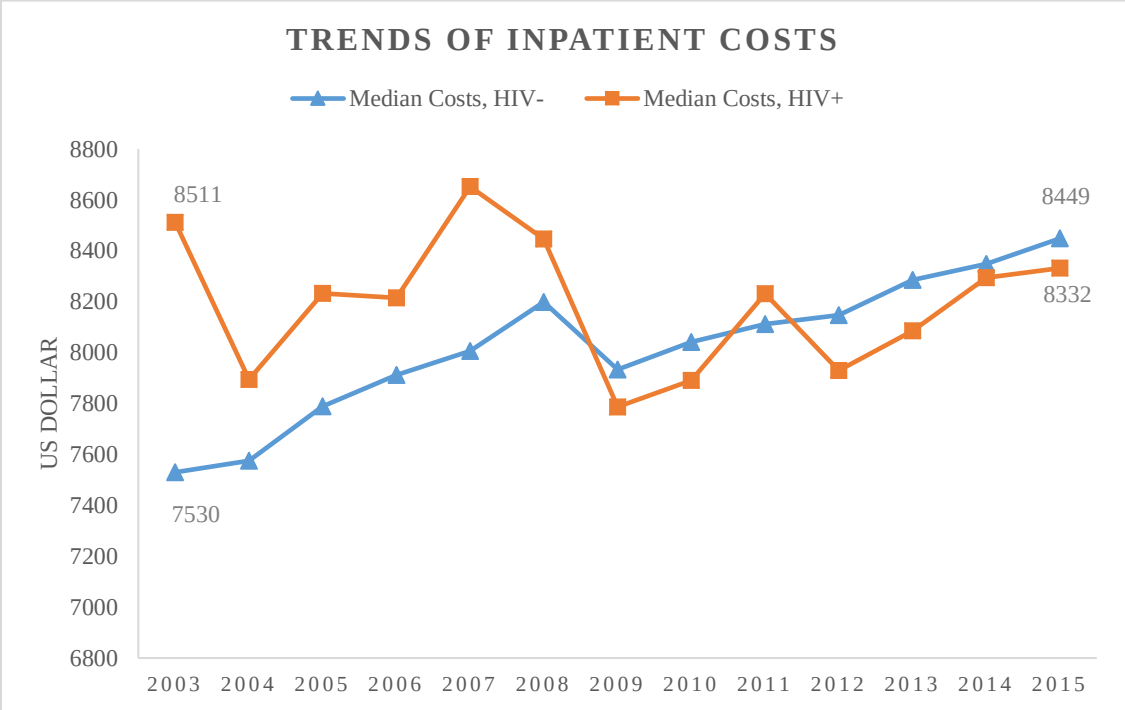


Figure 5. 2 Trends of median inpatient costs (US$) during hospital stays, 2003 to 2015

5.4.2 Trends of Age-Specific Resource Utilization and Costs (median), 2003 to 2015

Table 5.1 shows the median inpatient resource utilization (#procedures and LOS) and costs across age groups over the years. The median number of procedures decreased for both types of hospital stays for all age groups except patients aged 65+ years. Among patients of 65+ years old, the median number of procedures increased for both types of stays from 2003 to 2015, but the increase was higher for HSWH. The median inpatient

LOS decreased for HSWH among all age groups, while it increased among younger adults (18-35 and 36-49 years) but decreased among elderly (65+ years) for HSWOH. The median inpatient costs decreased among all age groups of patients during HSWH except for the elderly, compared to the over the year increase among all age groups for HSWOH (Table 5.1).

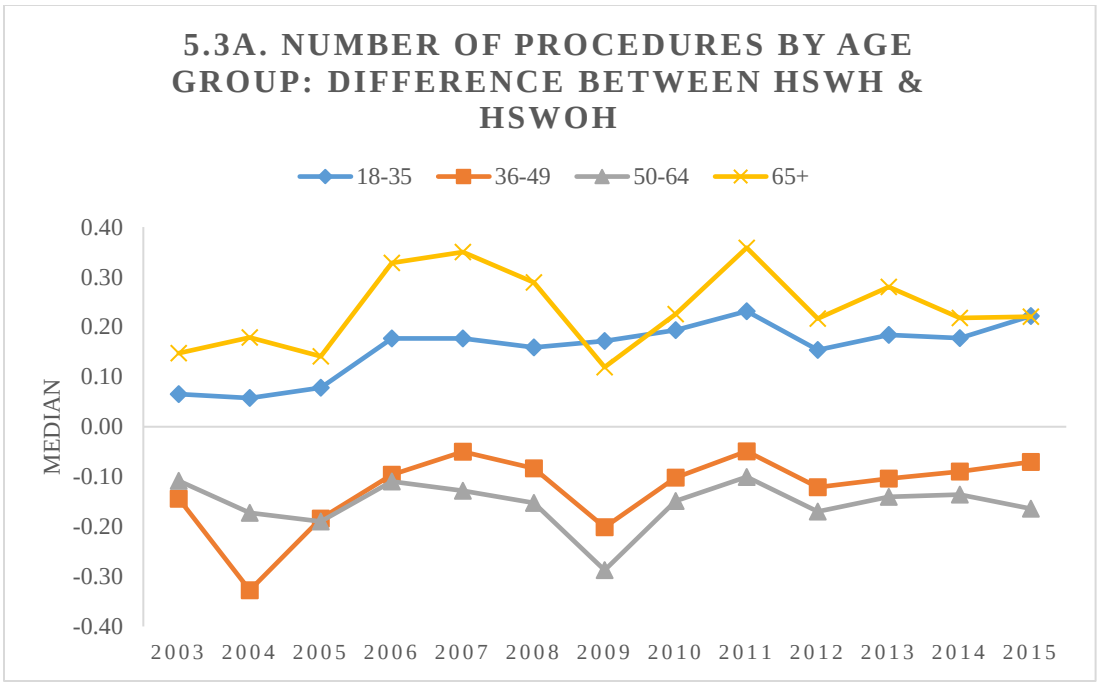
Figure 5.3 describes the differences between HSWH and HSWOH in terms of hospital resource utilization and costs. In figure 5.3A, differences in the median number of procedures for younger (18-35 years) and elderly (65+ years) were positive over the years, which indicates higher median procedure usages for HSWH. Procedure usages were lower for HSWH among aged 36-49 years and 50-64 years, which produces negative differences (HSWH<HSWOH) over the years. Increasing trends in difference lines suggest that the gap in procedure usage increased over the study period among aged 18-35, 36-49, and 65+ years, while the differences were almost stable among 50-64 years old patients.

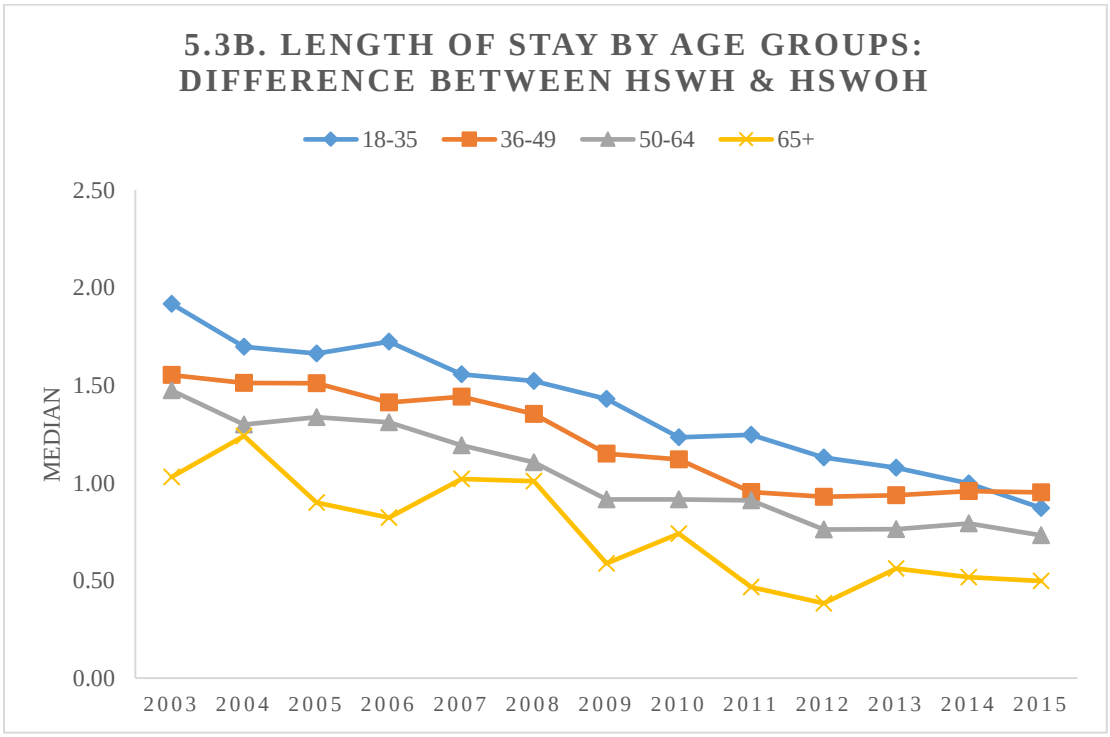
In figure 5.3B, differences in median LOS between HSWH and HSWOH were consistently positive (HSWH>HSWOH) but decreasing for all age groups over the years, which indicates that median LOS for HSWH and HSWOH were getting closer over the study period. Similarly, in figure 5.3C, differences in median inpatient costs were decreasing over time for all age groups, which indicates that the inpatient costs were getting similar for HSWH and HSWOH over the years. The positive cost differences (HSWH>HSWOH) among the patients aged 50-64 years became negative (HSWH<HSWOH) in 2008 and afterward, which suggests substantial changes in the hospital costs between HSWH and HSWOH over the years.

Table 5. 1 Inpatient resource utilization and costs (median) by age groups during hospital stays, 2003 to 2015.

# of Procedures														
	2003		2004		2005		2006		2007		2008		2009	
Age (years)	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
18-35	0.26	0.32	0.28	0.34	0.24	0.32	0.25	0.43	0.27	0.45	0.22	0.38	0.18	0.36
36-49	0.49	0.35	0.66	0.34	0.49	0.30	0.50	0.40	0.52	0.47	0.49	0.40	0.47	0.26
50-64	0.65	0.54	0.66	0.49	0.65	0.46	0.69	0.58	0.71	0.58	0.69	0.54	0.67	0.38
65+	0.31	0.45	0.33	0.51	0.34	0.48	0.37	0.69	0.42	0.77	0.37	0.66	0.39	0.51
Overall (yearly)	0.41	0.38	0.44	0.38	0.43	0.35	0.46	0.46	0.49	0.51	0.46	0.45	0.45	0.33
	2010		2011		2012		2013		2014		2015		All years	
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV-	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
18-35	0.25	0.45	0.20	0.43	0.17	0.32	0.16	0.34	0.12	0.30	0.08	0.30	0.21	0.37
36-49	0.52	0.42	0.49	0.44	0.48	0.35	0.47	0.37	0.47	0.38	0.42	0.35	0.49	0.37
50-64	0.71	0.56	0.67	0.57	0.66	0.49	0.66	0.52	0.64	0.51	0.61	0.44	0.67	0.51
65+	0.40	0.63	0.38	0.74	0.39	0.60	0.41	0.69	0.40	0.61	0.35	0.57	0.37	0.62
Overall (yearly)	0.49	0.48	0.45	0.50	0.45	0.42	0.46	0.45	0.45	0.44	0.40	0.40	0.45	0.43
LOS (days)														
	2003		2004		2005		2006		2007		2008		2009	
Age (years)	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
18-35	2.27	4.19	2.33	4.03	2.29	3.95	2.33	4.05	2.35	3.91	2.35	3.87	2.37	3.80
36-49	2.42	3.97	2.45	3.97	2.40	3.91	2.42	3.83	2.41	3.85	2.40	3.75	2.41	3.56
50-64	2.82	4.29	2.82	4.12	2.79	4.13	2.77	4.08	2.78	3.97	2.76	3.87	2.78	3.69
65+	3.58	4.60	3.54	4.78	3.52	4.41	3.43	4.25	3.40	4.42	3.38	4.38	3.31	3.90
Overall (yearly)	3.00	4.09	2.99	4.03	2.97	3.97	2.94	3.94	2.93	3.92	2.92	3.83	2.90	3.66

	2010		2011		2012		2013		2014		2015		All years	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV-**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	2.40	3.63	2.39	3.64	2.43	3.56	2.47	3.55	2.55	3.54	2.57	3.44	2.39	3.81
36-49	2.42	3.54	2.42	3.38	2.45	3.38	2.49	3.43	2.55	3.51	2.58	3.53	2.44	3.71
50-64	2.78	3.69	2.77	3.68	2.77	3.53	2.80	3.56	2.83	3.62	2.83	3.56	2.79	3.78
65+	3.30	4.04	3.23	3.69	3.19	3.58	3.22	3.78	3.22	3.74	3.23	3.72	3.35	3.95
Overall (yearly)	2.90	3.63	2.88	3.55	2.87	3.48	2.90	3.53	2.93	3.58	2.94	3.55	2.93	3.76
COSTS (U.S. Dollar)														
	2003		**2004**		**2005**		**2006**		**2007**		**2008**		**2009**	
Age (years)	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	5859	7997	5770	7313	6004	7635	6041	8018	6094	7980	6224	8041	5935	7565
36-49	6628	8255	6561	7697	6792	7891	6884	8018	6970	8367	7201	8094	6932	7364
50-64	8097	9617	8135	8641	8385	9250	8537	9047	8652	9305	8946	8915	8556	8296
65+	8084	9456	8224	9796	8357	10632	8514	10080	8576	10625	8710	10562	8515	9158
Overall (yearly)	7530	8511	7575	7895	7789	8233	7912	8215	8006	8652	8198	8447	7934	7787
	2010		**2011**		**2012**		**2013**		**2014**		**2015**		**All years**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
18-35	6100	7687	6089	7923	6064	7467	6096	7402	6100	7425	6169	7321	6035	7680
36-49	7075	7493	7204	7634	7205	7470	7288	7609	7365	7854	7396	7912	7001	7779
50-64	8740	8273	8796	8878	8806	8390	8946	8616	9025	8799	9110	8664	8675	8749
65+	8542	9318	8552	9263	8628	8898	8776	9654	8820	9472	8934	9849	8549	9638
Overall (yearly)	8042	7890	8112	8231	8147	7929	8286	8085	8348	8294	8449	8332	8019	8180


5.3A. NUMBER OF PROCEDURES BY AGE GROUP: DIFFERENCE BETWEEN HSWH & HSWOH
18-35
36-49
50-64
65+
MEDIAN
0.40
0.30
0.20
0.10
0.00
-0.10
-0.20
-0.30
-0.40
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015


5.3B. LENGTH OF STAY BY AGE GROUPS: DIFFERENCE BETWEEN HSWH & HSWOH
18-35
36-49
50-64
65+
MEDIAN
2.50
2.00
1.50
1.00
0.50
0.00
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015

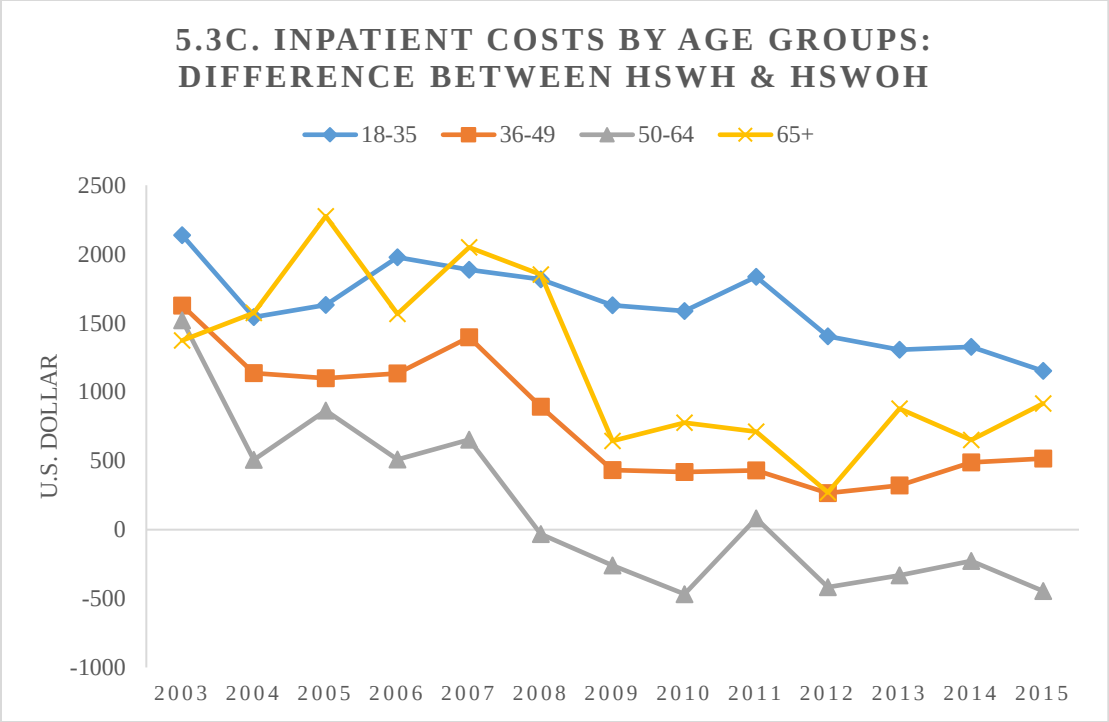


Figure 5. 3 Differences in inpatient resource utilization and costs (median) between hospital stays with and without HIV (HSWH-HSWOH), 2003 to 2015; (A) Number of procedures, (B) Length of stay (LOS), and (C) Inpatient costs.

5.4.3 Resource Utilization and Costs for Hospital Stays with Major HANA Conditions

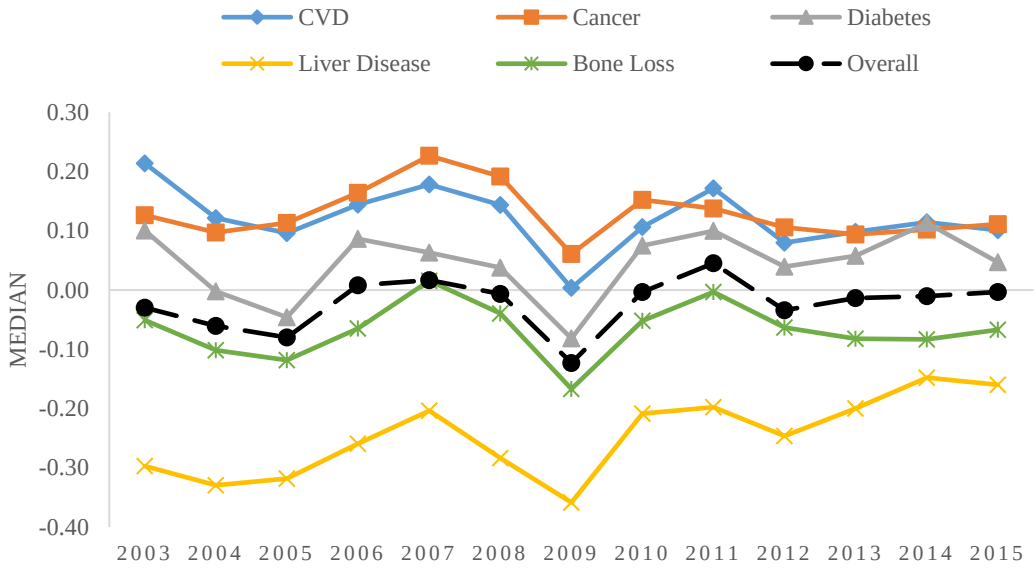
Figure 5.4 shows trends of the differences between HSWH and HSWOH in terms of median resource utilization and costs of care during hospital stays with five major HANA conditions. In figure 5.4A, differences in the median number of procedures over the years for five major HANA conditions were similar to the overall trends (all-cause hospital stays). Like overall trends, trends of differences in procedure usage for bone loss, diabetes, and cancer were mostly unchanged over the study period, after some fluctuations. However, differences in procedure usage for liver disease increased but decreased for CVD over the study period. Similar to the overall trend line, hospital stays with liver disease, and bone loss showed negative differences in procedure usage over this period, which

indicates a higher median number of procedures among HSWOH compared to HSWH. Trends for differences in resource usage during hospital stays with cancer, CVD, and diabetes had positive differences over time, which reflects a higher number of procedures for HSWH compared to HSWOH (Figure 5.4A).

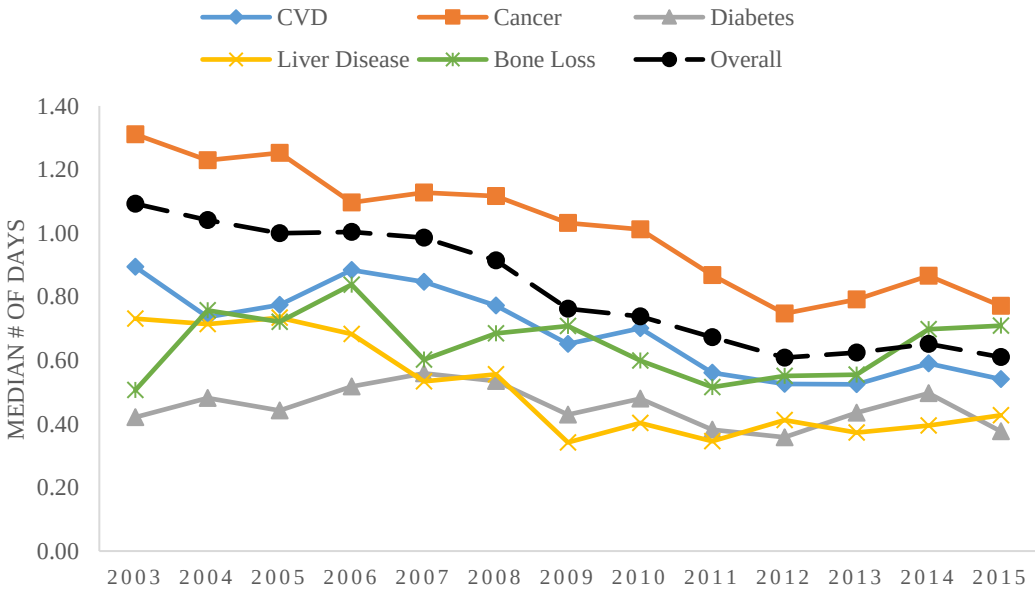
In figure 5.4B, similar to the overall (all-cause hospital stays) trend line, decreasing trends of difference in median LOS were observed for hospital stays with cancer, CVD, and liver disease. Increased differences in median LOS for hospital stays with bone loss represent the increasing gap between HSWH and HSWOH over time in terms of hospital LOS. Differences in median LOS were unchanged for diabetes after several fluctuations over the years. All years' positive differences in median LOS indicates that LOS were consistently higher for HSWH over the study period for general hospital stays as well as for hospital stays with five major HANA conditions (Figure 5.4B).

Figure 5.4C shows that differences in median costs for all-cause hospital stays (overall) were decreased over the study period and became negative (lower costs for HSWH) in 2009 and afterward. Decreased differences in median costs were also observed during hospital stays for all major five HANA conditions. Differences in median costs were positive (HSWH>HSWOH) for hospital stays with CVD and cancer, while it was negative (HSWH<HSWOH) for liver disease and bone loss. There were regular fluctuations in almost all trends line, but the drops in cost differences occurred for hospital stays with all five major HANA conditions during the recession period (2008 and 2009) (Figure 5.4C).

5.4A. PROCEDURE USE FOR MAJOR HANA CONDITION: DIFFERENCE BETWEEN HSWH & HSWOH



5.4B. LENGTH OF STAYS FOR MAJOR HANA CONDITION: DIFFERENCE BETWEEN HSWH & HSWOH



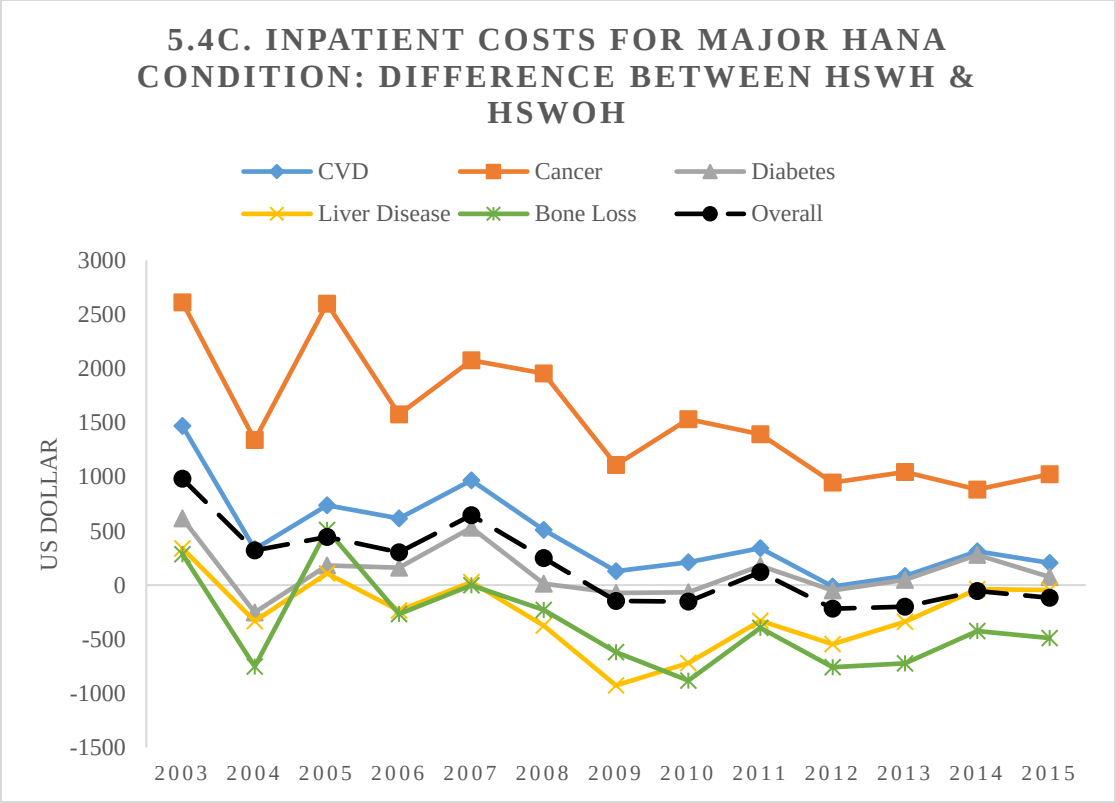


Figure 5. 4 Trends of differences in inpatient resource utilization and costs (median) between hospital stays with and without HIV (HSWH-HSWOH) for hospital stays with major HANA conditions, 2003 to 2015; (A) Number of procedures, (B) Length of stay (LOS), and (C) Inpatient costs.

5.4.4 Multivariable Analyses

The results of the multivariable analyses are presented in Table 5.2 using the exponential of β and 99% Confidence Interval (CI). Zero-inflated negative binomial model [zero-model is presented in Appendix B (Table B.1)] represents the predictors of the number of procedures used during hospital stays, and generalized linear models (GLMs) represent the predictors of hospital LOS and costs. All the estimates presented in table 5.2 were statistically significant at the *P*-value of less than 0.01 unless otherwise stated.

Number of Procedures: In the unadjusted model, the relationship between the number of procedures and hospital stays with HIV (HSWH) was negative (exp β<1). When

controlled for the patient and hospital-level covariates, HSWH had a 30% lower utilization of procedures compared to HSWOH. Each 10-year increase in patient's age increased the number of procedure counts by 3%.

In terms of covariates, females, African Americans, Hispanics, Medicare and Medicaid beneficiaries, and uninsured had lower procedure usage compared to their male, white, and privately insured counterparts, respectively. Weekend admission, inpatient stays in rural hospitals, and in Midwest and South also had fewer procedure counts compared to their respective reference categories. Besides, procedure usage increased for hospital stays by non-metro patients, highest median income quartile, large bed size hospitals, and when admission was elective, and that occurred in an urban teaching hospital, and West compared to their respective reference categories. Also, longer hospital LOS were the significant predictors of higher procedure use (Table 5.2).

Length of Stays: In the unadjusted model, the association of LOS with HIV and age were positive (exp β>1). Similarly, controlling for the patient and hospital-level covariates, the average length of stays was 32% higher for HSWH, and LOS increased slightly by 1% per ten years of age.

African Americans, Medicare and Medicaid beneficiaries, uninsured, and higher number of procedures were significant predictors of higher LOS during inpatient stays. Non-metro patient location, higher-income quartiles, elective admission, medium bed size hospitals, rural hospitals, and regions other than Northeast were significant predictors of lower LOS compared to their respective reference categories. Also, the number of procedures were strong predictors of LOS (Table 5.2).

Inpatient Costs: In the unadjusted model, the relationship between inpatient costs and HSWH and age were positive (exp β>1). Controlling for the patient and hospital-level covariates, the associations of age and HIV with the costs were the same. HSWH had 13% higher inpatient costs than HSWOH. A ten-years increase in age elevated the costs by 2%.

Females, Medicare and Medicaid recipients, uninsured, weekend admissions, medium and large bed size hospitals, and hospitals from rural and South were the predictors of lower inpatient costs compared to their reference categories. Hispanics, non-metro patient location, higher-income quartiles, elective admissions, urban teaching hospitals, and the West region were the predictors of higher costs during hospital stays. Also, hospital LOS and number of procedures were strong predictors of inpatient costs (Table 5.2).

5.4.5 Multivariable GLMs for hospital stays with major HANA conditions

Table 5.3 represents the estimates for resource utilization and costs for the independent variable, i.e., hospital stays with HIV and age, controlling for patient and hospital-level covariates. Unlike the all-cause procedure model, age affects the procedure usage negatively for hospital stays with major HANA conditions, except liver disease. For hospital stays with CVD, cancer, diabetes, and bone loss, utilization of procedures decreased by 3%, 2%, 1%, and 5% with per ten-year increase in age, respectively. The positive associations of hospital LOS with age and HSWH in the all-cause LOS model remained similar for all five major HANA conditions, even though the magnitude of the relationships expressed by the exponential of β and 99% CI differs across the HANA conditions (Table 5.3).

Table 5. 2 Predictors of inpatient resource utilization and costs during hospital stays, 2003-2015 from the Generalized Linear Models (GLM)[a].

	Number of Procedures			Length of Stay (LOS)			Inpatient Costs		
Variables	**Exp (*β*)***	**99% CI**		**Exp (*β*)***	**99% CI**		**Exp (*β*)***	**99% CI**	
		Min	Max		Min	Max		Min	Max
Unadjusted Model	N= 69,633,686 (weighted 343 million)			N= 69,633,686 (weighted 343 million)			N=65,582,213 (weighted 324 million)		
Intercept	1.34	1.34	1.34	4.04	4.03	4.04	10917	10910	10926
HSWH (Ref.= HSWOH)	0.79	0.78	0.81	1.63	1.62	1.65	1.11	1.10	1.12
Age (per 10 years)	1.05	1.05	1.05	1.04	1.04	1.04	1.03	1.03	1.03
Adjusted Model	N=55,231,368 (weighted 272 million)			N=55,231,368 (weighted 272 million)			N=51,704,466 (weighted 255 million)		
Intercept	1.10	1.09	1.10	3.51	3.50	3.52	4144	4139	4148
HSWH (Ref.= HSWOH)	0.70	0.68	0.71	1.32	1.31	1.34	1.13	1.12	1.14
Age (per 10 years)	1.03	1.03	1.03	1.01	1.01	1.01	1.02	1.02	1.02
Patient-level characteristics									
Sex									
Male	1.00			1.00			1.00		
Female	0.89	0.89	0.89	1.00 †	1.00	1.00	0.97	0.97	0.97
Race/ethnicity									
White	1.00			1.00			1.00		
African American	0.95	0.95	0.95	1.05	1.05	1.05	1.00	1.00	1.01
Hispanic	0.99	0.99	0.99	0.99	0.99	0.99	1.03	1.03	1.03
Others	1.04	1.04	1.05	1.04	1.04	1.04	1.03	1.03	1.03
Expected primary payer									

Private including HMO	1.00			1.00			1.00		
Medicare	0.86	0.86	0.86	1.19	1.19	1.19	0.97	0.97	0.97
Medicaid	0.83	0.83	0.83	1.30	1.30	1.30	0.93	0.93	0.93
Self-pay	0.86	0.86	0.87	1.06	1.06	1.06	0.94	0.94	0.94
Others (incl. No charge)	0.95	0.95	0.95	1.12	1.12	1.12	0.98	0.98	0.98
Patient's location (rurality)[b]									
Large metropolitan	1.00			1.00			1.00		
Small metropolitan	1.03	1.03	1.03	0.98	0.98	0.99	0.99	0.99	0.99
Micropolitan areas	1.23	1.23	1.24	0.97	0.97	0.97	1.05	1.05	1.05
Not metropolitan or micropolitan	1.15	1.15	1.16	0.98	0.98	0.98	1.04	1.04	1.04
Median Household Income in ZIP									
0-25th percentile	1.00			1.00			1.00		
26th to 50th percentile	1.04	1.04	1.04	0.97	0.97	0.97	1.04	1.04	1.04
51st to 75th percentile	1.04	1.04	1.04	0.95	0.95	0.95	1.07	1.07	1.07
76th to 100th percentile	1.06	1.06	1.06	0.94	0.94	0.94	1.11	1.11	1.11
Readmission scores	1.00	1.00	1.00	1.01	1.01	1.01	1.00	1.00	1.00
Mortality scores	1.01	1.01	1.01	1.01	1.01	1.01	1.00	1.00	1.00
Hospital-level characteristics									
Weekend admission									
No	1.00			1.00			1.00		
Yes	0.95	0.95	0.95	0.99	0.99	0.99	0.98	0.98	0.98
Elective admission									
Non-elective	1.00			1.00			1.00		

Elective	1.24	1.24	1.24	0.98	0.98	0.98	1.30	1.30	1.30
Bed size									
Small	1.00			1.00			1.00		
Medium	1.14	1.14	1.15	0.95	0.95	0.95	0.97	0.97	0.98
Large	1.25	1.25	1.25	1.01	1.00	1.01	0.96	0.96	0.97
Location/teaching status of the hospital									
Urban non-teaching	1.00			1.00			1.00		
Rural	0.66	0.66	0.66	0.97	0.97	0.97	0.97	0.96	0.97
Urban teaching	1.18	1.18	1.18	1.01	1.01	1.01	1.04	1.04	1.04
Region									
Northeast	1.00			1.00			1.00		
Midwest	0.96	0.96	0.96	0.88	0.88	0.88	0.99	0.99	0.99
South	0.97	0.97	0.97	0.92	0.92	0.92	0.95	0.95	0.95
West	1.02	1.02	1.02	0.88	0.88	0.88	1.22	1.22	1.22
LOS	1.03	1.03	1.03	N/A			1.07	1.07	1.07
Number of procedures	N/A			1.12	1.12	1.12	1.18	1.18	1.18

*All betas (*β)* were statistically significant at *P*<0.01, unless stated by [ɨ] superscript.

[ɨ] Estimate was not statistically significant at P<0.01.

(a) All models are controlled for year variables (2003 to 2015).

(b) Large metropolitan areas include central counties of metro areas (>1 million) and fringe counties of metro areas (≥1 million), and small metropolitan areas contain counties in metro areas with 50,000-999,000 population. See methods section for details.

In Table 5.3, multivariable cost models for hospital stays with liver disease and bone loss were very similar to general (all-cause hospital stays) cost models that HSWH and age are positively associated with costs. However, cost models for CVD and Diabetes are different from the general cost model; inpatient costs did not change significantly with patient's age. In the case of hospital stays with cancer, the multivariable model showed inverse relationships of age and HSWH that we found in the general cost models. For hospital stays with cancer, inpatient costs were significantly lower for HSWH and younger (Table 5.3).

5.5 Discussion

The current study described hospital resource utilization and costs in the United States for thirteen years and identified some critical issues. The procedure use during hospital stays was lower among HSWH, but it increased substantially among older HSWH compared to HSWOH. While the LOS and costs for HSWH were higher than that for HSWOH, differences narrowed down over the study period among all age groups. Multivariable analyses demonstrate that inpatient LOS and costs were significantly higher among HSWH and older.

Table 5. 3 Predictors of resource utilization and costs from the Generalized Linear Models (GLM)[a] for hospital stays with major HANA conditions, 2003-2015.

	Number of Procedures			Length of Stays (LOS)			Inpatient Costs		
Adjusted models	**Exp (*β*)***	**99% CI**		**Exp (*β*)***	**99% CI**		**Exp (*β*)***	**99% CI**	
		Min	Max		Min	Max		Min	Max
CVD	N=40,276,849 (weighted 198 million)			N=40,276,849 (weighted 198 million)			N=37,742,702 (weighted 186 million)		
Intercept	1.84	1.83	1.85	3.36	3.35	3.37	5057	5050	5064
HSWH (Ref.= HSWOH)	0.63	0.61	0.65	1.32	1.30	1.34	1.03	1.02	1.04
Age (per 10 years)	0.97	0.96	0.97	1.01	1.01	1.01	1.00 †	1.00	1.00
Cancer	N=9,118,172 (weighted 45 million)			N=9,118,172 (weighted 45 million)			N=8,543,770 (weighted 42 million)		
Intercept	1.48	1.47	1.49	3.52	3.50	3.54	5552	5534	5570
HSWH (Ref.= HSWOH)	0.76	0.72	0.80	1.43	1.38	1.48	0.98	0.96	1.00
Age (per 10 years)	0.98	0.97	0.98	1.02	1.02	1.02	0.98	0.98	0.98
Diabetes	N=15,408,908 (weighted 76 million)			N=15,408,908 (weighted 76 million)			N=14,454,669 (weighted 71 million)		
Intercept	1.42	1.41	1.43	3.40	3.38	3.41	4680	4669	4691
HSWH (Ref.= HSWOH)	0.59	0.56	0.63	1.26	1.22	1.31	1.07	1.05	1.09
Age (per 10 years)	0.99	0.99	0.99	1.02	1.02	1.02	1.01	1.01	1.01
Liver Disease	N=5,262,320 (weighted 26 million)			N=5,262,320 (weighted 26 million)			N=4,926,126 (weighted 24 million)		

Intercept	0.98	0.97	0.99	3.22	3.20	3.24	5119	5101	5138
HSWH (Ref.= HSWOH)	0.80	0.77	0.84	1.51	1.47	1.55	1.10	1.08	1.12
Age (per 10 years)	1.03	1.03	1.03	1.02	1.02	1.02	1.01	1.01	1.01
Bone Loss	N=13,648,868 (weighted 67 million)			N=13,648,868 (weighted 67 million)			N=12,804,190 (weighted 63 million)		
Intercept	1.85	1.83	1.86	3.19	3.18	3.21	5020	5007	5033
HSWH (Ref.= HSWOH)	0.51	0.48	0.55	1.42	1.36	1.47	1.12	1.09	1.15
Age (per 10 years)	0.95	0.94	0.95	1.03	1.03	1.03	1.01	1.01	1.01

*All betas (*β)* were statistically significant at $P<0.01$, unless stated by [†] superscript

[†] Estimate was not statistically significant at $P<0.01$

(a) HANA-specific models are controlled for sex, race/ethnicity, median household income, primary payer, patient's location, weekend, elective admission, bed size, location/teaching status of the hospitals, region, comorbidity scores, number of procedures, length of stay, and year.

The number of procedures used during the U.S. inpatient stays is an essential indicator of hospital resource utilization. This study found that on average HSWH used fewer procedures than HSWOH, which may indicate delay or avoidance of nonurgent procedures due to the risk of person-to-person transmission in healthcare settings from performing invasive procedures and exposure-prone procedures (Flint et al., 2011; Mitchell, Lewis, Maillard, Moore, & Weber, 2020; Polder et al., 1991). However, the aging of PLWH might allow less flexibility to delay or avoid those procedures, because the virus consistently activates the immune cells that make the individuals susceptible to inflammation-induced diseases and diminishes their capacity to fight some diseases (Fauci et al., 2010). Thus, the current study found disproportionate increase in procedure use among elderly patients for HSWH compared to HSWOH. Consistent with the increasing HSWH by older (Siddiqi, Olatosi, Ostermann, Zhang, & Khan), this study also showed an increased number of procedures over the years for HSWH. We found no studies which reported trends of procedures use during inpatient stays with all diagnoses; however, a study reported increasing trends of the number of procedures among patients with the Hepatitis C virus (Younossi et al., 2015). Studying procedure use is important because of its role as a principal hospital cost driver (McDermott, Freeman, & Elixhauser, 2017; Okunji et al., 2016). The number of procedures performed during inpatient stay contributes to the longer length of stay, which may impact overall inpatient costs (Younossi et al., 2015).

A longer duration of hospital stays is more common among the PLWH compared to non-PLWH (Akgün et al., 2013; Pearce et al., 2012). While LOS is significantly higher for HSWH, decreasing trends of differences in LOS between HSWH and HSWOH may

indicate that the hospital resource use for PLWH is getting similar to that of other patients. Previous hospital-based studies (Heslin & Elixhauser, 2016; Tai, Liu, & Merchant, 2015; Zhao et al., 2007) and population-based studies (Yehia et al., 2010) demonstrated decreasing trends of inpatient days among HSWH. This decrease among HSWH is probably due to improved HIV care and services and presenting with similar conditions as other hospital stays (Tai et al., 2015). However, this study observed overall higher length of inpatient stays among HSWH compared to HSWOH. Longer duration of stays by the symptomatic PLWH may contribute to keeping the average duration of stays up, when hospital stays by asymptomatic PLWH are very similar to that of non-PLWH patients (Rowell-Cunsolo et al., 2018).

Despite the positive effect of HIV infection on hospital LOS, the LOS decreased over time for HSWH among all age groups, which may indicate LOS for HSWH is less affected by the aging of PLWH. This may occur because LOS for HSWH is longer among younger; thus, little change is observed with increasing age. This is the opposite of HSWOH, where LOS increases with age. Similar to this finding, a previous study found higher mean LOS among older patients (Weiss & Elixhauser, 2014). These findings are the opposite of our hypothesis that HSWH have a higher burden of comorbidities and longer inpatient stays compared to their HSWOH with increasing age. The first paper of this series showed an overall lower prevalence of HANA conditions among any age groups of PLWH compared to non-PLWH during their hospital stays, yet the differences were getting narrower over time among older (Siddiqi et al.). This study demonstrates prolonged hospital stays for HSWH but the higher impact of aging on HSWOH. Previous studies showed that PLWH aged 50 years or older have higher hospitalization rates and length of

stay compared to younger PLWH in the United States (S. A. Berry et al., 2012; Fleishman et al., 2005; Tadros et al., 2012). However, these studies are lacked non-PLWH comparators. The lack of studies comparing hospital stays across age between HSWH and HSWOH made these study findings incomparable to the existing evidence.

Although previous studies showed increasing trends of inpatient costs over the years for HSWH (Zhao et al., 2007), our study observed decreasing trends of inpatient costs among HSWH over the study period. The sharp drops in inpatient resource utilization and costs for HSWH during the recession period (2008 and 2009) suggest that HSWH were disproportionately affected by the U.S. economic recession compared to HSWOH. In addition, due to the availability of HAART and fewer hospitalization with AIDS-defining illnesses, previous studies have projected lower health care costs for PLWH (Harling & Wood, 2007; Hellinger, 1998; Meyer-Rath et al., 2013; Shapiro et al., 1999). However, consistent with the previous studies (H. Krentz & Gill, 2015; Zingmond et al., 2017), overall inpatient costs were found higher among HSWH compared to HSWOH during the study period. The frequent and lengthy hospitalizations are common among some PLWH that are considered as important cost predictors (S. A. Berry et al., 2012; Bozzette et al., 2001; Guaraldi et al., 2013). Our study also found significantly higher LOS among HSWH and identified LOS as a significant predictor of inpatient costs. A large portion of these higher inpatient costs might be due to an increased proportion of HSWH by older patients (Siddiqi et al., unpublished). Previous studies suggest that the average cost of HIV care is consistently higher for older PLWH than younger PLWH (Gebo et al., 2010; Guaraldi et al., 2013). With the aging of PLWH, despite a CD4 count equivalent to those of younger patients, older patients still account for a higher burden of care and costs (H. Krentz & Gill,

2015). The reduction of total care cost observed with increased CD4 cell count was counterbalanced by the cost increase due to the increased age of the PLWH (Guaraldi et al., 2013). While the current study observed a substantial increase in inpatient costs for HSWOH over time among all age groups, costs for HSWH decreased over time among all age groups except the elderly. The Ryan White HIV/AIDS Treatment Extension Act of 2009 might have a great contribution to reduce inpatient costs because it enables both premium and cost-sharing coverage for the severely impacted areas or States through this extension (Crowley & Kates, 2013). Also, this extension might enable HSWH to keep inpatient costs lower than that of HSWOH in 2009 and afterward. An increase in overall all-cause inpatient costs among older patients (B. Moore, Levit, & Elixhauser, 2014) reflects the cost increase among HSWOH with age. Also, decreasing trends of median inpatient costs for HSWH and increasing trends for HSWOH and older in recent years also support the impact of aging on inpatient costs of HSWOH.

In our study, similar results from the models for hospital stays with major HANA conditions demonstrate that the impact of the aging of PLWH on inpatient resource utilization and costs does not vary for hospital stays with different major HANA conditions, except few exceptions. As discussed earlier, with increased age, inpatient costs for HSWH became similar to HSWOH; thus, our study did not observe substantial cost variations with the aging of PLWH. Similar things also observed in cost models for major HANA conditions. No significant variations were found between HSWH and HSWOH with the aging during hospital stays with CVD and diabetes. Previous studies projected higher resource utilization and costs as PLWH are living longer with multiple comorbidities (Ward et al., 2020); thus future studies incorporating multiple HANA

conditions are required to understand the effect of increased age-related comorbidities on inpatient costs. However, the real impact of aging PLWH on inpatient resource use and costs might be underreported in our study because of the higher hospital readmission by the PLWH than their non-PLWH counterparts (S. Berry et al., 2016; Coelho et al., 2017). Since NIS does not contain unique patient identifiers, it is not possible to identify readmission and measure the true inpatient resource utilization and costs. Therefore, hospital resource use patterns by the PLWH during hospital stays might be different from the other health care settings.

5.6 Limitations

While this study provides a detailed picture of the impact of the aging PLWH on U.S. inpatient stays, study findings should be interpreted with certain limitations (Hashimoto et al., 2014; Sarrazin & Rosenthal, 2012). First, the unit of analysis of this study is hospital stay, so all numbers and estimates represent the records of hospital stays, and does not reflect individual-level information. NIS is not a longitudinal survey; thus, there may be repeat hospitalization by an individual in a year or next (in case of pooled data) with the same or different conditions. Patients with a high number of repeat hospital stays may have skewed the findings. Unfortunately, the NIS did not contain unique patient identifiers that would enable linking multiple hospitalizations by the same patient. Nevertheless, given that the main objective of this study was to examine the association of HIV and aging with hospital resource utilization and costs, the study results still provide critical facts to inform the public health community. Second, this study excluded hospital records that were discharged on the same day, and that indicated neonatal or pregnant issues. Thus, the results are not reflective of all U.S. hospital stays, even though this study

represent all-cause U.S. hospital stays. Also, the results are not reflective of hospital stays in long-term care facilities, such as rehabilitation, psychiatric, alcoholism, and chemical dependency hospitals, because the NIS collects data from U.S. short-term U.S. community hospitals.

Third, the accuracy of claims data depends on the quality and consistency of coding by participating hospitals. Thus, the ICD-9-CM codes we used to characterize patients' illnesses may not accurately capture the primary reasons for patient's hospitalization because hospitals use these codes primarily for billing purposes. In this study, we described the principal diagnosis as well as all-listed diagnoses that may minimize the impact of coding bias substantially. Fourth, HCUP only provides hospital-wide cost-to-charge ratios, which help to understand overall (all-cause) inpatient costs but may bias HANA-associated costs in our study. Individual department- or disease-specific ratios might produce more accurate cost estimates for the U.S. inpatient department; however, these ratios are not available for NIS. Fifth, the number of diagnoses and procedures vary State by State; that is, while some States provide as many as 74 diagnoses and 47 procedures, others may provide as few as 9 diagnoses and 6 procedures. This could result in inconsistent prevalence estimates. We checked the impact of this inconsistent data structure by conducting sensitivity analyses. We calculated averages and reran the models after removing reporting discrepancies across the States, and found similar results due to the relatively few cases with a higher number of diagnoses and procedures. Finally, the analysis of a database containing a large sample can increase the possibility of a type-I error, i.e., falsely concluding that there is an important association where none exists (Lin, Lucas Jr, & Shmueli, 2013). A statistical test with a large sample is likely to produce lower *p*-value,

showing significance but not necessarily clinical importance (Dahiru, 2008; Perera et al., 2012). Therefore, we interpreted the study results emphasizing the 99% confidence interval and clinical relevance of the associations.

5.7 Conclusions

This study finding confirmed our hypothesis of longer hospital stays and higher costs by HSWH and increased procedures utilization for older HSWH. This study also demonstrates that there is no additional impact of aging PLWH on inpatient length of stays and costs for HSWH. Higher resource utilization and costs among HSWH by younger adults deserve further investigation using individual-level data to assess whether the onset of age-related comorbidities at the early age of PLWH contributes to this inpatient care utilization. Future studies need to look into the lower utilization of procedures by HSWH because this may indicate differential inpatient care utilization compared to HSWOH. The source of this difference might be the avoidance of nonurgent procedures for some PLWH due to the risk of person-to-person transmission in healthcare settings from performing invasive procedures and exposure-prone procedures. In general, resource utilization and costs increased with the older age, irrespective of the HIV status of the hospital stays. With the aging of PLWH, the U.S. inpatient departments need to incorporate HIV specific chronic disease management programs in inpatient care delivery to manage the future increases in older PLWH and their age-related comorbidities. Policymakers, administrators, and other stakeholders should investigate and focus on the types of surgical procedures and comorbidities that incur longer inpatient stays and higher costs to make the inpatient department more efficient as PLWH age in the United States.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

This study demonstrates an increased presence of some age-related medical conditions among HSWH, yet these higher comorbidities did not increase the length of stays and costs for HSWH compared to HSWOH. These findings are reflective of the lower impact of the aging of PLWH on inpatient care delivery. Lowering the gap in life expectancy might also decrease the differences between hospital stays with and without HIV in terms of inpatient resource utilization and costs. Nevertheless, the increased presence of older patients with HIV and major age-related chronic conditions during inpatient stays in recent years demonstrates the need for incorporating chronic disease management programs in inpatient care delivery. The health care need might be different for PLWH than the same-age non-PLWH during hospital stays because they might present with multiple age-related comorbidities at a younger age, and those multi-comorbidities and ART toxicities may results in frailty among younger PLWH. Thus, an adequate number of HIV trained inpatient workforce and geriatric care providers should be in place for the future. Studies using individual-level data that capture the onset of those chronic conditions are needed to understand whether PLWH are having those age-related comorbidities earlier than non-PLWH as they age.

Although some previous studies projected higher resource utilization and costs among older PLWH due to long-term ART toxicities and multiple comorbidities, this study only found increased procedure use with age; while, did not observe any differential trends

for inpatient length of stays and costs by age among PLWH compared to non-PLWH. The causes of this discrepancy can be two-folded: one, previous studies might not project for inpatient care separately; second, higher readmission or frequent stays among PLWH might underestimate the average length of stays and costs. Future studies capturing every hospital stay of the individual patient and using an appropriate non-PLWH control group will be able to give us more accurate results about the changing demand for inpatient resources by the aging of PLWH. Policymakers, hospital administrators, and other stakeholders should carefully observe the older patients with those disproportionately increased chronic conditions to understand how age-related comorbidities contribute to the resource utilization and costs during inpatient stays.

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APPENDIX A

SUPPLEMENT TABLES AND FIGURES FOR PAPER 1

Table A. 1 List of all diseases for five major types of HIV-associated non-AIDS (HANA) conditions.

Conditions	CCS code
Cardiovascular Disease (CVD)	
Heart valve disorders	96
Essential hypertension	98
Hypertension with complications and secondary hypertension	99
Acute myocardial infarction	100
Coronary atherosclerosis and other heart disease	101
Pulmonary heart disease	103
Other and ill-defined heart disease	104
Conduction disorders	105
Cardiac dysrhythmias	106
Cardiac arrest and ventricular fibrillation	107
Congestive heart failure; non-hypertensive	108
Acute cerebrovascular disease	109
Occlusion or stenosis of precerebral arteries	110
Other and ill-defined cerebrovascular disease	111
Transient cerebral ischemia	112
Late effects of cerebrovascular disease	113
Peripheral and visceral atherosclerosis	114
Aortic; peripheral; and visceral artery aneurysms	115
Aortic and peripheral arterial embolism or thrombosis	116
Other circulatory disease	117
Phlebitis; thrombophlebitis and thromboembolism	118
Varicose veins of lower extremity	119
Syncope	245
Cancer	
Cancer of head and neck	11

Cancer of esophagus	12
Cancer of stomach	13
Cancer of colon	14
Cancer of rectum and anus	15
Cancer of liver and intrahepatic bile duct	16
Cancer of pancreas	17
Cancer of testis	18
Cancer of bronchus; lung	19
Cancer; other respiratory and intrathoracic	20
Cancer of bone and connective tissue	21
Melanomas of skin	22
Other non-epithelial cancer of skin	23
Cancer of breast	24
Cancer of uterus	25
Cancer of cervix	26
Cancer of ovary	27
Cancer of other female genital organs	28
Cancer of prostate	29
Cancer of testis	30
Cancer of other male genital organs	31
Cancer of bladder	32
Cancer of kidney and renal pelvis	33
Cancer of other urinary organs	34
Cancer of brain and nervous system	35
Cancer of thyroid	36
Hodgkin`s disease	37
Non-Hodgkin`s lymphoma	38
Leukemias	39
Multiple myeloma	40
Cancer; other and unspecified primary	41
Secondary malignancies	42
Malignant neoplasm without specification of site	43
Diabetes	
Diabetes mellitus without complication	49
Diabetes mellitus with complications	50
Liver Disease	
Hepatitis	6

Biliary tract disease	149
Liver disease; alcohol-related	150
Other liver diseases	151
Bone Loss	
Osteoarthritis	203
Other non-traumatic joint disorders	204
Spondylosis; intervertebral disc disorders; other back problems	205
Osteoporosis	206
Pathological fracture	207
Other bone disease and musculoskeletal deformities	212
Fracture of neck of femur (hip)	226

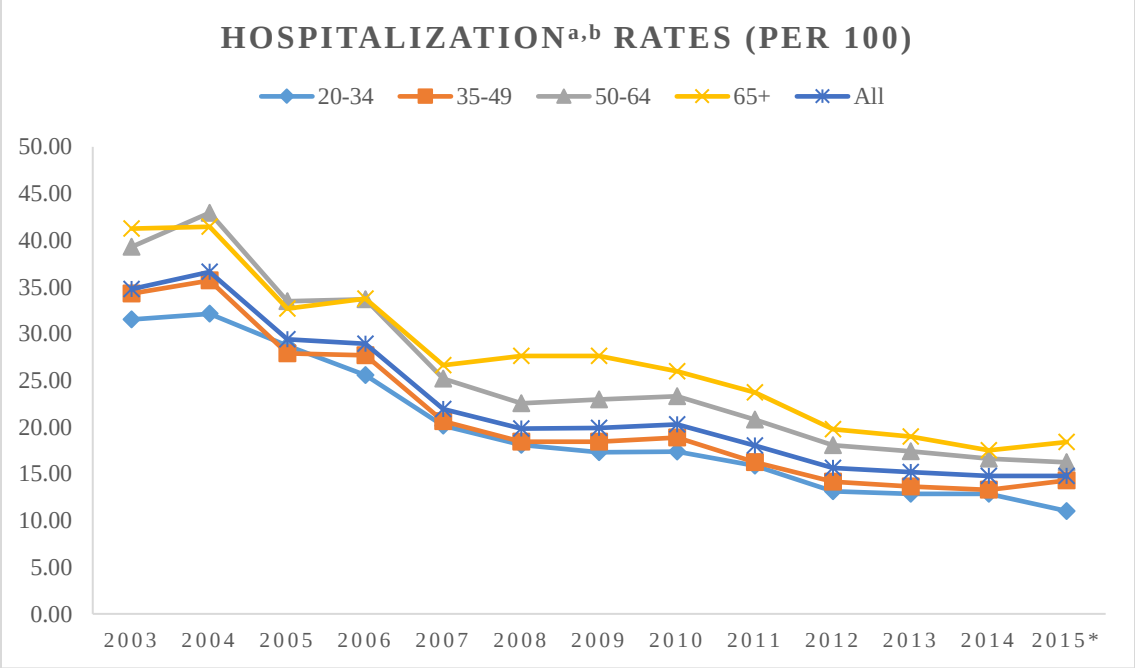

Figure A. 1 Hospitalization rates per 100 PLWH across age groups, 2003 to 2015 (single HIV hospitalization by a PLWH).

*Total number of hospitalizations in 2015 is for the first three quarters (January to September), however, the approximate rates were calculated by multiplying the number of PLWH by ¾ to make the rates consistent with other years.

[a] Source: HIV surveillance report, vol. 16-28, Center for Disease Control and Prevention (CDC).

[b]Excludes hospital stays by less than 18 years old, same-day discharges (LOS=0), and that with a diagnosis code for pregnancy, labor, delivery, or neonatal cases.

Table A. 2 Patient- and hospital-level characteristics of hospital stays, 2003, 2009, and 2015.

	2003				2009			
	HIV-		HIV+		HIV-		HIV+	
Characteristics	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**	**Unweighted n**	**Weighted %**
Overall	5505953	99.19	45765	0.81	5490815	99.15	46798	0.85
Admission source[a]								
Emergency Room	3050951	55.59	33214	72.76	653480	55.80	12988	72.22
Another hospital	214836	3.95	1195	2.64	54027	4.47	580	3.14
Another facility incl. long term care	100753	1.82	670	1.45	32752	2.83	434	2.35
Court/law enforcement	5728	0.10	67	0.15	1366	0.12	59	0.34
Routine/birth/other	2108079	38.54	10481	23.00	432235	36.78	4067	21.94
	2009				**2015 (Q1-Q3)[i]**			
Overall	5490815	99.15	46798	0.85	3813082	99.19	31179	0.81
Transfer Indicator								
Not a transfer	5077648	92.77	44074	94.86	3458880	91.25	28938	93.43
Transferred in from a different acute care hospital	268468	4.82	1525	3.24	228643	6.03	1391	4.49
Transferred in from another type of health facility	131513	2.41	873	1.89	102935	2.72	644	2.08

Control/owner[b]								
Government, nonfederal	685391	12.73	10668	23.16	455238	11.94	5766	18.49
Private, non-profit	3932248	72.74	29356	63.77	2773865	72.75	21117	67.73
Private, invest-own	774188	14.53	5856	13.07	583979	15.32	4296	13.78
(a) Many missing values (4,345,625) in 2009, thus there are vast differences in frequency (n) (b) Categories were dissimilar, therefore incomparable over the study periods ł This study analyzed data for quarter 1 to quarter 3 (January to September 2015), to avoid the transition in ICD codes from ICD-9-CM to ICD-10-CM codes effective on October 1, 2015.								

APPENDIX B

SUPPLEMENT TABLES AND FIGURES FOR PAPER 2

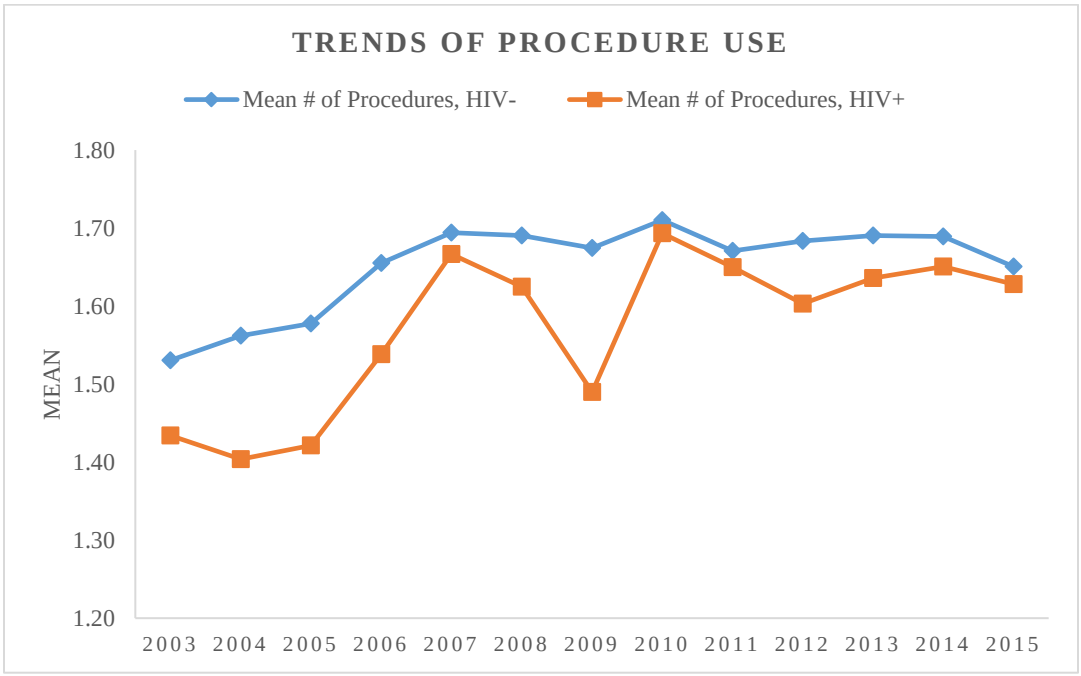

Figure B. 1 Trends of average procedure used during hospital stays, 2003 to 2015

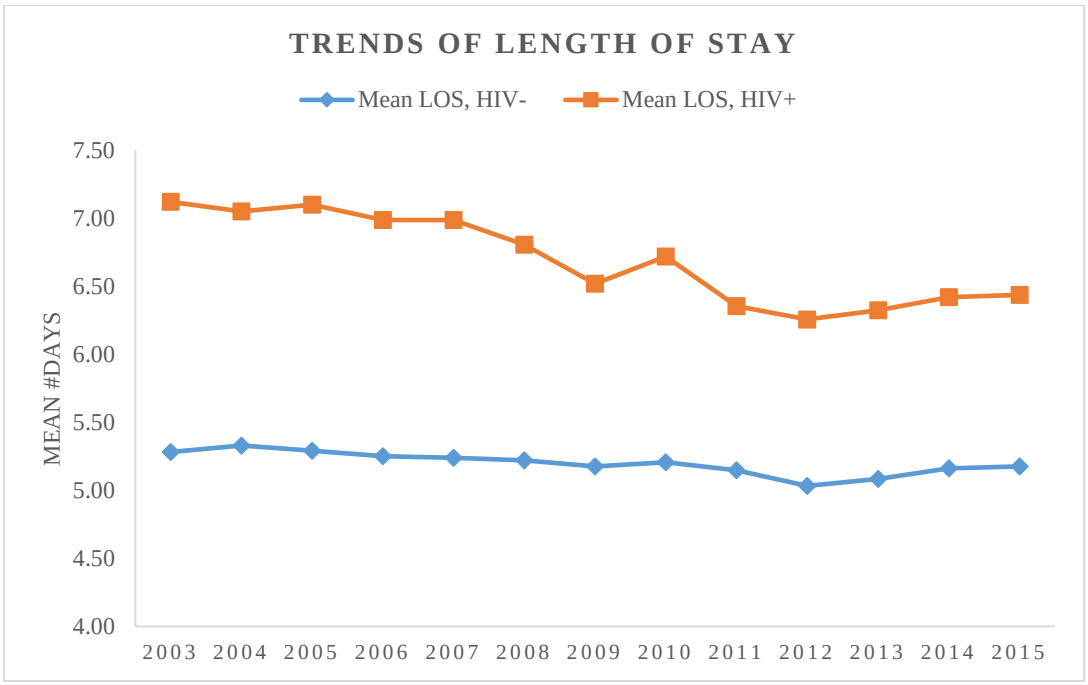

Figure B. 2 Trends of the average length of hospital stays (number of days), 2003 to 2015.

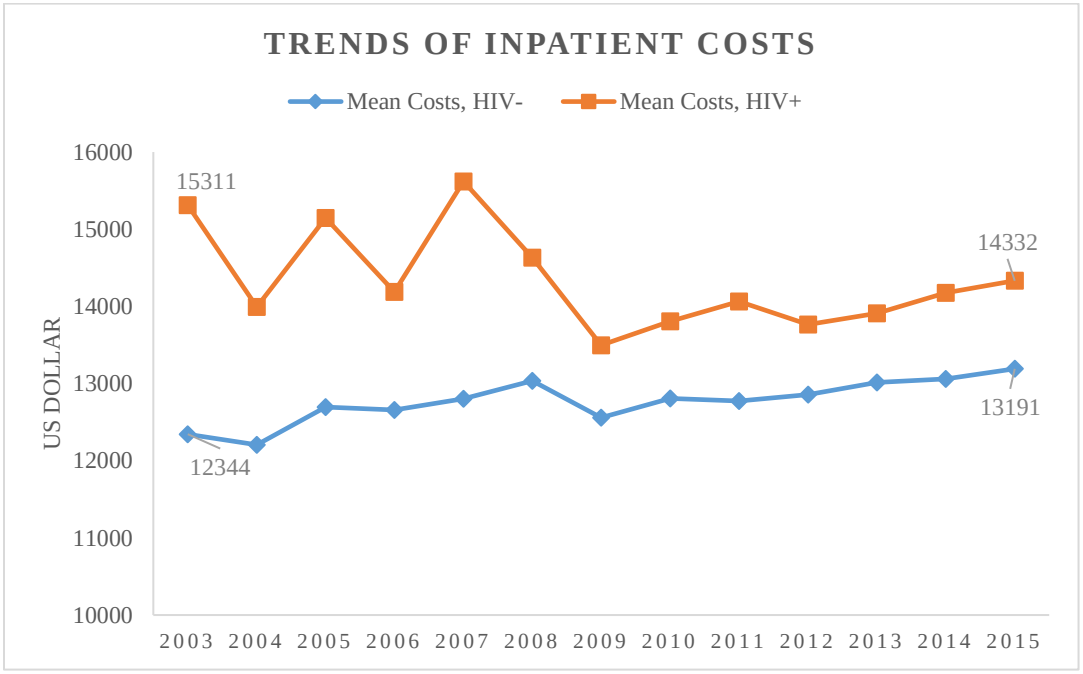

Figure B. 3 Trends of inpatient costs during hospital stays (US dollar), 2003 to 2015.

Table B. 1 Predictors of number of procedure use during hospital stays, 2003-2015 from the Zero-Inflated Negative Binomial (ZINB) Generalized Linear Models (GLM)[a].

	Number of Procedures (NPR)			**Zero-model (NPR=0)**		
Variables	**Exp (*β*)***	**99% CI**		**Exp (*β*)***	**99% CI**	
		Min	Max	**(OR)**	Min	Max
Unadjusted Model	N= 69,633,686 (weighted 343 million)					
Intercept	1.34	1.34	1.34	0.00		
HSWH (Ref.= HSWOH)	0.79	0.78	0.81	0.62[1]	0.06	6.68
Age (per 10 years)	1.05	1.05	1.05	3.65	3.63	3.66
Adjusted Model	N=55,231,368 (weighted 272 million)			N=55,231,368 (weighted 272 million)		
Intercept	1.10	1.09	1.10	0.40	0.40	0.41
HSWH (Ref.= HSWOH)	0.70	0.68	0.71	0.91	0.82	1.00
Age (per 10 years)	1.03	1.03	1.03	1.16	1.16	1.16
Patient-level characteristics						
Sex						
Male	1.00			1.00		
Female	0.89	0.89	0.89	1.12	1.12	1.13
Race/ethnicity						
White	1.00			1.00		
African American	0.95	0.95	0.95	0.96	0.96	0.97
Hispanic	0.99	0.99	0.99	0.80	0.79	0.80
Others	1.04	1.04	1.05	0.78	0.78	0.79

Expected primary payer						
Private including HMO	1.00			1.00		
Medicare	0.86	0.86	0.86	1.33	1.32	1.34
Medicaid	0.83	0.83	0.83	1.14	1.13	1.15
Self-pay	0.86	0.86	0.87	1.16	1.15	1.17
Others (incl. No charge)	0.95	0.95	0.95	1.15	1.14	1.16
Patient's location (rurality)[b]						
Large metropolitan	1.00			1.00		
Small metropolitan	1.03	1.03	1.03	1.04	1.04	1.04
Micropolitan areas	1.23	1.23	1.24	0.65	0.65	0.66
Not metropolitan or micropolitan	1.15	1.15	1.16	0.71	0.71	0.72
Median Household Income in ZIP						
0-25th percentile	1.00			1.00		
26th to 50th percentile	1.04	1.04	1.04	0.95	0.94	0.95
51st to 75th percentile	1.04	1.04	1.04	0.95	0.94	0.95
76th to 100th percentile	1.06	1.06	1.06	0.86	0.86	0.87
Readmission scores	1.00	1.00	1.00	0.99	0.99	0.99
Mortality scores	1.01	1.01	1.01	1.01	1.01	1.01
Hospital-level characteristics						
Weekend admission						
No	1.00			1.00		
Yes	0.95	0.95	0.95	1.15	1.14	1.15
Elective admission						
Non-elective	1.00			1.00		
Elective	1.24	1.24	1.24	0.0		
Bed size						

Small	1.00			1.00		
Medium	1.14	1.14	1.15	0.82	0.82	0.83
Large	1.25	1.25	1.25	0.77	0.77	0.78
Location/teaching status of the hospital						
Urban non-teaching	1.00			1.00		
Rural	0.66	0.66	0.66	1.63	1.62	1.64
Urban teaching	1.18	1.18	1.18	0.72	0.72	0.73
Region						
Northeast	1.00			1.00		
Midwest	0.96	0.96	0.96	1.51	1.50	1.52
South	0.97	0.97	0.97	1.31	1.30	1.31
West	1.02	1.02	1.02	1.07	1.06	1.08
LOS	1.03	1.03	1.03	0.76	0.76	0.76
Number of procedures	N/A			N/A		

*All betas (*β)* were statistically significant at $P<0.01$, unless stated by [†] superscript

[†] Estimate was not statistically significant at $P<0.01$

(a) All models are controlled for year variables (2003 to 2015)

(b) Large metropolitan areas include central counties of metro areas (>1 million) and fringe counties of metro areas (≥1 million), and small metropolitan areas contain counties in metro areas with 50,000-999,000 population. See methods section for details.