HEALTH-RELATED SOCIAL NEEDS AND CANCER BURDEN IN PERSONS LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS

by

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Submitted in partial fulfillment of the requirements

for the degree of Doctor of Philosophy

Department of Population and Quantitative Health Sciences

Clinical Translational Science Program

CASE WESTERN RESERVE UNIVERSITY

May, 2024

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List of Abbreviations

ADI	AIDS-defining Illnesses
ADC	AIDS-Defining Cancer
ADI	AIDS-Defining Illness
AIDS	Acquired Immunodeficiency Syndrome
AIN	Anal Intra-epithelial Neoplasia
AOR	Adjusted Odds Ratio
APR	Association Prevalence Ratio
CART	Classification and Regression Tree
CCS	Clinical Classification Software
CDC	Centers for Disease Control and Prevention
CIN	Cervical Intra-epithelial Neoplasia
EBV	Epstein-Barr Virus
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HCUP	Healthcare Cost and Utilization Project
HCV	Hepatitis C Virus
KFF	The Kaiser Family Foundation
HHV-8	Human Herpesvirus-8
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
HRSN	Health-Related Social Needs
HPV	Human Papillomavirus
KS	Kaposi's sarcoma
KSHV	Kaposi Sarcoma-associated Herpesvirus
MAX	Medicaid Analytic eXtract
MLWH	Men Living with HIV
NADC	Non-AIDS-Defining Cancer
NADI	Non-AIDS-Defining Illness
NHL	Non-Hodgkin's Lymphoma
OI	Opportunistic Infection
OR	Odds Ratio
PLWH	Persons Living with HIV
RWHAP	Ryan White HIV/AIDS Program
SDOH	Social Determinants of Health
SID	State Inpatient Databases
WLWH	Women Living with HIV Infection

Health-Related Social Needs and Cancer Burden in Persons Living with Human Immunodeficiency Virus

Abstract

by

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Objective: To assess the impact of health-related social needs (HRSN) on hospital readmission and cancer prevalence in persons living with HIV (PLWH).

Study population and methods: For the HRSN work, I utilized four-year (2016-2019) longitudinal State Inpatient Databases (SID) from Florida and Maryland. The study encompassed 43,229 HIV patients in Florida and 12,396 in Maryland. For the cancer burden work, I used one-year nationwide Medicaid enrollment files. Cancer burden in men and women living with HIV were examined separately. The sample of men included 82,495 with HIV and 7,302,523 without HIV, and that of women included 72,508 with HIV and 17,353,963 without HIV. The traditional statistical and data mining approaches were used to analyze data.

Results: Key findings include: (1) A significantly high prevalence of social needs was associated with increased PLWH hospital readmission, and these needs emerged as critical elements in predicting hospital readmission. (2) The spectrum of cancer burden differed by gender, but anal cancer and non-

Hodgkin's lymphoma (NHL) were consistently among the most prevalent cancer types in both men and women. (3) Among men living with HIV, the prevalence of non-AIDS defining cancers was about twice that of men without HIV, with anal cancer and non-Hodgkin's lymphoma having the highest prevalence. (4) Among women living with HIV, cervical cancer, Kaposi's sarcoma, anal cancer, and Hodgkin's and non-Hodgkin's lymphoma remained highly prevalent. (5) Age had a more robust modification effect in younger HIV patients compared to the non-HIV population of same age range.

Implications: This study both identified the pivotal role of health-related social needs in hospital readmission and elucidated cancer disparities in PLWH. It is imperative for healthcare providers and policymakers to acknowledge social factors as critical in reducing hospital readmissions for HIV patients. Recognizing cancer disparities is essential for developing targeted interventions and improving healthcare outcomes for both men and women living with HIV. Initiating HPV vaccination for anal and cervical cancer should target adolescents and young adults among HIV patients. Additionally, cancer prevention and screening should prioritize high-risk minority PLWH from an early age.

Chapter I

Background and Introduction

HIV care is one of the most significant health and social problems in the modern era. Persons living with HIV not only live longer and carry high disease burden but also face various social issues during their lives. HIV stigma and discrimination, and aging, are all intertwined with disease burden in complex ways.

1.1 Health-Related Social Needs in PLWH

Persons living with HIV (PLWH) often face social isolation as a result of HIV-related stigma and discrimination.[1] Such social factors play a vital role in their physical and mental health, as well as their social and economic well-being. Also, the social determinants (SDOH) can affect health conditions and mental health.[2] Reduced access to healthcare and other services is a significant issue for PLWH. Stigma and discrimination can prevent people from seeking care, leading to healthcare providers treating them differently or providing lower-quality care. The confluence of these factors can lead to poorer health outcomes and a decreased quality of life.[3]

1.1.1 Syndemic theory

In medicine and public health, the traditional epidemiological approaches conceptualize diseases as distinct entities. However, diseases often present in clusters and interact with each other to affect the health outcomes of particular groups locally. According to the theory of syndemic (or synergestic epidemic),

adverse health outcomes are hypothesized as the co-occurrence of specific sociocultural, economic, environmental, and geographic conditions that interact with and mutually influence each other.[4] The syndemic theory focuses on the interaction of diseases and social, economic and environmental factors. Without the interaction, the co-occurrence of these conditions is termed comorbidity or co-infection. Syndemic theory explains how large scale social forces (for example, poverty, social marginalization, and political oppression) influence co-occurrence of two or more conditions and interact to adversely affect health outcomes in disadvantaged communities. This theory has been widely adopted in the field of HIV treatment and prevention.[4]

In conjunction with the syndemic theory and HIV infection, previous research has shown that AIDS is more prevalent in the inner-city where substance use and violence cluster together - this is known as the epidemic of substance abuse, violence, and AIDS ("SAVA") in poor urban communities.[5] Also, the syndemic psychosocial problems and seroconversion of HIV infection co-occur in men who have sex with men.[6] The syndemic problem in PLWH indicates that there are mixed effects of local social, economic, environment and geographic factors that influence the co-occurrence of these conditions.

Figure 1.1 illustrates the complexity of co-infections of other pathogens and cancer development due to HIV-caused immunodeficiency. The cancer burden, in conjunction with the synergistic interaction (syndemic) of social factors and adverse mental health, formed the theoretical foundation of this dissertation.

1.1.2 Health-related social needs

According to the Center for Medicare and Medicaid (CMS), HRSN are defined as the individual's unmet adverse social conditions that contribute to poor health (Medicaid HRSN), such as food insecurity, social isolation, housing instability, unemployment, income inequality, poverty, and low education levels.[7] Social determinants of health (SDOH) refer to the conditions in which people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality of life.[7] Examples of SDOH include air quality, reliable transportation, and community safety measures. Therefore, HRSN are conditions at the individual level, while SODH are at the community level. An individual's HRSN are a result of their community's underlying SDOH. Although HRSN are nonmedical factors, they have profound impact on access to care and health outcomes. According to the county health-ranking model from University of Wisconsin, HRSN related conditions accounts for about 40% of health outcomes, while the medical factors only accounts for about 20% of health factors (Figure 1.2).[8]

1.1.3 Health-related social needs in PLWH

PLWH are vulnerable to compromised HRSN. Also, HIV infection can exacerbate vulnerabilities to social determinants, as PLWH may face additional challenges in accessing healthcare, housing, education, employment, and social support. For example, PLWH face stigma and discrimination that can impact their mental health, social relationships, and access to healthcare. This stigma can also contribute to social isolation and a

lack of social support, which can have negative impacts on physical and mental health outcomes.[2] PLWH also face financial challenges due to the cost of healthcare and treatment, which can make it difficult for them to access and adhere to HAART. This can lead to poorer health outcomes, such as decreased CD4 counts and increased risk of opportunistic infections (OI).[9] In addition, PLWH also face challenges related to food and housing insecurity, which can further contribute to negative health outcomes.[10,11] These challenges can make it difficult for PLWH to access healthcare and adhere to HAART, as well as increase their risk of exposure to infectious diseases.

1.1.4 Health Insurance and Access

Most PLWH have insurance coverage, particularly through Medicaid and private insurance, and many receive support from the Ryan White HIV/AIDS Program (RWHAP). There are several types of insurance coverage for PLWH. Medicaid provides the largest coverage and covers 33-37.5% of PLWH from 2006-2012 (Table 1.1).[12] According to the Kaiser Family Foundation (KFF) report, after the Affordable Care Act's Medicaid expansion, 40% of PLWH were covered by Medicaid in 2018.[13] The RWHAP is the largest federal program focused on HIV, serving as the nation’s safety net program for PLWH. The RWHAP funds HIV care and treatment services for low-income PLWH.[14]

1.2 Cancer burden in PLWH

In 2019, the most recent year for which the data are available, an estimated 1.2 million Americans were living with human immunodeficiency virus (HIV),[15] and nearly half of them were age 50 years and older.[16] It has been projected that by 2030, 70% of PLWH in the U.S. will be older than 50 years of age.[17] The introduction of highly active antiretroviral therapy (HAART) in the 1990s transformed the clinical care and outcomes of HIV patients. Now, HIV infection is treated as a manageable chronic condition. Due to the compounding effect of premature aging, impaired immune system, and other factors, PLWH remain vulnerable to opportunistic infections (OI), cancers and other diseases.

1.2.1 HIV and AIDS

HIV specifically targets CD4 positive (CD4+) T lymphocytes. HIV replicates in the infected persons for the duration of their lives. With the disease progression, HIV infection depletes the CD4+ T cells and causes systemic immune activation. The stages of HIV infection in the 2014 case definition are classified as stage 0, stage 1, stage 2, and stage 3. Stage 0 is the period until 6 months after the first positive test result. After that, the stages are reclassified as stage 1, stage 2, and stage 3 based on based on age-specific CD4+ counts or percentages of total lymphocytes.[18] As illustrated in Figure 1.3,[19] before HIV infection, a person's CD4+ T-cells percentage is typically around 40% of total lymphocytes. During stage 1, also known as acute infection, HIV propagates rapidly, and the CD4+ T-cells count is more than 500 or more than 26% of total lymphocytes. During stage 2, also known as

chronic infection, HIV spreads at very low levels, and the CD4+ cells count is between 200 to 499 or 15-25% of total lymphocytes. Without timely treatment, HIV infection advances to more severe stages over time, eventually leading to acquired immunodeficiency syndrome (AIDS), the most severe stage of HIV infection. In stage 3, the immune system is severely damaged, the CD4+ cell count is often less than 200, or the percent of CD4+ cells is less than 15% of all lymphocytes. People with AIDS are at high risk of developing opportunistic infections.

1.2.2 Highly Active Antiretroviral Therapy

Highly active antiretroviral therapy (HAART) regimen has been used to manage and treat HIV-1 infection since 1996. HAART treatment combines three or more antiretroviral drugs to inhibit HIV replication. HAART is also termed antiretroviral therapy (ART) or combination antiretroviral therapy (cART) at earlier time of HIV treatment. The combination of the specific drugs in HAART regimens varies depending on factors such as the individual's viral load, CD4 cell count, and other medical conditions. The time period from identification of first HIV case in 1981 to successful HAART treatment in 1996 is referring as pre-HAART era. The time after 1996 is HAART era. In pre-HAART era, HIV infection was nearly fatal. From the initiation of HAART in 1990s to widespread dissemination, the death rate of HIV infection in the global adult population declined by 50-90%.[20-22] According to the Center for Disease Control and Prevention (CDC), 90% of PLWH in the U.S. were linked to care within one month of diagnosis, and about 85% of them were receiving

HIV medical care, and 80% of them were effectively treated by HAART in 2020.[23] Because of the effective treatment and high percentage of engagement to HAART regimen, HIV infection is now well controlled.[24] PLWH in the U.S. already have much improved life expectancy compared to the pre-HAART era, thanks to the early provision of HAART.[25]

1.2.3 AIDS-defining illness and non-AIDS-defining illness

AIDS-defining illnesses (ADI) refer to several types of serious and life-threatening diseases. The CDC has developed a list of these illnesses (CDC, mmwr 1993).[26] ADI include opportunistic infection, wasting syndrome, Kaposi's sarcoma (KS), invasive cervical cancer in women, Burkitt's lymphoma, immunoblastic lymphoma, and brain lymphoma (Table 1.2). The latter three types of lymphoma typically refer to non-Hodgkin's lymphoma (NHL). Together, Kaposi's sarcoma, cervical cancer and Non-Hodgkin's lymphoma are classified as AIDS-defining cancers (ADCs). Other types of cancers are classified as non-AIDS-defining cancers (NADCs), including cancer of anus, lung, liver, Hodgkin's lymphoma (HL), and other types of cancers.

The common cause of death of HIV infection in the pre-HAART era was predominantly opportunistic infection (OI). Since the widespread dissemination of HAART, the mortality rate reduced dramatically. Previous work shows that cancer has been a major cause of death among PLWH in industrialized nations since the introduction of HAART.[27] Meanwhile, the fraction of mortality caused by ADC and NADC has shifted. In the pre-HAART era, ADCs were

more common among PLWH. In the HAART era, as HAART became more widely available, the incidence of ADCs decreased while the incidence of NADCs increased. Table 1.3 illustrates the change of mortality reported by French Mortalité survey 2005 study. The cause of death for PLWH has dramatically shifted from NADC (38% in 2000 and 50% in 2005) to ADC (55% in 2000 and 39% in 2005).[28] Figure 1.4 shows the combined data of the cancer-specific population-attributable fraction (PAF) of ADC and NADC from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [29] and HIV/AIDS Match Study.[30] Due to the different adjusted models and cohorts, the value of PAF from these two studies differs. However, there is a clear trend that the composition of cancer-attributable deaths has significantly shifted toward the increase of NADCs during 2001–2015. The HIV/AIDS Cancer Match Study found that the number of ADCs decreased by more than threefold whereas NADCs increased about threefold from pre-HAART era (1991-1995) to HAART era (2001-2005) (Figure 1.4). As shown in Figure 1.5, from 1991 to 2005, the number of people living with AIDS in the U.S. increased about three-fold (Figure 1.5A), and the numbers of ADCs gradually declined in most age groups, mostly among 20–39 year olds (Figure 1.5B). However, there was an increase in the cancer burden attributable to NADCs, mostly among people aged 40 years or older (Figure 1.5C). As a result of these changes, the total cancer burden in the AIDS population decreased during 1991–1998, but increased from 1999 to 2005, largely driven

by the increased number of NADCs (Figure 1.5D). Thus, the increases in NADCs are mainly driven by growth and aging of the AIDS population.[31]

1.2.4 HIV, aging and disease burden

HAART is a revolutionary success in the treatment of HIV infection. However, HAART does not eliminate the virus, and residual levels of HIV remain in deep tissues of PLWH. With the improved longevity of PLWH, aging-related diseases are more prevalent than HIV-related illnesses in PLWH in the HAART era.[32] Meanwhile, aging-related diseases occur earlier and faster in PLWH than the HIV-negative population.[33] Several aspects of recent work have highlighted the substantial impact on aging in PLWH. Firstly, residue levels of HIV remain replicable in PLWH after HAART. Thus, the persistent load of residue HIV can still lead to chronic inflammation, which can be either local (such as pulmonary, thymus, gut), or systemic.[34-36] The activation of the immune system contributes to premature aging and age-associated comorbidities.[37] Secondly, recent work shows that PLWH have accelerated or premature aging.[38] The biological evidence shows that HIV infection has substantial impact on the epigenetic aging process.[39] These data support the role of HIV infection in the earlier occurrence of clinical aging and exacerbation of diseases. Thirdly, HAART treatment could have cumulative toxicity and produce adverse effects.[36] Additionally, HIV infection and HAART treatment associated toxicity can cause mitochondrial comprise and cellular dysfunction, contributing to the aging process in PLWH.[40] The above arguments strongly support that HIV infection leads to accelerated aging process in PLWH.

The most common comorbidities in PLWH include cardiovascular disease (Myocardial infarction, Peripheral vascular diseases, and Deep vein thrombosis), essential hypertension, renal disease, fracture/osteoporosis, liver disease, and cancer, as well as neurocognitive disorders disease. [41,42] Table 1.4 lists the prevalence of several comorbidities in matched HIV and control study.[43] The recent systematic review estimates that the risk of cardiovascular disease is twice higher in PLWH than in the general population.[44] Accounting for the weaker immune system in the aged PLWH, we hypothesize that PLWH carry a much higher burden of aging-related disease burden. Gaining a better understanding disease burden or clinical conditions is crucial to improving the quality of life for the PLWH.

1.2.5 HIV and cancer

HIV infection has been linked to several types of cancers. While there is no direct evidence that HIV infection directly induces the development of all types of cancer, there is evidence that HIV infection can increase the risk of certain types of cancers, such as cancers of the cervix, anus, and Kaposi sarcoma, non-Hodgkin lymphoma, and Hodgkin lymphoma, and a few others.[45,46] Several mechanisms have been linked to HIV infection and cancer: (1) As reviewed in section 1.2.4, HIV-associated premature aging increases the development of age-related cancer, and aging PLWH carry high risk to develop many type of cancers;[47,48] (2) PLWH are prone to co-infection with oncogenic viruses, which are known to induce certain types of cancer, including Epstein-Barr virus (EBV),[49] human papillomavirus (HPV),[50] Kaposi's

sarcoma-associated herpesvirus (KSHV),[51] and Hepatitis B (HBV) [52] or Hepatitis C (HCV). [53] (3) HIV induced immune activation or immune deficiency could play a role on the cancer formation; (4) HIV may also activate pro-oncogenes or inhibit tumor suppressor, or induced genetic instability and increase susceptibility to effects of carcinogens, for example, it has been reported that HIV induces 6-fold higher number of microsatellite alterations of HIV-associated than in non–HIV-associated lung cancer. [54] (5) HIV induced endothelial/epithelial dysfunction contributes to some types of cancer development; (6) Other independent factors such as smoking and substance abuse could contribute cancer development.[55]

AIDS-defining cancers

AIDS-defining cancers (ADCs) include Kaposi's sarcoma (KS), non-Hodgkin's lymphoma, and cervical cancer. In the pre-HAART era, ADCs accounted for a large portion of cancer-related deaths. Because of the immunocompromised state caused by HIV infection, cancers associated with viral infections are commonly seen in PLWH.[47]

Kaposi's sarcoma

AIDS-related Kaposi sarcoma is the most common cancer in PLWH. The prevalence of Kaposi's sarcoma in the non-HIV infected population is low.[51] The advance of HAART has greatly reduced the prevalence of AIDS-related Kaposi's sarcoma. However, Kaposi's sarcoma still occurs in PLWH who are not responding to HAART. Kaposi's sarcoma usually appears as multiple pigmented cutaneous lesions on the skin. In AIDS-related Kaposi's sarcoma,

oral lesions are common. Kaposi's sarcoma is mainly caused by KSHV, also known as the human herpesvirus-8 (HHV). Saliva is considered to be one of the primary modes of transmission for KSHV.[56]

Non-Hodgkin's and Hodgkin's lymphoma

Non-Hodgkin's lymphoma is distinguished from Hodgkin's lymphoma based on the presence of Reed-Sternberg cells in Hodgkin's lymphoma and their absence in Non-Hodgkin's lymphoma. In PLWH, 90% of cases of Non-Hodgkin's lymphoma is of B-cell origin, with subtypes including large cell immunoblastic lymphoma, Burkitt's lymphoma, and primary central nervous system lymphoma.[49] HAART has significantly reduced the incidence of Non-Hodgkin's lymphoma in PLWH, but increased the incidence of Hodgkin's lymphoma. EBV and KSHV both belong to the gamma-herpesvirus family, and both viruses have been associated with the development of certain types of lymphoma.[49] In particular, EBV has been implicated in the pathogenesis of Burkitt lymphoma, as well as certain types of Hodgkin's lymphoma and Non-Hodgkin's lymphoma. HHV8 has also been linked to the development of primary effusion lymphoma, which is a rare type of Non-Hodgkin's lymphoma.[57]

Non-AIDS-defining cancer

Cervical cancer

Cervical cancer is the most common cancer in women with HIV infection, and invasive cervical carcinoma is the leading cause of cancer death in women worldwide.[58,59] Cervical cancer is highly associated with HPV infection.[60] HIV

infection enhances human papillomavirus (HPV)-induced carcinogenesis; thus, women living with HIV are at a high risk of cervical cancer. Cervical cancer is preceded by cervical intraepithelial neoplasia (CIN). CIN1 is low-grade precursor lesion, but CIN2 and CIN3 are high-grade lesions.[61]

Anal cancer

Men who have sex with men have a great risk of developing anal cancer, particularly among PLWH.[62] Anal sex, HIV and HPV infection are high risk factors for anal cancer. Like cervical cancer, anal intra-epithelial neoplasia (AIN) is the precursor lesion that leads to invasive anal cancer. AIN is divided into grades 1 to 3: AIN1 - mild, AIN2 - moderate, AIN3 – severe. AIN1 is low-grade lesion; and AIN2 and AIN3 are high-grade diseases that need to be treated. AIN-2 and AIN-3 are closely associated with the infection of high-risk HPV subtype 16 and 18, particularly subtype 16.[63]

Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is characterized for the presence of Reed-Sternberg cells. Hodgkin's lymphoma is more common in people living with HIV than in the general population. [64]

Liver cancer

PLWH have a higher burden of hepatocellular carcinoma (HCC) and end-stage liver disease compared with people without HIV.[65] Recent work has shown that the incidence rate of liver cancer in North America has increased over time from 1996 to 2015. [66] This increased incidence is due to several factors, including the higher prevalence of HBV and HCV co-infection, higher

HIV virus load and lower CD4+ cell counts, drug injection, and exposure to other risk factors such as alcohol and tobacco use. [66]

Lung cancer

Lung cancer is one of the major causes of death in PLWH, and the increased risk of lung cancer in PLWH is primarily due to higher rates of smoking.[55] In addition to smoking, immunosuppression-as measured by low CD4+ counts and chronic inflammation are also important contributors to the increased risk of lung cancer in the HAART era. There are also disparities in lung cancer treatment for PLWH, including lower rates of early detection with chest CT, and delayed diagnosis. These factors can lead to poorer outcomes, including higher mortality rates. [67]

Other NADC

While PLWH are at an increased risk for developing certain types of NADCs, the relationship between HIV and other types of NADCs has not always been clear. Some studies have found an increased risk of certain cancers, while others have found no clear association.

However, it is important to note that HIV/AIDS weakens the immune system, which can increase the risk of developing certain cancers. Additionally, lifestyle factors such as smoking and drug use, and unprotected sex can also increase the risk of cancer in people PLWH.

1.3 Machine Learning in Clinical Research

In recent years, the machine learning approaches have been applied to healthcare research. These approaches--supervised machine learning, unsupervised machine learning, and deep learning-- have the potential to transform many aspects of healthcare and improve the outcomes of patient care. In supervised learning, both input data and outcome are provided in the model. The common approaches of supervised learning include classification and regression. The classification is for the categorical variables while the regression is for the numeric variables. Common supervised methods include, classification and regression tree (CART), random forest, K-nearest neighbors, boosting, and support vector machine. Unsupervised learning methods are designed for unlabeled data and are used to identify patterns or relationships. The examples include the commonly used principal component analysis (PCA) and association rule mining (ARM). Deeping learning approaches involve the process of learning from data using multi-layer neural networks, including conventional neural networks (CNNs) and recurrent neural networks (RNNs). CNNs are primarily used for image recognition and classification tasks. RNNs are designed for time series data, natural language processing (NLP), and speech recognition.

Machine leaning approaches are highly suitable for managing large complex real-world patient data, identifying patterns, and predicting complex health outcomes. The care of HIV patients is a complex system with syndemic effects resulting from the interaction of social, biological and psychologic factors.

Machine learning has the potential to unveil the hidden barriers, from the co-occurrence of comorbidity to outcomes of patient care, which can contribute to enhancing the quality HIV care. For these reasons, I included machine learning in this research.

Specific Aims

The syndemic theory explains the interaction among HIV infections, pathogen co-infections, social factors, and psychological effect for PLWH. PLWH represent a socially marginalized population with a high disease burden due to the nature of HIV infection-related immunodeficiency. HRSN wield a robust influence on the occurrence of disease burden in PLWH, with cancer emerging as the leading cause of mortality.

HAART has significantly improved the life expectancy of PLWH. Consequently, the fraction of cancer-contributable mortality has shifted from AIDS-defining cancers (ADCs) to non-AIDS defining cancers (NADCs). To discern cancer burden in PLWH, HRSN play a crucial role as upstream factors that cannot be overlooked.

Cancer burden in PLWH could differ significantly between sexes. Epidemiological evidence indicate men are more prone to die from cancer. Overall, men have 2–3-fold greater risk of cancer than females at most shared anatomic sites.[68-69] Biologically, sex differences in cancer incidence are attributed to the regulation at the genetic and molecular level. Additionally, sex

hormones such as estrogen are the important regulators of cancer occurrence. In U.S., more than 80% of newly infected PLWH are male at birth, with less than 20% as female.[70] AIDS-related cancers, such as Kaposi's sarcoma has always been more common in males than females. [56] Therefore, the social needs in PLWH are the fundamental important factors influencing the health outcomes, and it is plausible to study the prevalence in man and women with HIV separately.

The objective of my dissertation is to examine cancer burden and health-related social needs in relation to hospital readmissions in persons living with HIV using multiple data sources – Medicaid enrollment and claim, and payer hospital discharge data from two states. The present study has three specific aims to achieve the objective:

Aim 1: To examine the prevalence of health-related social needs in PLWH receiving care in the inpatient setting, and to evaluate and its association with hospital readmissions.

Aim 2: To evaluate the cancer burden in men living with HIV stratified by age, race, and symptomatic status.

Aim 3: To evaluate of cancer burden in women living with HIV stratified by age, race/ethnicity, and ADC/NADC.

The three aims in this dissertation evaluate both social needs and cancer burden in PLWH. The attainment of these aims address crucial social and disease burden in PLWH, with each aim forming a publishable paper.

Chapter II:

Health-Related Social Needs Are Associated with High Readmission Rates in Persons Living with HIV: Findings from the State Inpatient Database from Florida and Maryland

Abstract:

Background: Health-related social needs (HRSN) significantly influence the physical and mental health of persons living with HIV (PLWH). Hospital readmission is one of the most important measures of quality of care in hospitals. The impact of social needs on hospital readmission in PLWH has not been investigated previously. We hypothesized that readmission rates are higher in PLWH documented with HRSN than their counterparts without HRSN.

Method: In this retrospective study using 2016-2019 state inpatient databases (SID) from Florida and Maryland, we examined the prevalence of HRSN among hospitalized PLWH using ICD-10 diagnosis codes representing five domains of employment, family, housing, psychosocial, and education. We developed multivariable logistic regression models to evaluate the independent association between hospital readmission and the presence of HRSN. In addition, we conducted Random Forest and Classification and Regression Tree (CART) analysis to identify the most important factors and combinations thereof predicting hospital readmission in our patient population.

Result: In 43,229 first admitted (index) PLWH patients from the state of Florida, 4,153 patients had HRSN (9.6%). Compared to patients without HRSN, PLWH with documented HRSN had significantly higher rates of readmission for both the 90-day readmission (46.0% *vs* 23.1%) and one-year readmission (73.6% *vs* 41.3%). The adjusted odds ratio (AOR) for the one-year readmission model for individuals with HRSN was 3.93 (95% confidence interval (CI): 3.62-4.27), In 12,396 index PLWH patients from the state of Maryland, 1,551 patients had HRSN (12.5%). PLWH with HRSN had a higher rate of readmission for the 90-day readmission (39.9% *vs* 20.4%) and one-year readmission rate (68.2% *vs* 37.9%). The AOR for one-year readmission model for individuals with HRSN was 3.80 (95% CI: 3.51-4.13). In both states, a dose-response effect was observed between the numbers of HRSN and 90-day or one-year readmission rates. Both CART and Random Forest models suggested that HRSNs were the most important factors for hospital readmission of PLWH.

Conclusion: The high prevalence of HRSN is closely associated with a high rate of hospital readmission among PLWH. Our findings highlight the importance of accounting for social factors when studying readmission, and call for the development of interventions targeting HRSN to reduce readmissions for PLWH.

Introduction

The advancement of HIV treatment by HAART has greatly improved the quality of life and longevity of PLWH. Consequently, the life expectancy of PLWH is now approaching that of the general population.[71] However, the disparity in HIV transmission and healthcare outcomes by race/ethnicity, age, and sex persists.[72] It is well-known that a significant proportion of HIV infections occur in sexual minorities and communities of color, highlighting the importance of social factors on HIV transmission.[73] The health inequities among PLWH cannot solely rely on biomedical interventions since the disparities are primarily driven by social and structural factors such as poverty, stigma and discrimination.[74,75] Recent work has demonstrated that social and economic factors greatly impact the care outcomes of PLWH.[76-78] At the root of health outcome disparities are social determinants of health (SODH). SDOH include the conditions in which people are born, live and work. SDOH encompass the social metrics at a community level, such as air quality, transportation, and community safety. Health-related social needs (HRSN) refer to the social and economic needs that individuals experience. HRSN often encompass aspects of food insecurity, social isolation, housing instability, unemployment, poverty, and low education.

It is essential to address the underlying HRSN to reduce health disparities and improve health outcomes for PLWH. There are calls to integrate social factors and establish the benefits of social needs in federal and state programs.[79] However, in the clinical setting, the codes for HRSN for individuals are not always recorded by clinicians because there is no standard guidance on the

documentation of social needs in clinical setting.[80,81] Fewer than 70% of PLWH in the U.S. have achieved durable viral suppression, and the successful treatment of HIV infection is often hindered by such barriers as social factors.[76,82] To improve the health outcomes in PLWH, it is therefore important to understand social barriers. Starting in 2015, specific diagnostic ICD-10 codes that begin with the letter Z were introduced to capture the patient's social needs. Recent work has extracted Z-code frequencies in the medical records and demonstrated the potential of using Z-codes in the study of health outcomes.[83,84] Unplanned hospital readmission is one of the key measures of quality of care and health outcome. High hospital readmission rates are associated with unfavorable patient outcomes and high financial costs.[85] Patients living in high-poverty and socioeconomically challenged neighborhoods are 24-70% more likely to be readmitted than others.[86,87] More recently, Bensken *et al*. showed that a dose-responsive relationship exists between the numbers of social factors and readmission rates at the national level,[84] highlighting the importance of these factors in negative healthcare utilization outcomes.

We hypothesized that PLWH with social needs could have an even higher readmission rate than those without social needs. Each U.S. state's State Inpatient Databases (SID) provides comprehensive information on all acute care hospitals in that respective state, making SID the largest collection of longitudinal hospital care data, covering all insurance payers and patient age groups. In this study, we investigated the prevalence of documented social

factors and their impacts on hospitalized PLWH in the states of Florida and Maryland from 2016 to 2019.

Methods

In this retrospective study, we investigated the impact of the health-related social needs (HRSN) in hospitalized PLWH from the states of Florida and Maryland. This study was determined to be exempt by Case Western Reserve University's Institutional Review Board.

Data source and study population

This study used the State Inpatient Databases (SID) from Florida and Maryland from 2016 to 2019. The SID contains nearly all hospitalizations at in the state with demographic information, diagnosis and procedure codes, and hospital-level characteristics. The SID data from Florida is about four times larger than the SID data from Maryland, so the latter was used for sensitivity analysis. PLWH of all age were identified using ICD-10 codes (B21, B22, B23, B24, and Z21).

Our study included 122,031 HIV diagnosis of records (43,229 patients) from Florida, and 32,262 HIV diagnosis records (12,396 patients) from Maryland from 2016 to 2019.

Key variables of interest

Main independent variable-presence of HRSN

We defined the presence of HRSN based on the presence of 5 domains using ICD-10 Z-codes (Table 2.1): employment, family, housing, psychosocial, and education, consistent with the work by Bensken et al.[84] We searched each domain by specific Z-codes within a four-year period for all the hospital records of PLWH, then the recorded numbers of each domain were summarized for each patient. If each domain had at least 1 count of records for a patient, then the individual was flagged to have a documented HRSN domain. The total number of domains was counted for each patient.

Outcome variables-readmission

We combined 4-year (2016-2019) SID data to increase the size of study population. Patients were identified as having a hospital readmission for 90-day or one-year follow-up if the patient had more than one discharge in a 4-year period. Patients were excluded if they died during the index hospitalization. For 90-day readmission, index records were excluded if index hospitalization occurred in October, November, or December of 2019. For one-year readmission, the index records during the entire 2019 year were excluded.

Covariates

We selected covariates that are potential confounders of the relationship between social needs and readmission, including symptomatic status (reference: asymptomatic, see the relevant codes listed in Table 2.2, sex

(reference: Male), payer (reference: privately insured), age group (We divided the age into 6-categories: under 18, 18-44, 44-54, 55-64, 65-74, and 75+. Reference: Under 18 years old), race (reference: white) income (reference: first quartile) and Elixhauser comorbidities. Symptomatic status was used as a proxy for patients experiencing symptoms such as AIDS-defining syndromes or the opportunistic infection. The Elixhauser comorbidities were commonly used in analyses of administrative data and are associated with death in hospitals, increased length of stay, and increased charges.[88] We used all available hospitalizations and all available diagnosis code slots (40 on each discharge for Florida, 78 on each discharge for Maryland) to identify comorbidities. Each comorbidity was coded as present or absent and entered into the model as its own covariate.

Statistical analysis

We conducted multivariable logistic regression to examine the relationship between the presence of HRSN and one-year readmission after adjusting for select covariates. In the model, the presence of HRSN was the main independent variable. Other independent variables included symptomatic status, age, race/ethnicity, income, payer type, and Elixhauser comorbidities. The model was optimized by backward elimination.

Classification and Regression Tree Models

Classification and Regression Tree (CART) analysis is a supervised tree-based machine-learning method. The CART algorithm uses recursive partitioning to create a tree like structure, with each node represents a partition of the data. The algorithm recursively splits the dataset into subsets based on the values of predictors to reduce impurity. Splits are chose to minimize some measure of impurity or heterogeneity within each resulting partition. The initial partition consists of all the data and is represented by the root node, and the process continues until additional splits no longer yield a reduction in impurity or meet stopping criteria, such as a minimum number of observations in terminal nodes. CART analysis creates a tree that shows the combination of the most important factors to predict an outcome. Also, the tree shows how these factors work in combination. In our model, the readmission status of one-year following-up was the outcome. The predictors included HRSN and other covariates described in the covariates section.

Random Forest Models

We also employed Random Forest models to validate our resulting CART model. Random Forest is an ensemble method of multiple deep decision trees with the advantage to mitigate over-fitting problem of individual decision tree. In this approach, the independent trees and the variables from different training dataset are combined by selecting the most common variables or averaging in a model, which give a more robust and accurate prediction. In this study, we used the Random Forest approach to evaluate if the same variables emerged as in our main CART trees. The approach served as

another form of validation of these trees. We reported the variables with a relative importance by mean Gini coefficient decrease (50% or higher). By using the relative importance, we scaled all the measures to be a percent of the most important variable. The important variables were plotted from the aggregation of 2000 trees. The readmission status of 90-day and one-year following-up were the outcomes. The predictors included HRSN and other covariates described previously in the covariates section.

Results

High prevalence of health-related social needs in PLWH

We identified 43,229 PLWH from Florida and 12,396 from Maryland, who were admitted to the hospital during the period 2016 to 2019. A total of 9.6% (4,153) of PLWH in Florida had documented HRSN at index hospitalization, while 12.5% (1,551) of PLWH in Maryland had HRSN (Table 2.3). Among the five domains of HRSN, housing insecurity was the most dominant domain in both cohorts (Florida: 7.71% and Maryland: 9.30%). Family situations (Florida: 1.82% and Maryland: 3.17%) and employment (Florida: 1.54% and Maryland: 2.99%) also remained significant. Psychosocial factors and education accounted for low numbers of total HRSN (Table 2.3).

Table 2.4 shows the characteristics of PLWH with or without HRSN from Florida. Notably, the distribution of age, insurance type, symptomatic status, and race/ethnicity differed considerably between those with and without HRSN. Compared to PLWH without HRSN, the percentages of the patients

with documented HRSN were higher in the age groups of 18-44 (42.2% vs 32.4%) and 45-54 (32.7% vs 27.4%), but were lower in the age group of 55-64 (20.5% vs 26.4%). The percentage of enrollment in Medicare and Medicaid programs were different: Medicaid (34.7% for HRSN group vs 23.5% for non-HRSN group); Medicare (26.0% for HRSN group vs 35.0% for non-HRSN group). PLWH with documented HRSN had a slightly lower percentage of symptomatic status (including opportunistic infection and AIDS-related syndrome) than those without HRSN (9.3% for HRSN group vs 10.2% for non-HRSN group). Patients with HRSN had a much high percentage of alcohol abuse (16.2% for HRSN group vs 6.5% for non-HRSN group), drug use (34.8% for HRSN group vs 11.2% for non-HRSN group) and psychoses (13.9% for HRSN group vs 5.8% for non-HRSN group).

Table 2.5 shows the characteristics of PLWH with or without HRSN from Maryland. The distribution by age, insurance type, symptomatic status, and race/ethnicity between two groups of patients from Maryland had similar pattern to PLWH from Florida. Compared to PLWH without HRSN, the percentages of the patients with documented HRSN were higher in the age group of 18-44 and 45-54, but were lower in the age group of 55-64. The coverage percentage of different payers was different, PLWH with HRSN had a higher Medicaid, lower Medicare, and Private payer enrollment. PLWH with HRSN had a lower percentage of symptomatic status, but a higher percentage of alcohol abuse, drug use, and psychoses than those without HRSN.

High readmission rate for PLWH with HRSN

In Florida, compared to PLWH without documented HRSN, the 90-day readmission rate for PLWH with HRSN was almost double (46.0% vs 23.1%), and one-year readmission rate for those with HRSN was 1.8-times higher (73.6% vs 41.3%) (Figure 2.1). There was a dose-responsive effect between the number of HRSN domains and the percentages of PLWH who were readmitted during the 90-day and one-year period: For PLWH with 1 domain, the readmission rate of 90-day was 43.5%, for patients who had 2 or 3, or more domains, the readmission rates steadily increased to 58.7% and 64.3%, respectively (Figure 2.2). Similarly, the readmission rate of one-year for PLWH with 1 domain was 71.3%, while the readmission rates for patients who has 2 or 3, or more domains were 84.4% and 93.4%, respectively (Figure 2.2).

For PLWH patients from Maryland, the readmission rate followed a similar pattern to those from Florida (Figure 2.3). There was a similar dose-responsive effect between the numbers of HRSN domains and the percentage of PLWH who were readmitted during 90-day and one-year (Figure 2.4).

The association of HRSN with high readmission rate

The higher readmission rate of PLWH with documented HRSN in the two studied states was striking. The fitted model of readmission of one-year readmission from Florida showed that the odds ratio of PLWH with HRSN was 3.93 (95% CI: 3.62-4.27) times higher than those without HRSN. Additionally,

insurance type (particularly enrollment in Medicaid and Medicare), multiple Elixhauser based comorbidities (particularly having a condition of metastatic cancer or cancer, renal failure, lymphoma) were important predictors for readmission (Table 2.6). By CART analysis, the presence of HRSN was at the top node of one-year readmission rate for fitted CART model, other contributable variables included renal failure, chronic lung disease, and anemia deficiency at the second and third nodes (Figure 2.5). Consistent with the CART model, Random Forest models showed that HRSN was the most prioritized variable for the readmission of PLWH (Figure 2.6).

In PLWH from Maryland, the very similarly fitted model of readmission of one-year readmission showed that the odds ratio of PLWH with HRSN was 3.60 (95% CI: 3.15-4.12) times higher than those without HRSN. Additionally, insurance type, particularly payer type such as Medicaid and Medicare, multiple Elixhauser based comorbidities having a condition of metastatic cancer or cancer, renal failure, pulmonary circulation disorder, congestive heart failure, and lymphoma were important major predictors for readmission (Table 2.7). By CART analysis, the documented HRSN was at the top node of one-year readmission rate for fitted model, and other variables at second and third nodes included renal failure, congestive heart failure, age, and anemia deficiency (Figure 2.7). Consistently, Random forest model mirrored the same conclusion that HRSN was the most prioritized variable for the readmission of PLWH (Figure 2.8).

Discussion

In this study, we reported a prevalence of health-related social needs (HRSN) among hospitalized PLWH in two states of the U.S (Florida: 9.6%; Maryland: 12.5%). PLWH with documented HRSN had nearly twice the 90-day and one-year readmission rate compared to those without HRSN. PLWH mainly carried three domains of health-related social needs, including inadequate housing, unemployment, and insufficient family/social support. Our findings revealed that social risk factors in PLWH was closely associated with high hospital readmission rate.

Hospital readmission is one of the indicators of quality of care for chronic diseases, and a high readmission rate is reported to be associated with substandard care during the index hospitalization.[89] Although HIV infection now is considered a manageable chronic disease, PLWH have a higher rate of readmission than non-HIV patients. For example, a multi-site study reports that the 30-day readmission rate of PLWH in the U.S. is about 19.3%, while it is only 13.3% for non-PLWH for the same follow-up time. [90] In a large study from all hospitals in the state of New York, the 30-day readmission of PLWH is 21.8%.[91] The various models indicate that the factors associated with 30-day readmission for PLWH include AIDS-defining illness, low CD4 cell count, laboratory abnormalities, psychoses, multiple comorbidities, and social factors such as insurance status, housing instability (including homelessness), distance from the hospital, and prior emergency department visits and

hospitalizations.[91,92] These findings indicate that non-medical social factors play an important role in the readmission to hospital. It has also been proposed that about half of 30-day readmission of HIV patients are potentially preventable, with measures such as early HAART initiation, adherence counseling, management of chronic conditions, and appropriate timing of discharge.[92] Our study results, along with the aforementioned studies indicate that, in addition to the medical factors, addressing HRSN for PLWH is essential to reduce their hospital readmission to hospitals. Our findings suggest that housing instability, unemployment, and family/social instability are the key factors contributing high readmission for PLWH in the states of Florida and Maryland. The elevated readmission rates of PLWH with HRSN imply substantial hospital expenditures for this patient group. Our findings underscore the necessity of incorporating social needs into the care of PLWH.

At index hospitalization, PLWH without HRSN had a much lower rates of several psychosocial related comorbidities than those with HRSN, including alcohol abuse, drug use, and psychoses (Table 2.4 and Table 2.5). This difference reflects the high prevalence of substance use and psychological diseases in PLWH. In the multivariable model, CART, and Random Forest analyses for the readmission rate, HRSN was the most dominant predictor of high readmission, reinforcing our hypothesis that HRSN is the prominent factor associated with high readmission.

Enrollment in the Medicare/Medicaid program was also significantly associated with high readmission rates. Additionally, the symptomatic patients at index admission was weakly associated with high readmission rate: the odds ratio was lower in PLWH with HSRN than without HRSN (Table 2.6 and Table 2.7). However, PLWH with documented HRSN actually had a slightly lower percentage of symptomatic status than those without HRSN (Table 2.4 and Table 2.5), indicating the presence of HRSN in the index admission may not be associated with patients' symptomatic status.

For PLWH from both Florida and Maryland, housing needs was the most prevalent social risk, followed by employment and family/social needs (Table 2.3). Several previous studies have found that homeless individuals and those facing housing instability, coupled with food insecurity, are more likely to have lower CD4 (T-cell) counts, poorer medication adherence, and incomplete suppression of HIV replication.[93-95] More recent work has shown that food insecurity was associated not only with poorer medication adherence but also with limited access to health care and inconsistent care, and lower quality of life.[96-98] Our findings, combined with those reported in the literature, support the notion that these social risks significantly impact PLWH's ability to manage their HIV treatment, subsequently contributing to the high risk of hospital readmissions.

The high readmission of PLWH with HRSN implies that PLWH with documented social needs are the most fragile group among vulnerable HIV patients, coupled with high prevalence of alcohol abuse, drug use, and psychoses. The strikingly high readmission rate signifies that PLWH with social needs require more adequate care, implying that social factors further widen the care gap between PLWH and non-HIV infected people. Addressing social factors in PLWH is essential for better care of marginalized PLWH. It is important to address these needs in PLWH to improve their health outcomes and reduce healthcare costs associated with frequent hospital readmissions.

The syndemic theory could be a better interpretation of worse outcomes arising from a combination of disease burden and social factors in PLWH. The syndemic theory has been used to explain the cluster of substance abuse, violence, and AIDS ("SAVA") in poor urban communities.[5] It is a typical scenario that PLWH are marginalized and face various social burdens, which could have a negative influence on health outcomes. HIV care providers may need to consider the likelihood of rising readmission and adverse outcomes if a HIV patient has documented social needs from the index admission. Policymakers should consider the magnitude of the various social factors on health outcomes to make decisions on better management and reimbursement of HIV medical services.

One of the major strengths of our study is that we analyzed readmission from two independent states, Florida and Maryland, with contemporary data spanning from 2016 to 2019. Even though the cohort size from Florida was about 4-times larger than the cohort from Maryland, and we had similar results from separate analyses of the two cohorts. Another strength of our current study is that we applied different models to assess the association of readmission and documented social needs from two independent cohorts. The data from the multivariable model, CART and Random forest analyses collectively provided the strong evidence that health-related social needs are key factors that impact the frequency of hospital readmission for PLWH.

We note the following limitations. First, we reported the high prevalence of HRSN in the PLWH population. However, since the codes of HRSN are not completely recoded by clinician, the actual prevalence of HRSN among PLWH could be much higher than the prevalence reported in this study. Second, the current study does not provide the clinical data for PLWH at index hospitalization. Due to the limitations of administrative data, this study could not provide some key factors of PLWH such as CD4 cell count and disease stage from the state inpatient database. Third, we only examined the PLWH form two states including Florida and Maryland. However, it is mostly likely the finding from these two states resemble the trend at the national level. Four, due to the unavailability of the discharge month variable in the state inpatient

data, this study only analyzed the 90-day and one-year readmission rates and did not include the 30-day readmission rate.

In conclusion, our study highlights a critical role of social needs on the readmission and outcomes of hospital care for PLWH. The high prevalence of social factors in PLWH is underscrutinized in current HIV care, and the combination of social factors and comorbidities that PLWH encounter have a syndemic effect on their health outcome. PLWH with chronic diseases or multiple comorbidities often have higher readmission rates, which can be further exacerbated by social factors. It is important to train clinicians to understand the impact of HRSN on health and record the social factors adequately. The ultimate goal is that healthcare providers, social workers, and community organizations work together to provide support and resources to meet health-related social needs and to improve PLWH's health outcomes and reduce healthcare costs associated with frequent hospital readmissions.

Chapter III

Excess Cancer Prevalence in men living with HIV

Abstract

Background: Cancer is one of the most common comorbidities in men living with HIV (MLWH). However, little is known about the MLWH subgroups with the highest cancer burden to which cancer prevention efforts should be targeted. Because Medicaid is the most important source of insurance for MLWH, we evaluated the excess cancer prevalence in MLWH on Medicaid relative to their non-HIV counterparts.

Methods: In this cross-sectional study using 2012 Medicaid Analytic eXtract data nationwide, we flagged the presence of HIV, 13 types of cancer, symptomatic HIV, and viral coinfections using codes from the International Classification of Diseases, Ninth Revision, Clinical Modification. The study population included individuals administratively noted to be of male sex (men), aged 18 to 64 years, with (n = 82,495) or without (n = 7,302,523) HIV. We developed log-binomial models with cancer as the outcome stratified by symptomatic status, age, and race/ethnicity.

Results: Cancer prevalence was higher in MLWH than in men without HIV (adjusted prevalence ratio [APR], 1.84; 95% confidence interval [CI], 1.78-1.90) and was higher among those with symptomatic HIV (APR, 2.74; 95% CI, 2.52-2.97) than among those with asymptomatic HIV (APR, 1.73; 95% CI,

1.67-1.79). The highest APRs were observed for anal cancer in younger men, both in the symptomatic and asymptomatic groups: APR, 312.97; 95% CI, 210.27-465.84, and APR, 482.26; 95% CI, 390.67-595.32, respectively. In race/ethnicity strata, the highest APRs were among Hispanic men for anal cancer (APR, 198.53; 95% CI, 144.54-272.68) and for lymphoma (APR, 9.10; 95% CI, 7.80-10.63).

Conclusion: Given the Medicaid program's role in insuring MLWH, the current findings highlight the importance of the program's efforts to promote healthy behaviors and vaccination against human papillomavirus in all children and adolescents and to provide individualized cancer screening for MLWH.

Introduction

Despite stabilization of the annual number of incident HIV cases, the prevalence of HIV in the United States has increased dramatically, largely as a result of the introduction of highly active antiretroviral therapy and improved longevity in people living with HIV (PLWH).[71] Recent estimates indicate that nearly 1.2 million adolescents and adults in the United States are living with HIV.[99] Nonetheless, the life expectancy of PLWH has never returned to that of the general population,[72] in great part because of the high comorbidity burden in PLWH.[99,100]

Among the most common comorbidities affecting PLWH are non–AIDS-defining cancers, such as lung, head and neck, and anal cancers, which are associated with significant morbidity and mortality.[101-105] A previous study

demonstrated that non–AIDS-defining cancer was the leading non-AIDS cause of death in PLWH,[106] responsible for 10-17% of deaths in PLWH.[107, 108] Although the cancer burden in the United States is expected to increase as the population ages,[109] it may affect PLWH more acutely because they are generally diagnosed with cancer 10 to 20 years earlier than people without HIV.[110, 62] This is caused in part by premature aging,[111] compromised immune function, and a high prevalence of non-HIV cancer risk factors (eg, smoking and coinfection by oncogenic viruses, such as human papillomavirus [HPV]).[47]

HIV disproportionately affects persons of color, men who have sex with men, transgender women, those who inject drugs, and those with lower socioeconomic status.[112] Medicaid is the most important source of health insurance for PLWH, providing coverage for 40% of PLWH in 2018.[113] This large representation of PLWH in Medicaid underscores the importance of evaluating their health care needs, including their needs for cancer prevention and control.

In this study, we measured the excess prevalence of various cancers in PLWH compared with the general population using 100% Medicaid data from all 50 states and the District of Columbia. We hypothesized that HIV status would be associated with excess cancer prevalence, especially in men with symptomatic HIV. We further hypothesized that excess prevalence would vary across age and race/ethnicity subgroups of men living with HIV (MLWH) who were on Medicaid. We focused on individuals administratively noted to be

male (which includes cisgender men and some transgender individuals) to provide a more in-depth analysis by anatomic cancer site, given differences in the prevalence of HPV-related conditions (eg, anogenital warts and anal cancer) between men and women with HIV.[114] We also focused on individuals in the 18-64 age group, given the demographic makeup of the Medicaid population.

Methods

In this cross-sectional study, we evaluated the excess prevalence of cancer in men with and without HIV, using 100% Medicaid Analytic eXtract (MAX) files covering all 50 states and the District of Columbia. Our study year was 2012, the most recent year for which national MAX data were available at the time the study was initiated.

This study was approved by the Case Western Reserve University's Institutional Review Board (protocol # 2017-1817) and the Centers for Medicare & Medicaid Services (Data Use Agreement #2017-51352).

Data source

The MAX database consists of: 1) the Personal Summary (PS) file, which we used to retrieve individuals' demographics and months of enrollment in Medicaid during the study year, as well as the U.S. Census divisions; and 2) claims files, including Inpatient (IP) and Other Therapy (OT) for care received

in inpatient and outpatient hospital and non-institutional care settings.

Study population

Our study population included 7,385,018 men, as defined by sex documented in their Medicaid file, between the age of 18-64 years. We excluded individuals in the following categories: 1) those with Kaposi's sarcoma and non-Hodgkin's lymphoma,given a potential overlap with the conditions we used to identify symptomatic MLWH (Table 3.1); 2) individuals dually enrolled in Medicare and Medicaid because of potentially incomplete claims data; 3) those who only had exclusively premium claims (or Recipient Indicator '2'), which had no valid diagnosis codes; and 4) those who had neither S-Chip enrollment months nor Medicaid enrollment months (Recipient Indicator '9').

Key variables of interest

Using the MAX files from each state, we created binary variables for each of HIV status and 13 common cancers based on the presence of relevant ICD-9 diagnosis codes included in the Agency for Healthcare Research and Quality Clinical Classification Software [115] (Table 3.2). For each diagnosis, we required at least one occurrence in the IP file or two more separate occurrences in the OT file, at least 30 days apart. The 13 cancer types consisted of: cancer of the head/neck, esophagus, stomach, colon, rectum, anus, liver and intrahepatic bile duct, pancreas, prostate, bronchus/lung, other respiratory and intrathoracic organs, lymphoma, and leukemia. The presence

of cancer (all cancers combined, and by type) was our outcome of interest, and HIV status was our main independent variable. Individuals with multiple cancers were included in each cancer site analysis.

Other independent variables included individuals' age in 2012 (18-44 and 45-64 years) and race/ethnicity (White, Black, Hispanic (including Hispanic or Latino and one or more races), Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, More than One Race, and Unknown or Missing). Given this categorization of the race/ethnicity variable, we assumed that all those not grouped in the Hispanic category were of non-Hispanic ethnicity. We chose to dichotomize age at 44 years based on the age distribution of the cancers with the highest excess prevalence -- anal cancer and lymphoma -- in men with and without HIV (Figure 3.1A-C). We chose these categorizations of age and race/ethnicity, because of the limited sample size for men with HIV and cancer. Additionally, our models accounted for the U.S. Census divisions (New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, and Pacific).[116] Lastly, to account for a greater opportunity to capture the diagnoses of interest in individuals with longer periods of enrollment in Medicaid, we included a continuous variable reflecting the total number of months of enrollment in Medicaid during 2012.

To leverage the richness of Medicaid claims data, we used all available claims

data to further identify individuals with HIV as symptomatic or asymptomatic, in the presence or absence of diagnosis codes indicating the presence of opportunistic infections and AIDS-related symptoms, as a proxy for compromised immune status. We also flagged co-infections by hepatitis B or hepatitis C virus (HBV and HCV), or HPV (see the relevant diagnosis codes in Table 3.1).

Statistical Analysis

We estimated prevalence ratios by HIV status using log-binomial models, but resorted to log-Poisson regression models when the models failed to converge.[117] We calculated the prevalence ratio for cancer overall and for specific cancers. In each model, HIV status was the main independent variable. Other independent variables included age, race/ethnicity, U.S. Census divisions, enrollment months, and co-infection by HBV/HCV (in models for liver cancer) or HPV (in models for head/neck, rectal, and anal cancers). When combining different cancer types, we accounted for co-infections by including a binary variable indicating the presence of HBV, HCV, and/or HPV. We did not adjust for co-infections in models for lymphoma.

We set our level of statistical significance at alpha < 0.05. However, given the large size of our study population, we focused our attention on the clinical meaningfulness of the findings and the varying magnitude of APRs across the comparison groups.

To examine effect modification, we stratified our analysis by HIV symptomatic status, and further, by age group and race/ethnicity, focusing on the most common cancers: rectal and anal cancers, and lymphomas. To address small numbers in our stratified analysis by race/ethnicity (Table 3.3), we presented our data for non-Hispanic Whites, non-Hispanic Blacks, Hispanics, and All Others. The latter category aggregated data for all other race categories to allow for more stability in our models.

Finally, we note the following additional analyses: First, to ensure that we captured claims for all Medicaid beneficiaries, regardless of their enrollment in managed care, we conducted extensive analysis on the patterns of missingness of diagnosis codes in claims data. We excluded Medicaid/Medicare dually eligible and with Recipient Indicator '2' (recipient only had premium payment claims [i.e. no healthcare services claims]) or '9' (recipient was not enrolled in the State Children's Health Insurance Program (SCHIP) or Medicaid for any months in the study period). We included enrollment and claims data for all other Medicaid beneficiaries, including for non-users. While we detected no systematic missingness for diagnosis codes among Medicaid beneficiaries with claims or encounter data in our final study population, we note that managed care "encounters" may be less complete than fee-for-service claims.[118] Second, we conducted sensitivity analysis to examine excess prevalence after including

MLWH with Kaposi's sarcoma and certain lymphomas in the symptomatic group. The results did not change in any meaningful way (Table 3.4).

We used SAS, Version 9.4 for UNIX (SAS Institute, Inc., Cary, North Carolina) for data processing and analysis, and ggplot2 package under R Studio Version 1.3.1093 environment to generate the forest plots for APRs.

Results

Our study population included 82,495 men living with HIV (MLWH) and 7,302,523 men without HIV. Table 3.5 details their distribution by demographics, co-infections, and type of cancer. Compared with men without HIV, a higher percentage of MLWH were in the 45-64 age group (59.79% vs 29.84%), were non-Hispanic Black (48.62% vs 19.36%), or presented with cancer (5.06% vs 1.32%). The age distribution for men with anal cancer, lymphoma, and all other cancers is provided in Figure 3.1A-C. For both anal cancer and lymphoma, the median age was lower for MLWH than in men without HIV (54 vs 45 years, and 50 vs 47 years, respectively). For all other types of cancer, however, the median age was comparable between the two groups (56 vs 54 years).

Among men with HIV, 8.78% were identified with symptomatic HIV. Compared with MLWH in the asymptomatic group, a larger percentage of MLWH in the symptomatic group were 18-44 years of age (45.18% vs

39.73%). However, with few exceptions (those with more than one race or Unknown/missing race), the distribution by race/ethnicity was comparable between symptomatic and asymptomatic MLWH. With regard to cancer prevalence, however, a higher percentage of symptomatic than asymptomatic MLWH presented with cancer during 2012 (8.07% vs 4.77%). In the two groups, lymphoma, rectal, and anal cancers represented 59.83% and 63.61% of all cancers, respectively.

Figure 3.2 presents the age-adjusted and race/ethnicity adjusted prevalence ratios (APRs) for symptomatic, asymptomatic, and all MLWH before stratifying by age and race/ethnicity. For both the symptomatic and asymptomatic groups combined and for all cancers, the APR was 1.84 (95% confidence interval [CI], 1.78-1.90), indicating that the prevalence of cancer was nearly twice as high in MLWH than in men without HIV. However, the APR was markedly higher in symptomatic MLWH than in asymptomatic MLWH (APR, 2.74 [95% CI, 2.52-2.97] and 1.73 [95% CI, 1.67-1.79], respectively). The highest APR was observed for anal cancer (APR, 42.64 [95% CI, 34.15-53.24] in symptomatic MLWH and 70.43 [95% CI, 63.77-77.82] in asymptomatic MLWH), followed by lymphoma (APR, 14.56 [95% CI, 12.71-16.68] and 5.14 [95% CI, 4.76-5.54] in symptomatic and asymptomatic MLWH, respectively). Other cancers for which we observed excess prevalence included esophageal cancer (APR, 3.63; 95% CI, 2.36-5.57) and leukemia (APR, 3.30; 95% CI, 2.33-4.66) in the symptomatic group only, and rectal cancer (APR, 3.52 [95% CI, 2.61-4.75] and

2.40 [95% CI, 2.14-2.70]) in the symptomatic and asymptomatic groups, respectively. For liver cancer, however, we noted comparable prevalence in the symptomatic group (APR, 1.09; 95% CI, 0.85-1.40) and lower prevalence in the asymptomatic group (APR, 0.70; 95% CI, 0.62-0.79) after adjusting for HBV/HCV coinfections in the multivariable models.

The APRs stratified by age and symptomatic status presented in Table 3.6 showed a significant effect modification by age. For all cancers combined, the APR was 9.38 (95% CI, 8.80-10.01) in the younger age group but 1.30 (95% CI, 1.25-1.35) in the older age group, indicating that, compared with men without HIV, the prevalence of cancer was over 9 times greater in MLWH in the younger age group but 1.3 times higher in the older age group. In addition, the APR was considerably higher in the symptomatic group than in the asymptomatic group (APR, 13.28 [95% CI, 11.45-15.42] vs 8.82 [95% CI, 8.23-9.45], respectively, in the younger age group; and APR, 1.83 [95% CI, 1.66-2.02] vs 1.24 [95% CI, 1.19-1.29], respectively, in the older age group).

Among specific cancers, the highest APR was for anal cancer in both age groups: It was nearly 500 in the younger age group (APR, 480.28; 95% CI, 390.27-591.04), which was markedly more than that observed in the older age group (APR, 36.18; 95% CI, 32.27-40.57). In addition, in the younger age group, the APR for anal cancer was higher in the asymptomatic group (APR, 482.26; 95% CI, 390.67-595.32) than in the symptomatic group (APR, 312.97; 95% CI, 210.27-465.84), but it was somewhat lower for rectal cancer in the

asymptomatic group (APR, 11.55; 95% CI, 9.04-14.77) than in the symptomatic group (APR, 16.78; 95% CI, 9.67-29.11). For lymphoma, the APR was 16.42 (95% CI, 14.75-18.29) and 4.29 (95% CI, 3.93-4.67) in the younger and older age groups, respectively. In both age groups, the APR for lymphoma was considerably higher in the symptomatic group than in the asymptomatic group.

Table 3.7 presents the age-adjusted APRs for select cancers by HIV symptomatic status and race/ethnicity. For all cancers and for the symptomatic and asymptomatic groups combined, the highest and lowest APRs were observed among Hispanic men (APR, 2.25; 95% CI, 2.07-2.44) and non-Hispanic Black men (APR, 1.59; 95% CI, 1.51-1.67), respectively. In addition, with a few exceptions (eg, for anal cancer), we observed higher APRs in the symptomatic group than in the asymptomatic group. Among those in the All Others category, the APRs were similar in the symptomatic groups (APR, 1.78; 95% CI, 1.31-2.42) and the asymptomatic groups (APR, 1.89; 95% CI, 1.70-2.10).

For cancer-specific APRs, we noted considerable variations in the APRs across race/ethnicity categories and by symptomatic status. For both the symptomatic and asymptomatic groups combined, the highest APRs for anal cancer and for lymphoma were observed among Hispanic men (APR, 198.53 [95% CI, 144.54-272.68] and 9.10 [95% CI, 7.80-10.63], respectively). Conversely, the lowest APRs for anal cancer and for lymphoma were

observed in non-Hispanic White men (APR, 55.36; 95% CI, 48.17-63.61) and non-Hispanic Black men (APR, 4.92; 95% CI, 4.42-5.48), respectively.

Discussion

Using national Medicaid data, we found excess prevalence of cancer in MLWH, particularly for anal cancer, rectal cancer, and lymphoma. Overall, cancer prevalence was nearly twice as high in MLWH than men without HIV on Medicaid. However, the excess prevalence was markedly higher in younger than in older MLWH, attesting to the younger ages at cancer diagnosis in people with HIV.[110] Consistent with previous studies, the prevalence of anal cancer was higher among MLWH, compared with their non-HIV counterparts, and this association was stronger in the younger age group [62,110] – nearly 500 times higher in the younger age group, compared with 36 times higher in the older age group. These findings suggest that the burden of anal cancer is of a much greater magnitude than previously described in PLWH, although most prior studies have reported hazard or risk ratios, rather than prevalence ratios, as we do in this study.[62,119,120]

Our findings also showed variations in excess cancer prevalence by HIV symptomatic status and across cancer sites. MLWH experienced higher cancer prevalence than men without HIV for all cancer types, whether they were in the symptomatic or asymptomatic groups. With the exception of anal cancer, however, the magnitude of APRs was considerably smaller in asymptomatic than in symptomatic MLWH, attesting to the higher cancer

burden in symptomatic MLWH.

To our knowledge, this is the first national study to examine excess cancer prevalence in MLWH on Medicaid, by symptomatic status. In the absence of conditions such as opportunistic infections, asymptomatic HIV status implies viral suppression and a relatively healthy immune system. Although viral suppression has been shown to contribute to cancer prevention,[121] the lower APRs in the asymptomatic group in our study should be interpreted with caution, as these findings pertain to people on Medicaid and not to the general population. With Medicaid being a safety net program, individuals who seek to enroll in Medicaid have not only low incomes, but also present with complex mental and physical health care needs, and/or the diagnosis of a catastrophic illness, such as cancer. Hence, we hypothesize that, rather than decreased risk to develop cancer, the lower cancer prevalence in asymptomatic MLWH for most cancers likely reflects that men in this group may not have the complex health care needs that would prompt them to enroll in Medicaid, except when they are diagnosed with certain cancers. To test this hypothesis, future studies should compare the co-occurrence of mental and physical chronic conditions in MLWH on Medicaid by symptomatic status.

To our knowledge, this is also the first study, to use nationwide Medicaid data to study excess prevalence for cancers other than those associated with HPV. Given that there are additional risk factors (e.g., smoking and non-HPV co-

infections) that increase the risk of cancer in PLWH,[55,122] our findings highlight the importance of individualized education and cancer screening, depending on the risk factors present in each individual with HIV,[123] as well as a proactive stance by the Medicaid program to promote HPV vaccination in all children and adolescents. The fact that screening for anal cancer remains controversial, and that the present study is cross-sectional (rather than prospective) in nature, we are unable to recommend screening for anal cancer. As for lymphoma, while there is no screening for lymphoma, improved access to health care allows for a timely evaluation of symptoms, diagnostic evaluation, and treatment initiation.

Our findings should be interpreted in light of the following limitations. First, given our use of administrative data, the demographic variables (age, race/ethnicity, and sex) are as documented in the administrative records. Hence, we assumed that the sex variable in the Medicaid database is the individual's sex assigned at birth, and thus our study population primarily included individuals assigned male sex at birth. Second, we did not have any reliable measures in claims data on behavioral health and risk factors, including smoking, alcohol consumption, or sexual behaviors. However, the very large magnitude of many of our APRs, it is unlikely that including these risk factors in our models would have completely explained the observed associations. Third, our method to identify the presence of cancer in Medicaid beneficiaries relied exclusively on diagnosis codes in claims data. Absent

additional data from cancer registries, we were unable to ascertain cancer incident/prevalent status or age at cancer diagnosis. Lastly, we note that these results reflect data from 2012. Since then, Medicaid enrollment increased substantially as a results of Medicaid expansion in 2014, declined in the years 2017-2019,[124] and increased again during the pandemic.[125] Going forward, it will be important to examine whether these changes have had any effect on the patterns of cancer burden in Medicaid-insured MLWH observed in the present study. Regardless, a major component of today's Medicaid population consists of people with low incomes defined by pre-expansion eligibility criteria, and people with slightly higher income levels in the expanded eligibility group. In the absence of substantial secular trends, it is reasonable to assume that the patterns reported herein will remain in the Medicaid population, and that our findings are still highly relevant today. We also suggest the need for subsequent work in the development of targeted prevention measures.

In conclusion, cancer is a significant source of morbidity and mortality among PLWH, and the burden of cancer will likely increase in the future as this population ages. Medicaid plays a key role in insuring PLWH, a role that has only increased since the passage of the Affordable Care Act and post-pandemic. Our findings call for a proactive stance by Medicaid to adopt a multipronged approach, to not only improve HIV-specific care, but also to promote individualized cancer screening and more widespread HPV

vaccination in children and adolescents.

Chapter IV

Cancer Burden in women living with HIV

Abstract:

Background: Cancer is the leading cause of death in people living with human immunodeficiency virus (PLWH). In the U.S., nearly 1 in 4 PLWH are women, more than half of whom rely on Medicaid for healthcare coverage.

Objective: To evaluate the cancer burden of women living with HIV (WLWH) on Medicaid.

Design: We conducted a cross-sectional study of women 18-64 years of age enrolled in Medicaid during 2012, using data from Medicaid Analytic Extract (MAX) files.

Methods: Using ICD-9-CM diagnosis codes, we identified WLWH (n=72,508) and women without HIV (n= 17,353,963), flagging the presence of 15 types of cancer and differentiating between AIDS-defining cancers (ADCs) and non-ADCs (NADCs). We obtained adjusted prevalence ratios (APRs) and 95% confidence intervals (95% CIs) for each cancer and for all cancers combined, using multivariable log-binomial models, and additionally stratifying by age and race/ethnicity.

Results: The highest APRs were observed for Kaposi's sarcoma (81.79 (95% CI: 57.11-117.22)) and Non-Hodgkin's Lymphoma (27.69 (21.67-35.39)). The APRs for anal and cervical cancer, both of which were human papillomavirus (HPV)-associated cancers, were 19.31 (17.33-21.51)) and 4.20 (3.90-4.52),

respectively. Among WLWH, the APR for all cancer types combined was about 2-fold higher (1.99 (1.86-2.14)) in women 45-64 years of age than in women 18-44 years of age. For NADCs but not for ADCs, the APRs were higher in older than in younger women. There was no significant difference in the APRs for all cancer types combined in the race/ethnicity-stratified analyses of the WLWH cohort. However, in cancer type-specific sub-analyses, differences in APRs between Hispanic versus non-Hispanic women were observed. For example, the APR for Hispanic women for Non-Hodgkin's lymphoma was (2.00 (1.30-3.07), and 0.73 (0.58-0.92) for breast cancer. Conclusions: Compared to their counterparts without HIV, WLWH on Medicaid have excess prevalence of cervical and anal cancers, both of which are HPV-related, as well as Kaposi's Sarcoma and lymphoma. Older age is also associated with increased burden of NADCs in WLWH. Our findings emphasize the need for not only cancer screening among WLWH, but also for efforts to increase HPV vaccination among all eligible individuals.

Introduction

Currently, there are nearly 1.2 million persons living with HIV (PLWH) in the U.S. Among PLWH, approximately 25% are women, of whom, 75% are from racial or ethnic minorities.[126] In addition, transgender women, those with substance use disorders, and those with lower socioeconomic status are disproportionately represented among women living with HIV (WLWH).[127] With the early initiation of highly active antiretroviral therapy (HAART), life

expectancy of WLWH has improved significantly.[128] Nevertheless, it remains shorter among WLWH than in the general population.[99]

Cancer in WLWH is a major cause of morbidity and mortality. In the pre-HAART era, AIDS-defining cancers (ADCs), including Kaposi's sarcoma (KS), non-Hodgkin's lymphoma, and cervical cancer, accounted for a large portion of cancer-related deaths. Because of the immunocompromised state caused by HIV infection, cancers associated with viral infections are commonly seen in people with HIV. While Kaposi sarcoma is the most common cancer in PLWH [51], the prevalence of Kaposi's sarcoma in non-HIV infected population is low. As a result, the incidence of Kaposi's sarcoma in the United States has remained stable in recent decades. Kaposi's sarcoma mainly results from the HHV8 (also known as KSHV).[48,51] Non-Hodgkin's lymphoma (NHL) is distinguished from Hodgkin's lymphoma (HL) based on Reed-Sternberg cells in the lymph fluid. Non-Hodgkin's lymphoma and a proportion of Hodgkin's lymphoma are linked to EBV.[49] Both HHV8 and EBV belong to the same gamma-herpesvirus family. Cervical cancer is the most common cancer in WLWH, and cervical cancer is caused by HPV.[50] Despite the availability of HPV vaccination and screening, cervical cancer is the leading cause of cancer-related deaths in this population.[58,59] In the post-HAART era, improved healthcare has dramatically reduced the incidence of ADCs in WLWH,[129,130] and non-AIDS-defining cancers (NADCs) now account for a significantly increased fraction of the overall cancer burden in WLWH.[101]

The improvements in viral suppression and survival afforded by HAARTs will likely continue to alter the types of cancers that most impact WLWH. It is projected that while the burden of ADCs will likely further decrease, NADCs, which are mainly comprised of Hodgkin's lymphoma and cancers of the anus, mouth, throat, liver, lung, and breast, will increase slightly.[131] The current consensus is that the HIV infection itself does not have any direct carcinogenic effect.[132] However, with the aging of the population and increased longevity associated with HAART, WLWH are at increased risk of cancer, due to compromised immune function and co-infection by oncogenic viruses, such as HPV, hepatitis B or C virus.[47,60] Furthermore, prevalence of smoking and alcohol drinking, which are independent risk factors for lung, head/neck, liver, and other types of cancer, is much higher in WLWH than in non-infected women, contributing to the increased mortality and morbidity in WLWH. [55] In addition, substance use and high-risk sexual behavior increases exposure to HIV and other oncogenic viruses. [46,48,133]

Despite the substantial morbidity and mortality caused by cancer in PLWH, the cancer burden in WLWH specifically has not been evaluated comprehensively given that men comprise the majority of PLWH, and studies have traditionally focused on this population. This is an important knowledge gap that needs to be addressed because interventions to reduce cancer burden in WLWH may differ from those of men. Medicaid data provides a unique opportunity to better

understand cancer burden in WLWH since 54% of WLWH were enrolled in Medicaid as of 2018.[134] Additionally, given that Medicaid is a safety-net program for women with low incomes, Medicaid data allow us to capture those with complex medical needs and heightened vulnerability for poor outcomes. Thus, in this study, we used Medicaid data from all 50 states and the District of Columbia to investigate the prevalence of 15 common types of cancer in WLWH compared to women without HIV on Medicaid.

Methods

Medicaid Database and Study population

This is a cross-sectional study using data from the Medicaid Analytic eXtract (MAX) database, which includes the following files: 1) the Personal Summary (PS) file, which we used to retrieve individuals' demographics and months of enrollment in Medicaid during the study year; and 2) claims files, including Inpatient (IP) and Other Therapy (OT) for care received in inpatient hospital and institutional and non-institutional outpatient care settings, respectively. We used the claims files to identify the relevant diagnosis codes for HIV and 15 types of cancer (Table 4.1). [135]

The study population included 17,426,471 individuals 18-64 years of age and were noted to be female in the administrative records. We excluded Medicaid/Medicare dually eligible individuals and those with Recipient Indicator '2' (recipient only had premium payment claims [i.e. no healthcare services claims]) or '9' (recipient was not enrolled in State Child

Insurance Health Program (S-CHIP) or Medicaid for any months in the study period), consistent with our previous study.[135] We included enrollment and claims data for all other Medicaid beneficiaries, including for non-users (people who were enrolled in Medicaid during 2012 but did not have any claims).

Key variables of interest

Main independent variable-HIV status

We identified HIV status based on relevant ICD-9 diagnosis codes included in the Agency for Healthcare Research and Quality (AHRQ) Clinical Classification Software (CCS).[115] To identify WLWH, we required one or more occurrences in the IP file or two more separate occurrences in the OT file, at least 30 days apart. Women were classified as HIV negative in the absence of claims carrying HIV diagnosis.

Outcome ascertainment - Cancer

We defined each of the 15 types of cancers as binary variables in women based on relevant ICD-9 diagnosis codes included in AHRQ CCS.[115] These included cancer of the breast, cervix, head/neck, esophagus, stomach, colon, rectum, anus, liver and intrahepatic bile duct, pancreas, bronchus/lung, and other respiratory and intrathoracic organs, as well as Hodgkin's and non-Hodgkin's lymphoma, Kaposi's sarcoma, and leukemia. Similar to HIV status, we required at least one occurrence in the IP file or two more separate occurrences in the OT file, at least 30 days apart, to ascertain their cancer

diagnosis. ADCs included Kaposi's sarcoma, non-Hodgkin's Lymphoma and cervical cancer. NADCs included cancer of head/neck, esophagus, stomach, colon, rectum, anus, liver, pancreas, bronchus/lung, other respiratory & intrathoracic organs, breast, Hodgkin's Lymphoma, and leukemia.

Covariates

Independent variables included age categories (18-24, 25-34, 35-44, 45-54, and 55-54 years) and race/ethnicity (Non-Hispanic White; Non-Hispanic Black; Hispanic of any race including Hispanic or Latino and one or more races; Asian; American Indian or Alaskan Native; Native Hawaiian or Other Pacific Islander; More than One Race; and Unknown or Missing). Due to the small numbers in the latter race/ethnicity categories, we grouped individuals in the All Other category when examining cancer prevalence. Additionally, our models accounted for the U.S. Census divisions (New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, and Pacific), based on the states from which the Medicaid data originated.[116] We also identified and adjusted for co-infections by hepatitis B or hepatitis C virus (HBV and HCV), and/or by cervical HPV or any type of HPV (see the relevant diagnosis codes in Table 4.1). Since the length of enrollment in Medicaid may be associated with greater odds to capture HIV and cancer diagnoses, our multivariable models also accounted for the total number of months of enrollment in Medicaid during 2012. In our models, we did not include the behavioral factors that are known to be high

risk for certain types of cancers, given the potential under-reporting of these factors in administrative data (for example, we did not identify patients with smoking behavior by ICD-9 codes).[136]

Statistical Analysis

We estimated prevalence ratios for each cancer type by HIV status using log-binomial models,[117] in which cancer (specific cancer type or cancer types combined) was the dependent variable, and HIV status was the main independent variable. Covariates included age group, race/ethnicity, U.S. Census divisions, enrollment months, and co-infection by HBV/HCV (in models for liver cancer) or HPV (in models for head/neck, rectal, and anal cancers). For all APRs, the reference category was women without HIV. In the analyses that examined all cancer types combined, we accounted for co-infections by including a binary variable indicating the presence of HBV, HCV, and/or HPV. We did not adjust for co-infections in models for Non-Hodgkin's and Hodgkin's lymphoma, Kaposi Sarcoma, and breast cancer.

We conducted the stratified analyses to examine cancer prevalence by age and race/ethnicity within the WLWH population. We used similar regression models to estimate cancer prevalence in age and race/ethnicity strata with approximately equal proportion in each subgroup. We divided the WLWH into two age groups (18-44 and 45-64 years) based on the age distribution of the cancers with the highest prevalence in WLWH – cervical, breast, and anal

cancer. For the APRs of the older age group (45-64), the reference category was younger age group (18-44). For the APRs of a given race/ethnicity stratum, the reference category was comprised of women in all other race/ethnicity categories (for example, APRs for non-Hispanic Black women are presented in comparison to all other women in this study population). To address small numbers in our stratified analyses, we focused on the most common cancer types (breast, anal, rectal, and lymphoma), and all other NADCs in one category. In the stratified race/ethnicity analyses, we presented our data for non-Hispanic Whites, non-Hispanic Blacks, Hispanics, and All Others.

We used SAS software, version 9.4 for UNIX (SAS Institute, Inc., Cary, North Carolina, USA) for data processing and analysis, R version 4.0.0, R Studio 1.3.1093 and the *ggplot2* package to generate the forest plots for adjusted prevalence ratios.[137]

Results

We identified 72,508 WLWH and 17,353,963 women without HIV. Table 4.2 shows the characteristics of the population by demographics, co-infections, and type of cancer. Compared to women without HIV, a higher percentage of WLWH were in the 45-64 age group (46.54% vs 17.48%). Similarly, there was a greater representation of non-Hispanic Black women in WLWH among their non-HIV counterparts (58.55% vs 21.18%).

Cancers were more common among WLWH than among women without HIV (4.79% vs 1.18%). Among WLWH with ADCs (1,027 cases), cervical cancer was the most prevalent cancer type and comprised 81% of ADC cases, while non-Hodgkin's lymphoma and Kaposi's Sarcoma comprised 12% and 7% of ADC cases, respectively. Breast, anal, and lung cancers were the most common NADCs, accounting for about 28%, 23%, and 14% of total NADCs (2,560 cases), respectively. In women without HIV, breast cancer, cervical cancer, and lung cancers were the most prevalent cancer types, accounting for 49%, 19%, and 10% of total cancers respectively.

In Figure 4.1, we present the adjusted prevalence ratios (APRs) obtained from the log-binomial models for each cancer type. Among ADCs, the highest APR was for Kaposi's sarcoma (81.79 (57.11-117.22)), followed by non-Hodgkin's lymphoma (27.69 (21.67-35.39)), and cervical cancer (4.20 (3.90-4.52)). Among NADCs, the highest APRs were observed for anal cancer (19.31 (17.33-21.51)) and Hodgkin's lymphoma (4.92 (4.47-5.41)). The APRs of cancer of head/neck, rectal, bronchus/lung, esophageal, stomach, pancreas, colon, and leukemia were significantly higher in WLWH compared to women without HIV. However, for breast cancer, we observed a lower prevalence (0.70 (0.65-0.76)) in WLWH, compared to women without HIV. For liver cancer, the APR was 33% lower (0.75 (0.61-0.92)) after adjusting for HBV/HCV co-infection in the multivariable models.

Table 4.3 presents the adjusted prevalence ratios for cancers among WLWH in the older age group (45-64 years) compared to the younger age group (18-44 years), based on the number of cancer cases in the two age groups listed in Table 4.4. Our results showed that the overall APR for all cancer types combined was about 2-fold higher (1.99 (1.86-2.14)) in older WLWH compared to their younger counterparts. Among WLWH with ADC, there was no statistical difference in the APRs of each type of cancer in the older WLWH compared to those of younger WLWH. For NADCs, the APRs for cancer of the anus, rectum, breast, Hodgkin's lymphoma, and other NADCs combined (including cancer of head/neck, esophagus, stomach, colon, liver, pancreas, lung, other respiratory & intrathoracic organs and leukemia) were significantly higher in older than in younger WLWH.

Table 4.5 presents the age-adjusted APRs by race/ethnicity in WLWH based on the numbers of cancer cases in the four race/ethnicity groups listed in Table 4.6. Across four race/ethnicity groups, the APR for all cancer types combined did not differ significantly. For cancer-specific APRs, we noted some variation in the APRs across race/ethnicity categories. Among ADCs, the highest APR for Non-Hodgkin's lymphoma was observed in Hispanic women (2.00 (1.30-3.07)). For NADCs, lower APRs for breast cancer (0.73 (0.58-0.92)), and other NADC cancer types combined (0.76 (0.63-0.93)) were observed among Hispanic women. Other types of cancers were not different across the four race/ethnicity groups.

Discussion

Using national Medicaid data, we documented a high burden of ADCs and several types of NADCs in WLWH than in women without HIV on Medicaid. Our findings showed large differences in prevalence across cancer sites and age groups. Compared to women without HIV on Medicaid, the prevalence of cervical cancer was about 4.2-fold higher, and the prevalence of anal cancer was about 19.3-fold higher among WLWH. Given that additional risk factors (e.g., smoking and non-HPV co-infections) increase cancer risk in PLWH,[122] our findings highlight the importance of cancer risk evaluation and screening. Preventive measures should address multiple risk factors, [123,137] and promote HPV vaccination in all eligible individuals. As noted in previous reports,[110,139,140] these highly prevalent cancer types should be targeted for cancer screening in WLWH. Related to HPV infection, both cervical and anal cancer are preceded by high-grade squamous intraepithelial lesions (HSILs), and precancerous cells are even more common on anal pap test than cervical pap test for WLWH.[139] Screening of cervical HSIL has been shown to be critical in preventing cervical cancer for WLWH, but the evidence-based guidelines for the screening anal HSIL in WLWH is still lacking. Recently, the multi-site anal cancer HSIL outcomes research (ANCHOR) study suggested that the treatment of anal HSIL reduced the risk of anal cancer by more than half,[141] highlighting that the screening and timely treatment of HSIL could prevent anal cancer in WLWH.

The highest APR observed in our study was for Kaposi's sarcoma, which was 82 times higher in women with HIV than women without HIV, a notable but unsurprising finding. Kaposi's sarcoma rarely develops in healthy persons carrying HHV8, the virus responsible for this type of cancer, and less than 5% of the general U.S. population is infected by HHV8.[51] In contrast, the risk of HIV-associated Kaposi's sarcoma is high, even among patients who receive effective HAART, and have normal CD4+ counts.[51]

To account for the increased risk of cancer due to advanced age, we conducted age-specific analyses. The crude numbers from the younger and older age strata showed a higher prevalence of NADCs in the older age group than in the younger age group (Table 4.4). Thus, the age-stratified analysis of adjusted prevalence ratio (APR) is necessary to show site-specific cancer prevalence in WLWH population (Table 4.3). Indeed, the result of age-specific analyses showed the prevalence for NADC at specific sites was higher in older than in younger WLWH, demonstrating that the NADC prevalence increased with age in women with HIV infection across multiple cancer sites. Interestingly, our study showed that the adjusted prevalence of three types of ADCs (Non-Hodgkin's lymphoma, cervical cancer, and Kaposi's lymphoma) were similar for young and old age group, possibly suggesting that the co-infection of HIV and HPV/ EBV virus is an even more potent risk factor for the prevalence of ADCs than age.

WLWH are at an increased risk for contracting a range of co-infections by oncogenic viruses, particularly various types of HPV.[120,142,143] Our data show that HPV-associated cancers (primary sites such as cervical, anal, rectal, head/neck) contribute the most to the cancer burden in WLWH enrolled in Medicaid. Invasive cervical cancer is the most common cause of cancer-associated death in WLWH, and often occurs at a relatively young age and presents at a more advanced stage than women without HIV.[143] Therefore, screening for cervical cancer at the appropriate age is highly recommended for this group of women.[144] Given the time window from HIV/HPV infection to progress to the precancerous lesion and malignancy formation, early HPV vaccination would be crucial to prevent anogenital cancer. However, studies have shown that most HIV-infected women have not received timely vaccination to prevent initial HPV infection.[63] Thus, ensuring completion of the HPV vaccine series in teens and eligible adults is paramount. In addition, both hepatitis B and C can cause hepatocellular carcinoma. In the United States, about 6~10% of PLWH have co-infection of hepatitis B,[145] and approximately 6%-16% of them have co-infection with hepatitis C.[146] Furthermore other non-infection-related risk factors, such as smoking, alcohol abuse, and drug use, could contribute to the increased risk of cancer in WLWH.

After adjusting for hepatitis B and C infection, our findings suggest that HIV infection was not associated with higher risk of liver cancer among WLWH compared with women without HIV. This may be explained by the sustained

viral suppression afforded by HAART since liver cancer risk has been directly associated with HIV-related immunodeficiency level. Furthermore, some HAART regimens can also be used to manage HBV co-infection concurrently, so people on HAART may have a lower liver cancer risk than the general population with un-diagnosed HBV infection [65].

One of the major strengths of our study is that it included a large fraction of all WLWH. As previously mentioned, 54% of WLWH were enrolled in Medicaid in 2018,[133] our study represented the WLWH population in the United States at large. Another strength of this study is our in-depth stratified analysis of prevalence by age and race/ethnicity group. In particular, while the overall prevalence of all cancer types was similar across race/ethnicity groups, the prevalence varied by cancer sites across race/ethnicity group (Table 4.5, Table 4.6).

Our study has several limitations. First, given our use of data from the Medicaid program, demographic variables (age, race/ethnicity, and sex) are as documented in the administrative records. This limits our ability to examine certain subpopulations, such as transgender individuals, for whom documented sex may be incorrect or incomplete. Second, due to the nature of administrative data, we did not have any reliable measures on behavioral risk factors such as, smoking, drug abuse, or sexual behaviors. Third, this study did not account for the co-infection of all oncogenic viruses. While we

accounted for HPV and HBV/HCV co-infection, we could not account for EBV and other oncogenic infection or opportunistic infections, given the limited sensitivity of administrative ICD-9 codes to identify these conditions. Fourth, we note that these results reflect data from 2012. Since then, Medicaid enrollment fluctuated considerably, first by increasing due to its expansion in 2014, then declining in 2017–2019,[124] and increasing again during the pandemic.[125] Given that the pool of Medicaid is dynamic, obtaining a fully representative snapshot of the Medicaid population is difficult. Nonetheless, the associations identified in this study are likely to be consistent over time. Fifth, our findings from this study should apply to WLWH on Medicaid and may not be generalizable to the WLWH population overall, especially given that many individuals join the Medicaid program upon being diagnosed with cancer, or after having depleted their resources. Finally, the sample in this study includes those women diagnosed with HIV but does not include those who have HIV but were not yet diagnosed. Therefore, it will be necessary to continuously monitor cancer burden in Medicaid-insured WLWH.[147]

Conclusion

This study highlights the high prevalence of ADCs and certain NADCs in WLWH, compared with women without HIV on Medicaid. Our findings highlight the importance of proactive measures to promote cancer screening and more widespread HPV vaccination to reduce the burden in this population.

Chapter V

Conclusion and Implication

Summary of findings

Using data from Medicaid at the national level and state inpatient data from two states (Florida and Maryland), this dissertation applied various statistical approaches as well as machine learning techniques to study the impact of social needs on quality of care and the cancer burden among persons living with HIV. This dissertation revealed the profound impact of health-related social needs (HRSN) on health outcomes and the spectrum of cancer burden in persons living with HIV (PLWH). Three major findings emerged. First, HRSN are highly prevalent in PLWH compared to the population without HIV, and the prevalence of social needs is significantly associated with a high rate of hospital readmission in PLWH. Second, the spectrum of cancer burden differs but shares certain common features between men and women living with HIV. Anal cancer and non-Hodgkin's lymphoma are consistently among the most prevalent cancer types in both genders. However, in women living with HIV, HPV-related cervical cancer remains highly prevalent, along with other AIDS-defining cancers. Notably, the prevalence ratio of non-AIDS defining cancers is higher in men living HIV than women living with HIV. Third, age has a more robust modification effect in younger PLWH compared to the non-HIV population at same age range.

I have strategized to examine the cancer burden in men and women living with HIV through two separate studies, considering the following key aspects. First, the major cause of mortality differ between men and women living with HIV. In men living with HIV, the non-AIDS-defining cancers are the leading cause of non-accidental death. In women living with HIV, AIDS-related cervical cancer is the leading cause of non-accidental death. Second, susceptibility to specific cancers, especially reproductive cancers in men or women living with HIV, varies. Third, the sizes of eligible study populations differ significantly. In the U.S., roughly, 70% of newly diagnosed HIV patients are men, and only about 30% are women. In the available nationwide Medicaid data, more women were enrolled. After exclusion, there were 132% more women (17,426,471) than men (7,385,018) insured by Medicaid in 2012.

In the first study (Chapter II), I assessed the impact of health-related social needs on hospital readmission and health outcomes in persons living with HIV. From 2016 to 2019, out of all hospitalized HIV patients from the states of Florida and Maryland, 9.6% and 12.5% have been documented to have at least one type of health-related social needs. Persons living with HIV with documented social needs have nearly twice the rate of 90-day readmission than those without social needs. Persons living with HIV with documented social needs have a 70-80% higher rate of one-year readmission than those without social needs. In both states, there is a dose-response association

between the numbers of social needs and readmission rate for 90-day and one-year readmission rate. The various models suggest health-related social needs are closely associated with the high readmission rate and health outcomes. I concluded that social needs are critical non-medical factors for high hospital readmission for HIV patients. This study highlights a critical role of social needs on the readmission and outcomes of hospital care of PLWH. The high prevalence of social factors in PLWH has been overlooked in current HIV care, and the combination of social factors and comorbidity that PLWH encounter have a syndemic effect on their health outcome. PLWH with chronic diseases or multiple comorbidities often have higher readmission rates, which can be further exacerbated by social factors. The call to implement social determinants in hospital care could be one of the most important factors when reducing readmission rate of PLWH.

In the second study (Chapter III), I examined the prevalence of cancer burden in men living with HIV insured by Medicaid in 2012. The cancer spectrum in this study included 13 types of cancer, including cancer of the head/neck, esophagus, stomach, colon, rectum, anus, liver and intrahepatic bile duct, pancreas, bronchus/lung, and other respiratory and intrathoracic organs, as well as Hodgkin's lymphoma, and leukemia. Overall, I found that the prevalence of non-AIDS-related cancer was nearly twice as high in men living with HIV than men without HIV. Among specific sites, anal cancer and lymphoma were most prevalent cancer types, followed by cancer of the

esophagus, rectum, and leukemia. Furthermore, the stratified analyses by symptomatic and asymptomatic HIV, by age groups, and by race/ethnicity revealed a disproportionately high cancer burden in subgroups of men living with HIV. There are several notable highlights. First, Hispanic men had the highest adjusted prevalence ratio (APR). Second, symptomatic men also had a higher burden of cancer. Third, excessive cancer prevalence was significantly higher in younger men (18-44 years old) with HIV than the same age group of men without HIV.

In the third study (Chapter IV), I examined the cancer burden in women living with HIV. The spectrum of cancers included 15 types of cancers, including cancer of the breast, cervix, head/neck, esophagus, stomach, colon, rectum, anus, liver and intrahepatic bile duct, pancreas, bronchus/lung, and other respiratory and intrathoracic organs, as well as Hodgkin's and non-Hodgkin's lymphoma, Kaposi's sarcoma, and leukemia. Among specific sites, Kaposi's sarcoma, anal cancer, non-Hodgkin's lymphoma, and cervical cancer were among the most prevalent cancer types. Among PLWH, the overall cancer prevalence was about twice as high in women 45-64 years of age than in women 18-44 years of age. The overall cancer prevalence was not different across race/ethnicity categories, but the prevalence of non-Hodgkin's Lymphoma in Hispanic women was twice as high as in other races/ethnicities.

These findings (Chapter III and IV) reveal that cancer poses a significant disease burden but differs among subgroups based on sex, age, race/ethnicity, symptomatic status, and cancer types. Cancer prevalence will likely increase in the future as the population ages, and with the improved longevity in PLWH. For both men and women living with HIV, HPV-related anal and cervical cancer cancers are among the most prevalent cancer types. Therefore, the widespread vaccination in child and adolescents is essential to the cancer prevention program for HIV patients. Medicaid serve as a safety net to ensure a large portion of both men and women living with HIV, our study calls for the program to adopt a more proactive and flexible approach to improve needs-specific HIV care.

Limitations

The studies in this dissertation identified an HIV and non-HIV cohorts and conducted advanced epidemiological analyses using administrative data (Stat Inpatient Data in Chapter II) and claim-based analytic files (Medicaid Analytic eXtract, Chapter III and IV). The advantage of these study designs was its suitability for population-based outcome research, which is the main goal of this dissertation. However, several major limitations must be discussed.

First, there were very limited clinical measurements collected in the current studies due to the nature of the data source. For the cancer prevalence studies, we were unable to determine the cancer stage and histological

features. In both cancer prevalence and outcome studies, we could not provide data on CD4+ count in the blood, which is the best indicator of disease progression and treatment efficiency.[148] The cohort we collected had 12% symptomatic status (Table 3.3), which could be served as the proxy of co-infection or AIDS-related diseases, however we could determine how many patients were at AIDS stage. The lack of these critical clinical data measurements limited the depth and scope of our conclusions. Second, the syndemic effect of diseases and social factors has not been fully explored, leaving the door open for future studies. One of the hinder barrier is the Z-codes of social needs are not completely recoded by clinician, as discussed in chapter II. Third, the current studies only assessed the prevalence of cancer burden; however, investigating the prevalence of other comorbidities or the co-occurrence pattern of these conditions is warranted to fully capture the disease burden in the future directions.

Translational Implications

According to the translational phases of epidemiologic research described by Khoury and colleagues,[149] the studies in this dissertation are classified in the early T1 stage. This dissertation investigated the real-world impacts of health-related social needs and cancer burden of HIV patients in the U.S, focused on population-level outcomes. The acquired knowledge reveals the vital aspects of the intertwining relationship among social factors and disease burden on health outcome in persons living with HIV.

The findings in Chapter II provided important knowledge that social factors significantly increased risk to hospital readmission for PLWH. The three domains of social needs, which include housing instability, social/family, and employment, could be the major drivers of the high readmission rate for PLWH. Furthermore, the aggregation of these factors appears to have a dose-response association with PLWH's hospital readmission rate. It is likely patients with these social needs are at higher risk of readmission due to complication or comorbidities or poor adherence to medication and engagement in care. Therefore, it is important for healthcare providers and policymakers to acknowledge social factors as the critical elements in reducing the hospital readmission for HIV patient. The clinician and care team should be educated that addressing the non-medical factors through interventions such as social support programs, housing assistance, and food security, could improve health outcomes and reduce hospital readmissions in this population.

The findings from Chapter III and IV, covering the whole spectrum of cancer burden in men and women living with HIV, revealed the similarity and disparity of cancer burden. This finding is important for multiple reasons. First, the comprehensive understanding of these differences and commonalities is essential for developing targeted interventions and improving healthcare outcomes in both genders. As anal cancer and Hodgkin's lymphoma are among the most prevalent cancer types in both men and women living with HIV, these two types of cancers constitute the primary burden among non-

AIDS defining cancers. However, the prevalence of invasive cervical cancer pose the greatest threats in women living, along with other high prevalence cancers. The preventive measure of cervical cancers to prevent cervical cancer are to get vaccine against HPV. The co-infection of HPV in HIV is about 7 times high than non-HIV population (Table 3.3), which suggests HPV vaccination is critical preventive measure. The vaccination of HPV for anal and cervical cancer should be initiated at an early stage, focused on adolescent and young adult. Second, it is important for HIV care providers and caregivers to recognize disparities of cancer burden across these subgroups of the population. The cancer prevention, screening, and surveillance system should prioritize high-risk minority population from an early age. Scientifically, non-AIDS-related cancers have been recognized as manageable chronic conditions, and policymakers and health professionals should consider the long-term effect of cancer burden to ensure timely access to care and better quality of care.

Future research directions of this field could take advantage of current advance in machine learning approaches to dissect the interaction of health-related social needs and disease burden. As illustrated in Figure 5.1, future study should focus on the addressing the syndemic effect from multiple dimensions and layers, including co-infection virus, comorbidities, and aspects of social needs. In 2020, the initiation of the federal program Ending the HIV Epidemic (EHE) in the U.S. aims to reduce HIV infection by at least 90%

before 2030.[150] Acting upon the knowledge that is generated from research investing the syndemic effect will be essential to this initiative.

Appendix -- Figures and Tables

Chapter I

Figure 1.1: The illustration of syndemic theory in HIV treatment and prevention. Syndemic explains that HIV infection, co-infections, and occurrence of cancers is interweaved with social conditions and mental health.

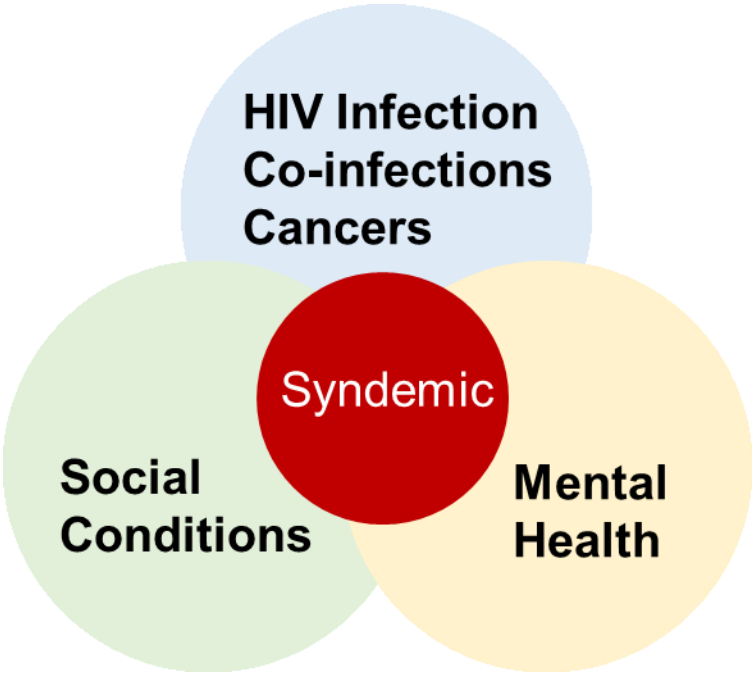


Figure 1.2: The County Health-Rankings models are based on a conceptual model of population health that includes both Health Outcomes (length and quality of life) and Health Factors (determinants of health). Adapted from County Health Rankings & Roadmaps from the University of Wisconsin Population Health Institute. The models are cited by National Academy of Medicine (http://www.countyhealthrankings.org/our-approach (accessed October, 2023).

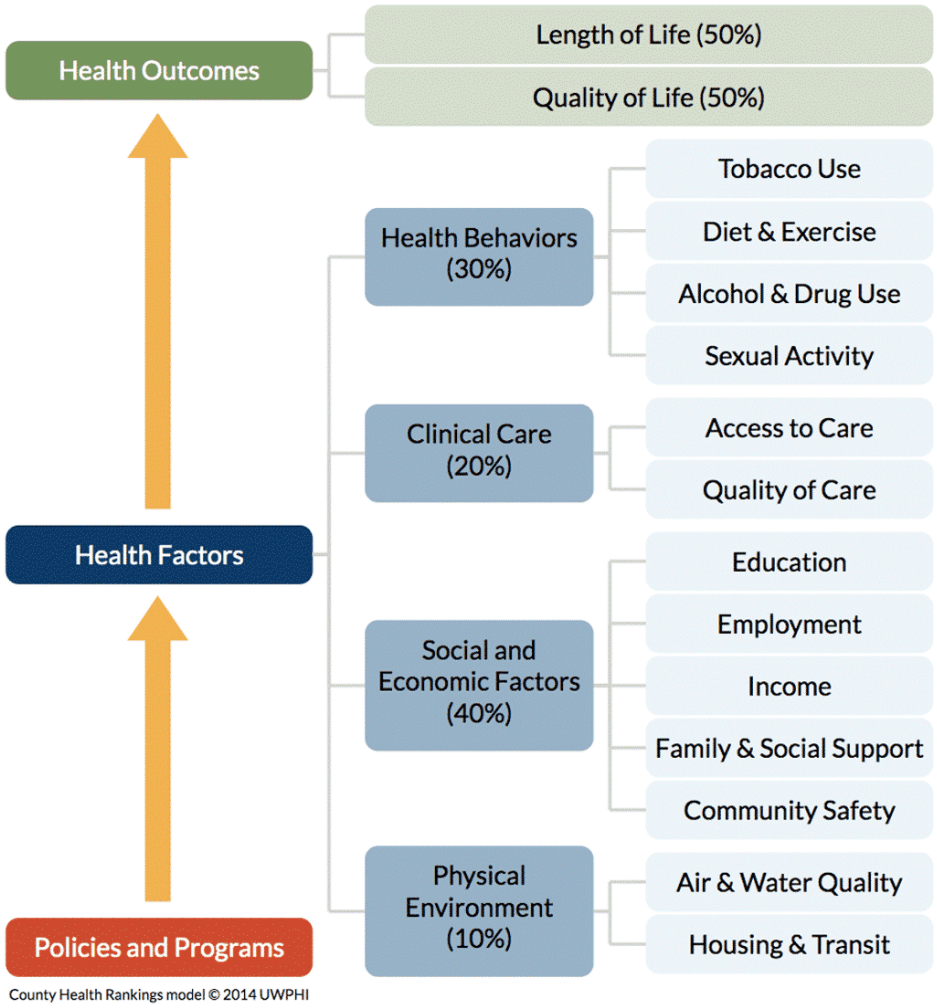


Figure 1.3: Three stages of HIV infection. Adapted from National institute of Health. https://hivinfo.nih.gov/understanding-hiv/fact-sheets/stages-hiv-infection

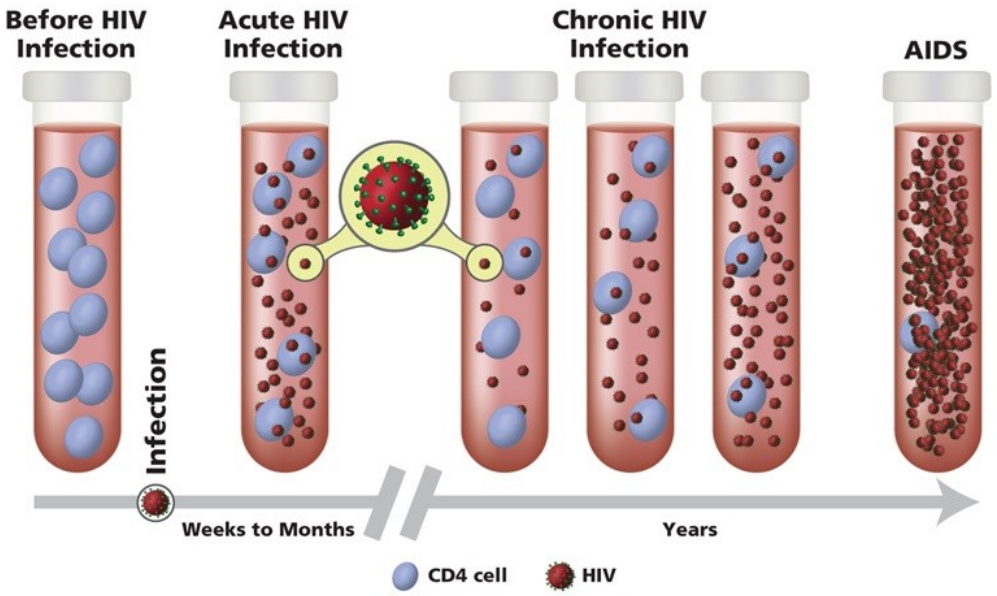
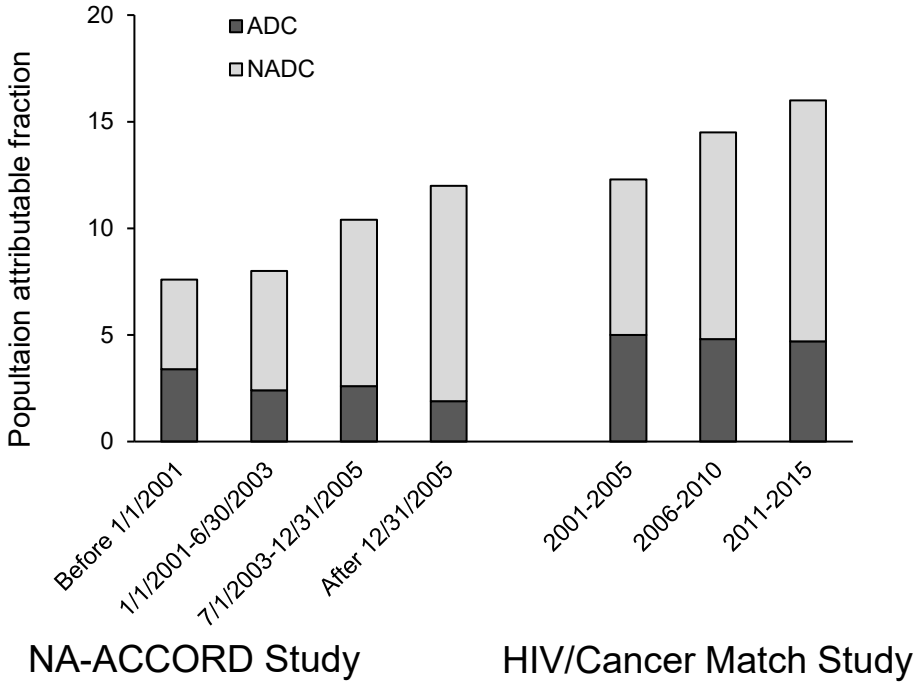


Figure 1.4: Combined data of population contributable fraction of cancer mortality in NA-ACCORD and HIV/AIDS Match Study (Clin Infect Dis. 2017;65(4):636-643; Clin Infect Dis. 2021; 72(9): e224-e231).



ADC: AIDS-defining cancers

NADC: non-AIDS-defining cancers

NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design and poorly specified cancers.

Figure 1.5: The 15-year trend of cancer burden in the AIDS population in USA from 1991 to 2005. A) Number of people living with AIDS by calendar year and age group. B) The numbers and incidence rates of AIDS-defining cancers among people living with AIDS by calendar year and age group. C) The Number and incidence rate of non-AIDS-defining cancers among people living with AIDS by calendar year and age group. D) The numbers and incidence rates of total cancers among people living with AIDS, stratified by AIDS-defining cancers, non-AIDS-defining cancers, and poorly specified cancers. Bars depict the estimated number of cancers, and points connected by lines depict incidence rates standardized to the 2000 US AIDS population by age group, race, and sex. Source: J Natl Cancer Inst 2011;103:753-762.

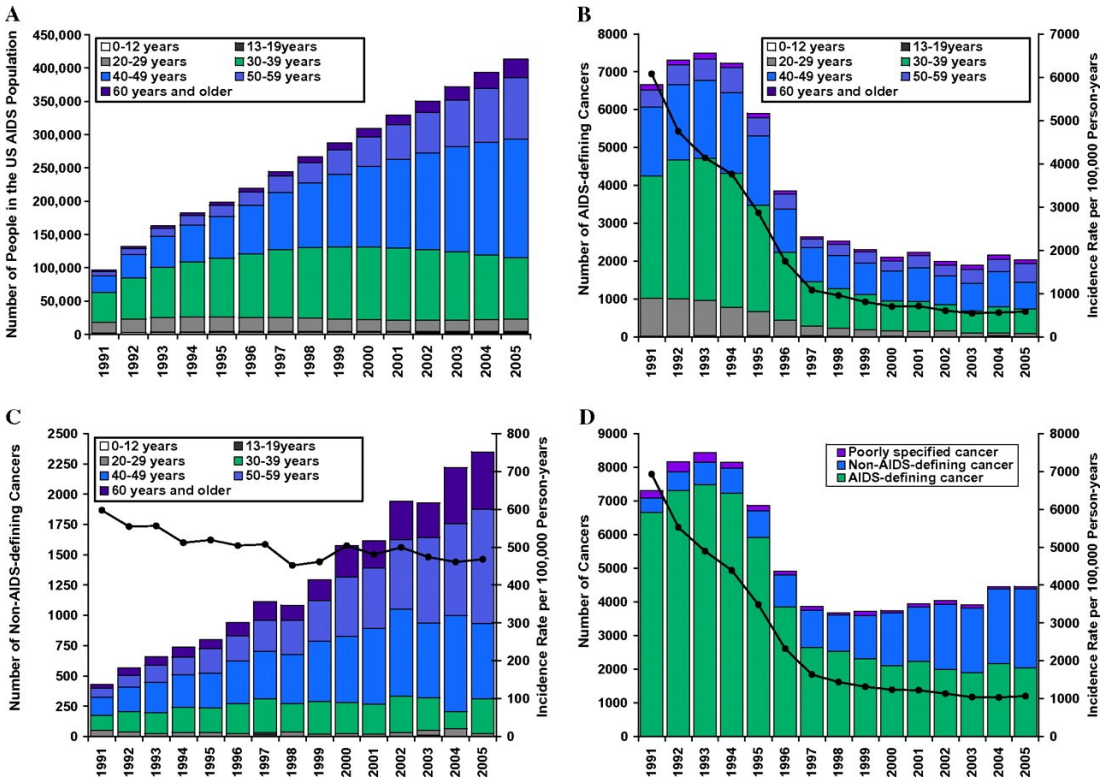


Table 1.1: Proportion of patients with each insurance type by calendar year by HIV Research Network (HIVRN). Excerpted from the study by Yehia et al., 2014

Year	Private (%)	Medicaid (%)	Medicare (%)	Uninsured (%)
2006	14.9	**35.9**	20.1	29.1
2007	16	**36.0**	19.9	28
2008	16.4	**37.5**	19.6	26.5
2009	16.2	**36.5**	19.9	27.4
2010	16.1	**35.7**	20.1	28.1
2011	15.4	**34.9**	20.1	29.6
2012	16.2	**33.5**	20.7	29.6

Table 1.2: AIDS Defining Illnesses. Excerpted from CDC

Opportunistic infection
Candidiasis (pulmonary or esophageal)
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis (extrapulmonary)
Cryptosporidiosis, chronic intestinal
Cytomegalovirus (other than liver, spleen, or nodes)
Encephalopathy
Herpes simplex: chronic ulcers or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal
Mycobacterium avium complex or *Mycobacterium kansasii,* disseminated or extrapulmonary
Mycobacterium tuberculosis of any site
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome attributed to HIV
Cervical cancer, invasive
Kaposi sarcoma
Lymphoma, Burkitt's
Lymphoma, immunoblastic
Lymphoma, primary, of brain

Table 1.3: The mortality data from Mortalite Survey 2005. Excerpted from Bonnet et al., Cancer 2004;101:317–324 2004; and Bonnet et al., 2009 Clinical Infectious Diseases 2009; 48:633–639.

Cause of Death	2000 (N=924)	2005 (N=1,013)
Cancer (all)	269	344
AIDS-defining cancer	149 (55%)	134 (39%)
Non-AIDS-defining cancer	103 (38%)	173 (50%)
Hepatitis related	17 (6%)	37 (11%)

Table 1.4: Prevalence of comorbidities among PLWH patients treated with HAART & matched controls in U.S.,2003-2013. Excerpted from Gallant et al., J Infect Dis. 2017;216(12):1525-1533.

	Commercial Insurance		Medicaid	
	PLWH (N=20,159)	Controls (N=46,763)	PLWH (N=16,020)	Controls (N=36,791)
Cardiovascular Events	6.7%	4.0%	10.4%	7.6%
Renal Impairment	8.8%	2.80%	15.2%	5.9%
Fracture or Osteoporosis	7.6%	6.4%	13.0%	10.0%
Liver Diseases	6.2%	2.4%	11.3%	4.5%
Cancer	8.0%	4.1%	9.8%	4.2%
Hepatitis C	5.4%	0.5%	22.9%	3.7%
Alcoholism	3.1%	1.6%	12.2%	5.9%

Chapter II

Figure 2.1: The readmission is twice high in HIV patients with health-related social needs (HRSN) than without HRSN from Florida state inpatient data (2016-2019)

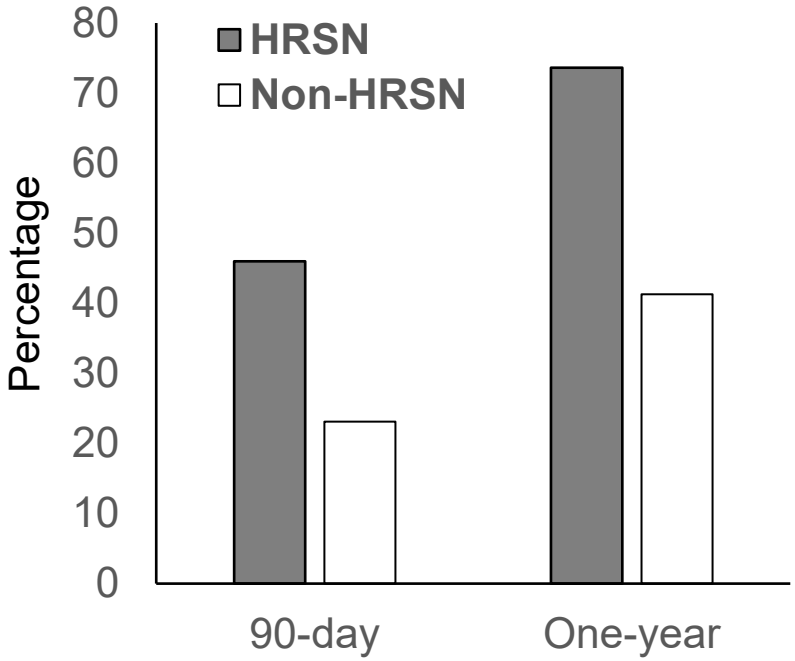


Figure 2.2: The readmission of 90-day (A) and one-year (B) following-up by the number of health-related social needs (HRSN) from index hospitalized HIV patients from Florida state inpatient data (2016-2019)

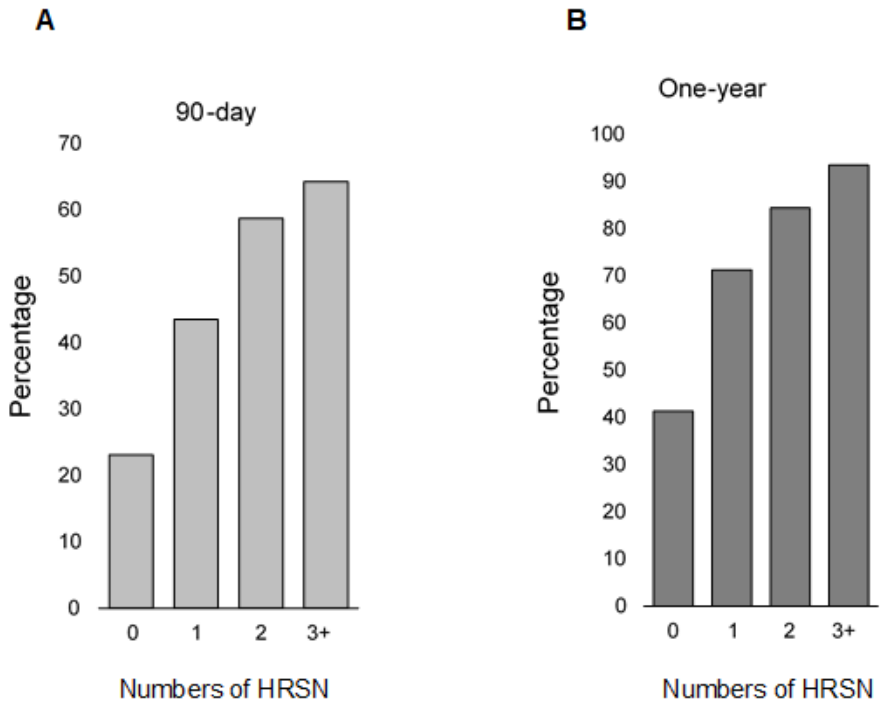


Figure 2.3: The readmission is roughly twice high in HIV patients with health-related social needs (HRSN) than without HRSN from Maryland state inpatient data (2016-2019)

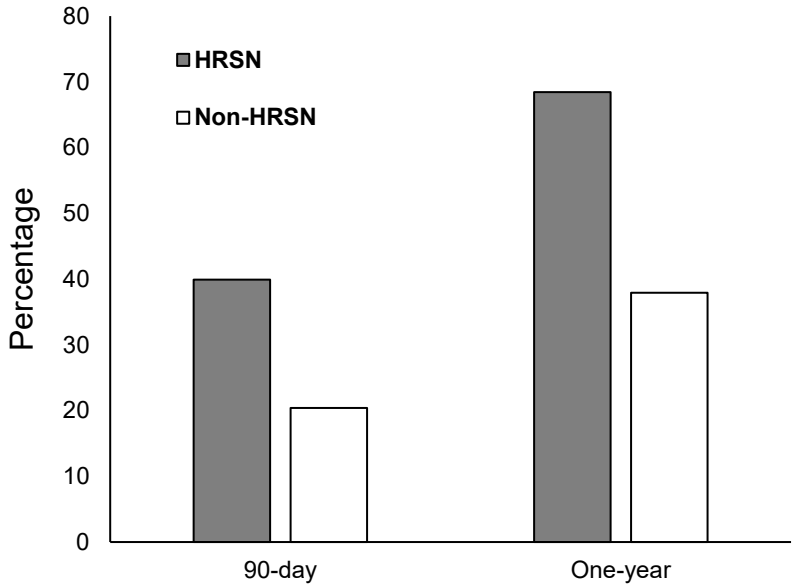


Figure 2.4: The readmission of 90-day (A) and one-year (B) following-up by the number of health-related social needs (HRSN) from index hospitalized HIV patients from Maryland state inpatient data (2016-2019).

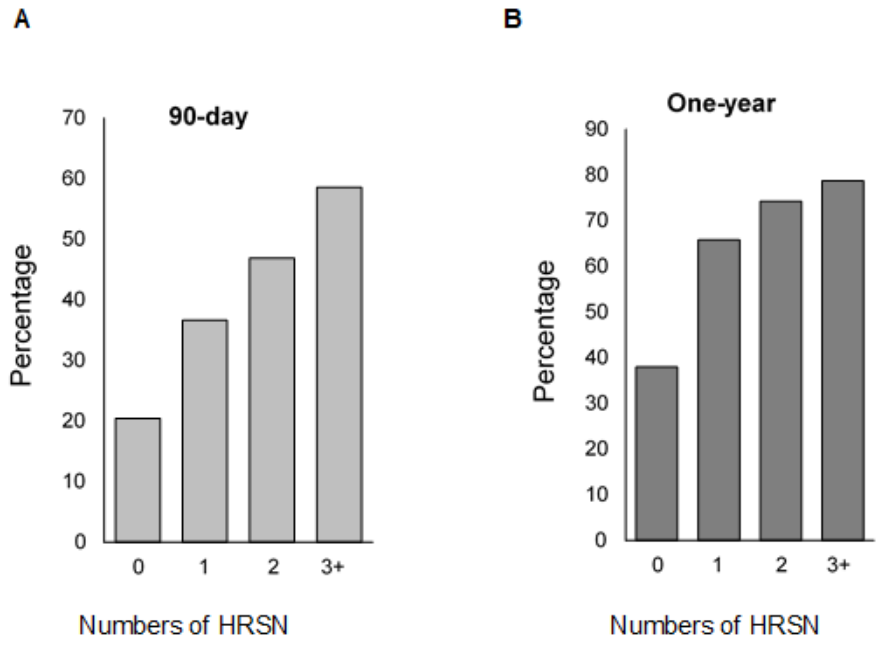


Figure 2.5: CART Model for one-year readmission of HIV patients from Florida state inpatient data (2016-2019). CART is an abbreviation for classification and regression trees.

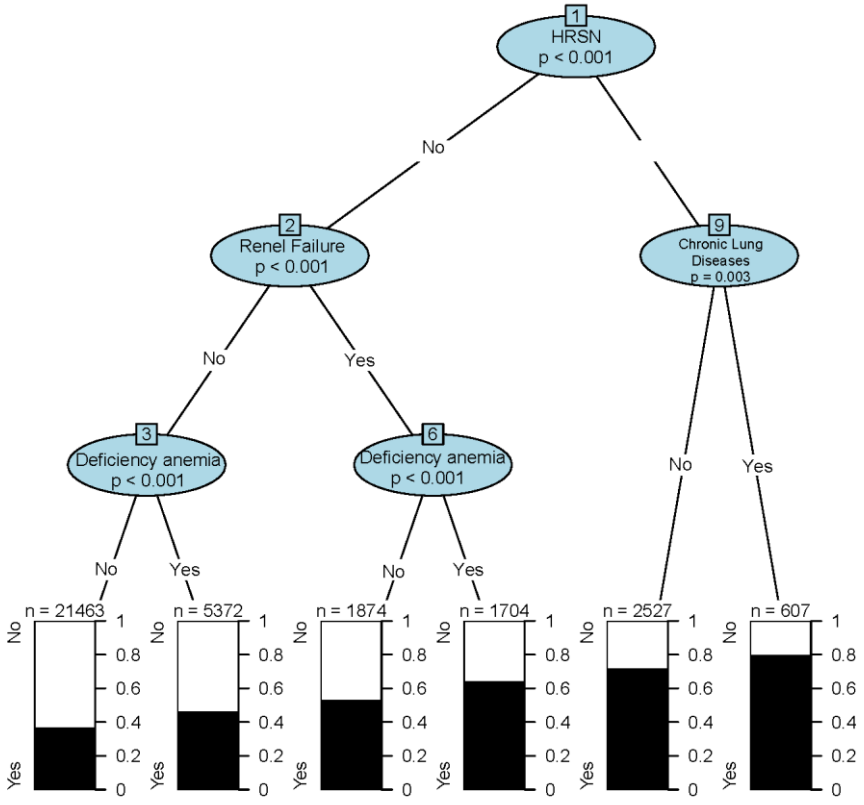


Figure 2.6: The plot of ensemble of 2000 trees by Random Forest model for one-year readmission of PLWH from Florida state inpatient data (2016-2019). We plotted variables with the relative importance by mean Gini coefficient decrease.

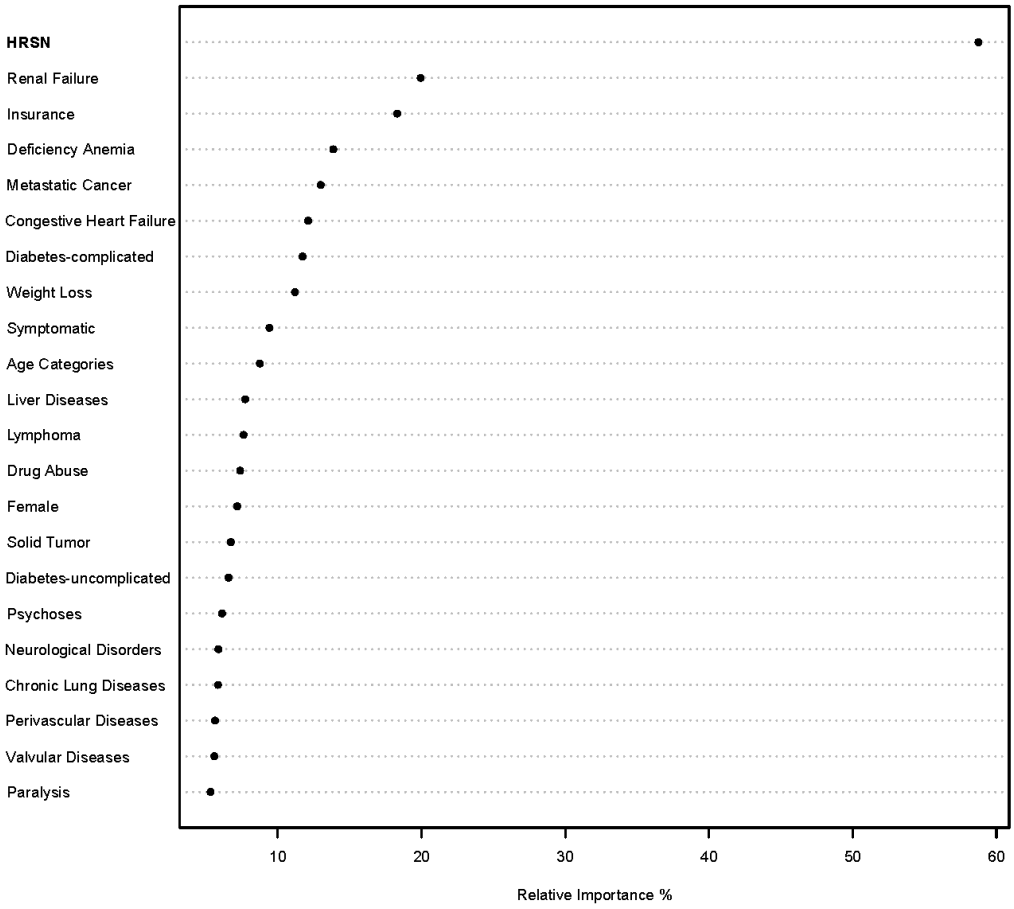


Figure 2.7: CART Model for one-year readmission of HIV patients from Maryland state inpatient data (2016-2019). CART is an abbreviation for classification and regression trees.

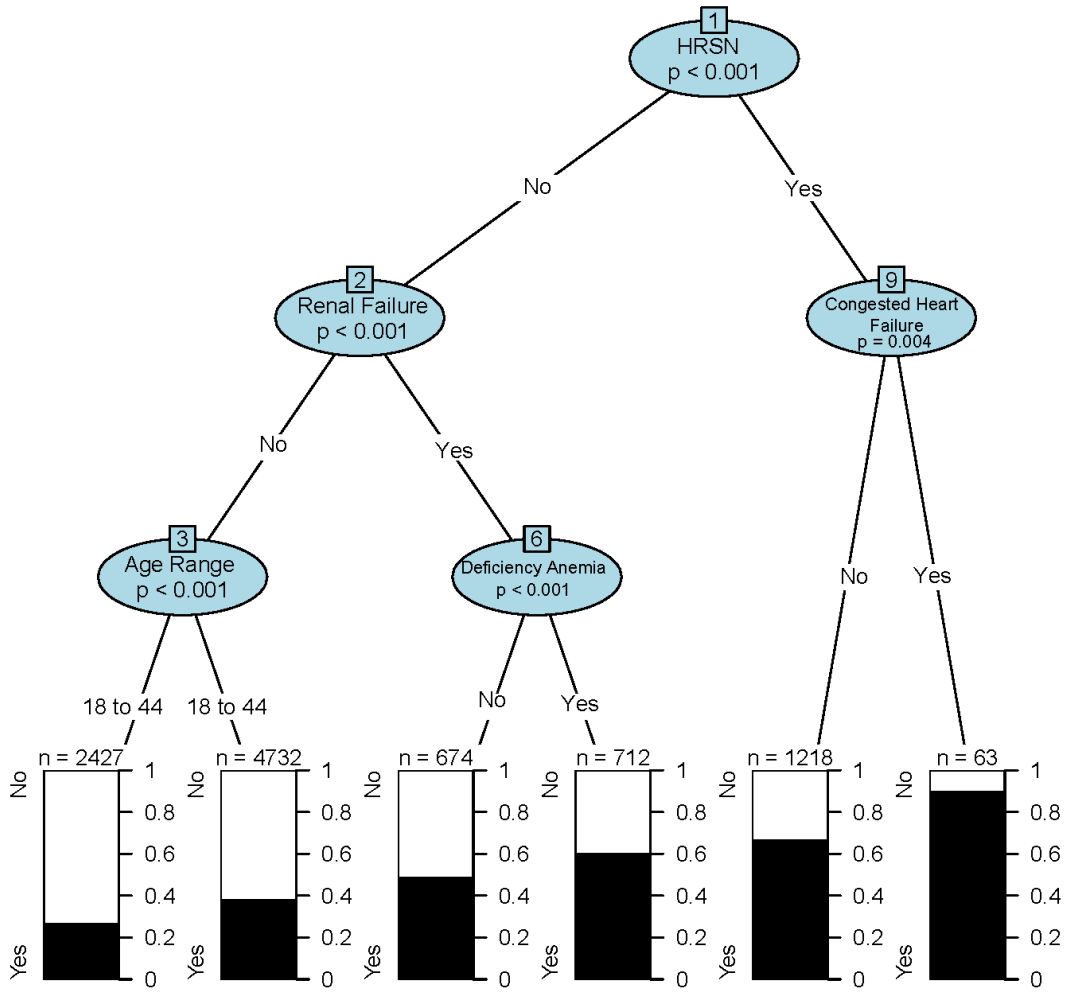


Figure 2.8: The plot of ensemble of 2000 trees by Random Forest model for one-year readmission of PLWH from Maryland state inpatient data (2016-2019). We plotted variables with the relative importance by mean Gini coefficient decrease.

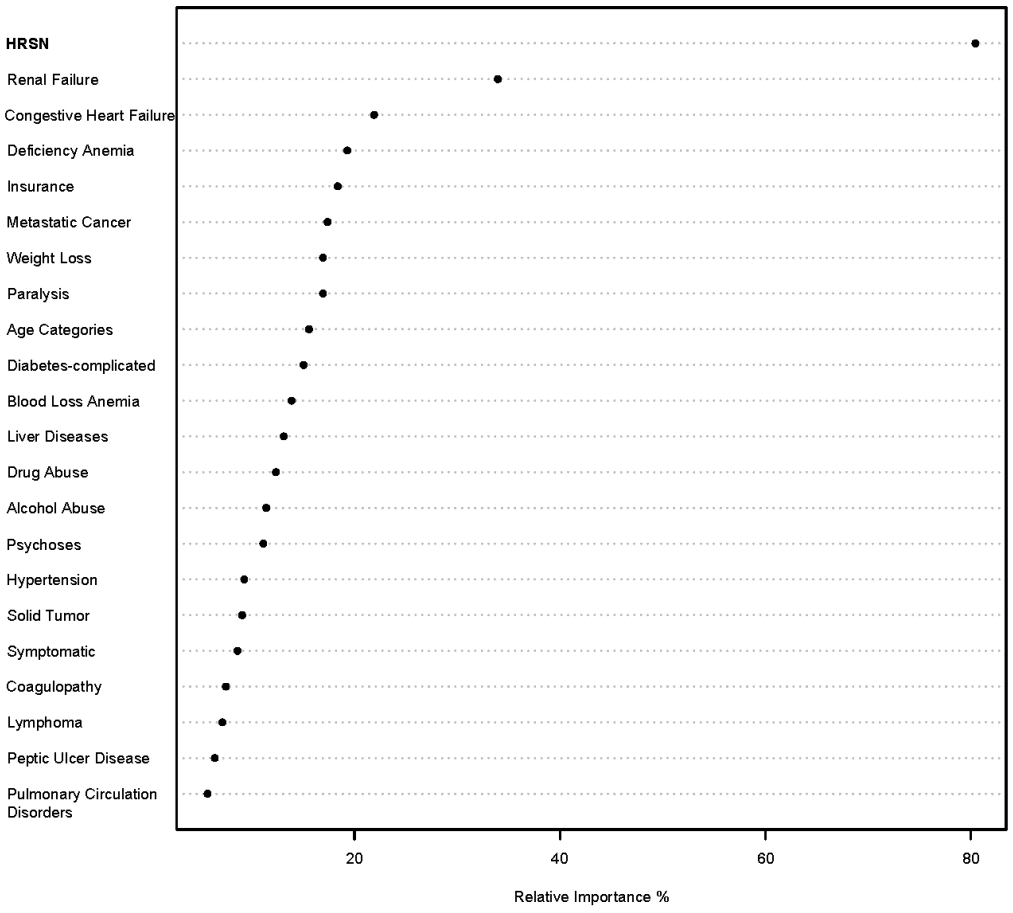


Table 2.1: ICD-10 Z-codes used in this study to identify health-related social needs

ICD-10 code	Description	Domain
Z55.0	Illiteracy and low-level literacy	Education
Z55.1	Schooling unavailable and unattainable	Education
Z55.2	Failed school examinations	Education
Z55.3	Underachievement in school	Education
Z55.4	Educational maladjustment and discord with teachers and classmates	Education
Z55.8	Other problems related to education and literacy	Education
Z55.9	Problems related to education and literacy, unspecified	Education
Z56.0	Unemployment, unspecified	Employment
Z56.1	Change of job	Employment
Z56.2	Threat of job loss	Employment
Z56.3	Stressful work schedule	Employment
Z56.4	Discord with boss and workmates	Employment
Z56.5	Uncongenial work environment	Employment
Z56.6	Other physical and mental strain related to work	Employment
Z56.81	Sexual harassment on the job	Employment
Z56.82	Military deployment status	Employment
Z56.89	Other problems related to employment	Employment
Z56.9	Unspecified problems related to employment	Employment
Z57.0	Occupational exposure to noise	Employment
Z57.1	Occupational exposure to radiation	Employment
Z57.2	Occupational exposure to dust	Employment
Z57.31	Occupational exposure to environmental tobacco smoke	Employment
Z57.39	Occupational exposure to other air contaminants	Employment
Z57.4	Occupational exposure to toxic agents in agriculture	Employment
Z57.5	Occupational exposure to toxic agents in other industries	Employment
Z57.6	Occupational exposure to extreme temperature	Employment
Z57.7	Occupational exposure to vibration	Employment
Z57.8	Occupational exposure to other risk factors	Employment
Z57.9	Occupational exposure to unspecified risk factor	Employment
Z59.0	Homelessness	Housing
Z59.1	Inadequate housing	Housing
Z59.2	Discord with neighbors, lodgers and landlord	Housing
Z59.3	Problems related to living in residential institution	Housing
Z59.4	Lack of adequate food and safe drinking water	Housing
Z59.5	Extreme poverty	Housing
Z59.6	Low income	Housing
Z59.7	Insufficient social insurance and welfare support	Housing
Z59.8	Other problems related to housing and economic	Housing
Z59.9	Problem related to housing and economic circumstances,	Housing
Z60.0	Problems of adjustment to life-cycle transitions	Social/Family
Z60.2	Problems related to living alone	Social/Family
Z60.3	Acculturation difficulty	Social/Family
Z60.4	Social exclusion and rejection	Social/Family
Z60.5	Target of (perceived) adverse discrimination and persecuation	Social/Family
Z60.8	Other problems related to social environment	Social/Family
Z60.9	Problem related to social environment, unspecified	Social/Family
Z62.0	Inadequate parental supervision and control	Social/Family
Z62.1	Parental overprotection	Social/Family
Z62.21	Child in welfare custody	Social/Family

Z62.22	Institutional upbringing	Social/Family
Z62.29	Other upbringing away from parents	Social/Family
Z62.3	Hostility towards and scapegoating of child	Social/Family
Z62.6	Inappropriate (excessive) parental pressure	Social/Family
Z62.810	Personal history of physical and sexual abuse in childhood	Social/Family
Z62.811	Personal history of psychological abuse in childhood	Social/Family
Z62.812	Personal history of neglect in childhood	Social/Family
Z62.813	Personal history of forced labor or sexual exploitation in	Social/Family
Z62.819	Personal history of unspecified abuse in childhood	Social/Family
Z62.820	Parent-biological child conflict	Social/Family
Z62.821	Parent-adopted child conflict	Social/Family
Z62.822	Parent-foster child conflict	Social/Family
Z62.890	Parent-child estrangement NEC	Social/Family
Z62.891	Sibling rivalry	Social/Family
Z62.898	Other specified problems related to upbringing	Social/Family
Z62.9	Problem related to upbringing, unspecified	Social/Family
Z63.0	Problems in relationship with spouse or partner	Social/Family
Z63.1	Problems in relationship with in-laws	Social/Family
Z63.31	Absence of family member due to military deployment	Social/Family
Z63.32	Other absence of family member	Social/Family
Z63.4	Disappearance and death of family member	Social/Family
Z63.5	Disruption of family by separation and divorce	Social/Family
Z63.6	Dependent relative needing care at home	Social/Family
Z63.71	Stress on family due to return of family member from	Social/Family
63.72	Alcoholism and drug addiction in family	Social/Family
Z63.79	Other stressful life events affecting family and household	Social/Family
Z63.8	Other specified problems related to primary support group	Social/Family
Z63.9	Problem related to primary support group, unspecified	Social/Family
Z64.0	Problems related to unwanted pregnancy	Psychosocial
Z64.1	Problems related to multiparity	Psychosocial
Z64.4	Discord with counselors	Psychosocial
Z65.0	Conviction in civil and criminal proceedings without imprisonment	Psychosocial
Z65.1	Imprisonment and other incarceration	Psychosocial
Z65.2	Problems related to release from prison	Psychosocial
Z65.3	Problems related to other legal circumstances	Psychosocial
Z65.4	Victim of crime and terrorism	Psychosocial
Z65.5	Exposure to disaster, war and other hostilities	Psychosocial
Z65.8	Other specified problems related to psychosocial	Psychosocial
Z65.9	Problem related to unspecified psychosocial circumstances	Psychosocial

Table 2.2: ICD-10 diagnosis codes to identify persons with symptomatic HIV infection, co-infections, and AIDS-defining cancers

Conditions	Class	ICD-10 diagnosis codes
Candidiasis pulmonary esophageal	Opportunistic infection	B371' 'B3781
Coccidioidomycosis, disseminated extrapulmonary	Opportunistic infection	'B383' 'B384' 'B381' 'B3889'
Cryptococcosis extrapulmonary	Opportunistic infection	'B450' 'B457' 'B459' 'B451'
Cryptospidiosis, chronic intestinal	Opportunistic infection	'A072'
Cytomegalovirus other than liver, spleen, nodes	Opportunistic infection	'B259'
Encephalopathy	Opportunistic infection	'G9340' 'G9349' 'I6783'
Herpes simplex: chronic ulcers bronchitis, pneumonitis, esophagitis	Opportunistic infection	'A609' 'A6004' 'A6001' 'A6009' 'B0081' 'B0089'
Histoplasmosis, disseminated extrapulmonary	Opportunistic infection	'B394' 'B393' 'B395'
Isospiasis, chronic intestinal	Opportunistic infection	'A073'
Mycobacterium avium complex Mycobacterium kansasii, disseminated extrapulmonary	Opportunistic infection	'A312'
Mycobacterium tuberculosis of any site	Opportunistic infection	A15' 'A17' 'A18' 'A19' 'A310' 'A311'
Mycobacterium, other species unidentified species, disseminated extrapulmonary	Opportunistic infection	'A318' 'A319'
Pneumocystis jirovecii pneumonia	Opportunistic infection	'B59'
Progressive multifocal leukoencephalopathy	Opportunistic infection	'A812'
Salmonella septicemia, recurrent	Opportunistic infection	'A021'
Toxoplasmosis of brain	Opportunistic infection	'B582' 'B589' 'B5889'
Hepatitis C virus	Co-infection	'B182' 'B192'
Hepatitis B virus	Co-infection	'B180' 'B181' 'B191'
HPV infection	Co-infection	'B977' 'A630"R8581' 'R8582' 'R87810' 'R87811' 'R87820' 'R87821'
Carcinoma in situ, anal canal anal unspecified	AIDS-defining symptom	'D013' 'D4010'
Wasting syndrome attributed to HIV	AIDS-defining symptom	‘'B222'
Disseminated Herpes simplex virus infection	AIDS-defining symptom	'B0089'
Kaposi sarcoma	AIDS-defining cancer	'C460'
Lymphoma, Burkitt	AIDS-defining cancer	'C837'
Lymphoma, immunoblastic	AIDS-defining cancer	'C833'
Lymphoma, primary, of brain	AIDS-defining cancer	'C729'
HPV related cervical cancer	AIDS-defining cancer	'D0730' 'D0739'
Cervical cancer, invasive	AIDS-defining cancer	'C53'

Table 2.3: The counts of five health-related social needs (HRSN) domains among PLWH from state of Florida and Maryland (2016-2019).

	Florida (N=43,229)	Maryland (N=12,396)
Z-code domain	N (%)	N (%)
Family	786 (1.82)	393 (3.17)
Housing	3,334 (7.71)	1,153 (9.30)
Psychosocial	112 (0.26)	113 (0.91)
Education	4 (0.01)	22 (0.18)
Employment	667 (1.54)	371 (2.99)
Total	4,153 (9.6)	1,551(12.5)

Table 2.4: The characteristics of hospitalized PLWH with or without documented health-related social needs (HRSN) from Florida (2016-2019)

	No HRSN		HRSN		P value
Total	39,076	90.4%	4,153	9.6%	
Age (Year)					<0.0001
Under 18	69	0.2%	*	*	
18 - 44	12,649	32.4%	1,754	42.2%	
45 - 54	10,705	27.4%	1,358	32.7%	
55 - 64	10,305	26.4%	853	20.5%	
65 - 74	4,085	10.5%	162	3.9%	
75 +	1,263	3.2%	*	*	
Sex					<0.0001
Male	25,829	66.1%	2,875	69.2%	
Female	13,247	33.9%	1,278	30.8%	
Race					
White	13,395	34.3%	1,464	35.3%	
Black	18,624	47.7%	2,111	50.8%	<0.0001
Hispanic	6,021	15.4%	511	12.3%	
Other	775	2.0%	47	1.1%	
Missing	261	0.7%	20	0.5%	
Income (median)					<0.0001
1st quartile (lowest)	20,669	52.9%	2,206	53.1%	
2nd quartile	10,846	27.8%	905	21.8%	
3rd quartile	5,349	13.7%	442	10.6%	
4th quartile (highest)	1,340	3.4%	75	1.8%	
Missing	872	2.2%	525	12.6%	
Insurance					<0.0001
Medicaid	9,184	23.5%	1,441	34.7%	
Medicare	13,695	35.0%	1,078	26.0%	
Other	2,722	7.0%	455	11.0%	
Private	8,875	22.7%	302	7.3%	
Uninsured	4,600	11.8%	877	21.1%	
Symptomatic status	3,995	10.2%	386	9.3%	0.0592
AIDS syndrome	441	1.1%	32	0.8%	
Opportunistic infection	3,684	9.4%	365	8.8%	
Comorbidities					
AIDS	8,983	23.0%	1,083	26.1%	<0.0001
Alcohol abuse	2,536	6.5%	671	16.2%	<0.0001
Deficiency anemia	9,037	23.1%	911	21.9%	0.083
Rheumatoid arthritis	442	1.1%	41	1.0%	0.4016
Blood loss anemia	647	1.7%	41	1.0%	0.0011
Congestive heart failure	1,772	4.5%	114	2.7%	<0.0001
Chronic lung disease	6,829	17.5%	796	19.2%	0.0066
Coagulopathy	3,269	8.4%	270	6.5%	<0.0001

Depression	4,114	10.5%	596	14.4%	<0.0001
Diabetes mellitus - uncomplicated	3,730	9.5%	323	7.8%	0.0002
Diabetes mellitus - complicated	3,427	8.8%	209	5.0%	<0.0001
Drug abuse	4,368	11.2%	1,447	34.8%	<0.0001
Hypertension	17,402	44.5%	1,416	34.1%	<0.0001
Hypothyroidism	1,700	4.4%	114	2.7%	<0.0001
Liver disease	2,627	6.7%	343	8.3%	0.0002
Lymphoma	461	1.2%	31	0.7%	0.0123
Fluid and electrolyte imbalance	12,689	32.5%	1,142	27.5%	<0.0001
Metastatic cancer	474	1.2%	15	0.4%	<0.0001
Neurological disorders	2,536	6.5%	386	9.3%	<0.0001
Obesity	4,152	10.6%	187	4.5%	<0.0001
Paralysis	1,000	2.6%	71	1.7%	0.0008
Peripheral vascular disease	1,177	3.0%	85	2.0%	<0.0001
Psychoses	2,258	5.8%	576	13.9%	<0.0001
Pulmonary circulation disorders	271	0.7%	26	0.6%	0.6168
Renal failure	4,567	11.7%	286	6.9%	<0.0001
Solid tumor without metastasis	621	1.6%	36	0.9%	0.0003
Peptic ulcer disease	336	0.9%	24	0.6%	0.0573
Valvular disease	779	2.0%	43	1.0%	<0.0001
Weight loss	3,136	8.0%	393	9.5%	0.0022

Table 2.5: The characteristics of PLWH with or without documented health-related social needs (HRSN) from Maryland (2016-2019)

	No HRSN		HRSN		P value
Total	10,845	88%	1,551	12.5%	
Age (Years)					<0.0001
Under 18	30	0.3%	*	*	
18 - 44	3,318	30.6%	648	41.8%	
45 - 54	2,916	26.9%	509	32.8%	
55 - 64	3,158	29.1%	322	20.8%	
65 - 74	1,124	10.4%	60	3.9%	
75 +	299	2.8%	*	*	
Sex					0.0002
Male	6,580	60.7%	1,018	65.6%	
Female	4,265	39.3%	533	34.4%	
Race					<0.0001
White	1,782	16.4%	325	21.0%	
Black	8,381	77.3%	1,154	74.4%	
Hispanic	359	3.3%	31	2.0%	
Other	243	2.2%	27	1.7%	
Missing	80	0.7%	14	0.9%	
Income (median)					<0.0001
1st quartile	3,555	32.8%	626	40.4%	
2nd quartile	1,417	13.1%	207	13.3%	
3rd quartile	3,142	29.0%	386	24.9%	
4th quartile	2,604	24.0%	261	16.8%	
Missing	127	1.2%	71	4.6%	
Insurance					<0.0001
Medicaid	4,274	39.4%	1,004	64.7%	
Medicare	3,445	31.8%	352	22.7%	
Other	369	3.4%	74	4.8%	
Private	2,524	23.3%	92	5.9%	
Uninsured	233	2.1%	29	1.9%	
Symptomatic status	1,223	11.3%	129	8.3%	0.0005
Syndrome	125	1.2%	12	0.8%	
Opportunistic infection	1,133	10.4%	122	7.9%	
Comorbidities					
AIDS	3,255	30.0%	474	30.6%	0.6603
Alcohol abuse	839	7.7%	340	21.9%	<0.0001
Deficiency anemia	3,162	29.2%	412	26.6%	0.0577
Rheumatoid arthritis	119	1.1%	15	1.0%	0.6429
Blood loss anemia	306	2.8%	20	1.3%	0.0004
Congestive heart failure	669	6.2%	74	4.8%	<0.0001
Chronic lung disease	2,564	23.6%	382	24.6%	0.393

Coagulopathy	1,194	11.0%	156	10.1%	0.2605
Depression	1,675	15.4%	304	19.6%	<0.0001
Diabetes mellitus-uncomplicated	959	8.8%	103	6.6%	0.0038
Diabetes mellitus - complicated	1,201	11.1%	99	6.4%	<0.0001
Drug abuse	1,903	17.5%	743	47.9%	<0.0001
Hypertension	5,257	48.5%	634	40.9%	<0.0001
Hypothyroidism	485	4.5%	66	4.3%	0.6984
Liver disease	1,283	11.8%	232	15.0%	0.0004
Lymphoma	157	1.4%	9	0.6%	0.0054
Fluid and electrolyte imbalance	4,451	41.0%	517	33.3%	<0.0001
Metastatic cancer	165	1.5%	8	0.5%	0.0016
Neurological disorders	920	8.5%	155	10.0%	0.048
Obesity	1,446	13.3%	103	6.6%	<0.0001
Paralysis	421	3.9%	33	2.1%	0.0006
Peripheral vascular disease	432	4.0%	34	2.2%	0.0005
Psychoses	751	6.9%	218	14.1%	<0.0001
Pulmonary circulation disorders	96	0.9%	11	0.7%	0.4834
Renal failure	1,710	15.8%	147	9.5%	<0.0001
Solid tumor without metastasis	195	1.8%	10	0.6%	0.0009
Peptic ulcer disease	82	0.8%	10	0.6%	0.6327
Valvular disease	370	3.4%	51	3.3%	0.8017
Weight loss	787	7.3%	134	8.6%	0.0521

Table 2.6: Model for one-year readmission rate of PLWH from Florida, adjusted odds ratios with 95% confidence intervals. The covariates were chose by backward selection method.

Predictor Variables	Outcome: One-year readmission	
	Odds Ratio (95% CI)	p-value
HRSN	3.93(3.62-4.27)	<0.0001
Age (Yrs)		
Under 18	Reference	Reference
18-44	1.34(0.78-2.30)	0.2847
45-54	1.43(0.84-2.45)	0.1926
55-64	1.32(0.77-2.26)	0.3131
65-74	1.22(0.71-2.11)	0.4702
75+	1.25(0.72-2.17)	0.4374
Race		
White	Reference	Reference
Black	1.11(1.05-1.17)	0.0001
Hispanic	1.02(0.95-1.09)	0.6795
Missing	0.62(0.45-0.86)	0.004
Other race	0.91(0.77-1.08)	0.2916
Insurance		
Medicare	1.68(1.56-1.80)	<0.0001
Medicaid	1.87(1.74-2.00)	<0.0001
Other	1.11(1.00-1.22)	0.0470
Private	Reference	Reference
Self	1.16(1.07-1.26)	0.0006
Symptomatic status	1.30(1.20-1.40)	<0.0001
Comorbidities		
HIV/AIDS	1.11(1.05-1.17)	0.0001
Alcohol abuse	1.14(1.05-1.25)	0.0034
Deficiency Anemia	1.31(1.24-1.39)	<0.0001
Arthritis	1.32(1.07-1.64)	0.0105
Blood Loss	0.63(0.52-0.76)	<0.0001
Congestive Heart Failure	1.40(1.25-1.58)	<0.0001
Chronic Lung Disease	1.28(1.21-1.36)	<0.0001
Coagulopathy	1.15(1.06-1.26)	0.0011
Depression	1.13(1.05-1.21)	0.0012
Diabetes	1.29(1.20-1.40)	<0.0001
Diabetes w/ complications	1.42(1.31-1.55)	<0.0001
Drug abuse	1.30(1.22-1.40)	<0.0001
Liver disease	1.21(1.11-1.33)	<0.0001
Lymphoma	1.62(1.31-2.02)	<0.0001
Electrolyte disorder	1.08(1.03-1.14)	0.0023
Metastatic cancer	2.02(1.63-2.51)	<0.0001
Neurological diseases	1.18(1.08-1.29)	0.0003
Peripheral vascular disease	1.35(1.18-1.55)	<0.0001
Psychoses	1.28(1.17-1.40)	<0.0001
Renal failure	1.62(1.51-1.75)	<0.0001
Tumor	1.50(1.25-1.80)	<0.0001
Ulcer	1.51(1.17-1.94)	0.0015
Valvular disease	1.26(1.06-1.49)	0.0084

Weight loss	1.11(1.02-1.21)	0.0194

Table 2.7: Model for one-year readmission rate of hospitalized PLWH from Maryland (2016-2019), adjusted odds ratios with 95% confidence intervals. The covariates were chosen by backward selection method.

Predictor Variables	Outcome: 1-year readmission	
	Odds Ratio (95% CI)	p-value
HRSN	**3.60(3.15-4.12)**	<0.0001
Age (Yrs)		
Under 18	Reference	Reference
18-44	1.37(0.56-3.35)	0.4867
45-54	1.80(0.74-4.40)	0.1969
55-64	1.73(0.71-4.24)	0.2278
65-74	1.60(0.65-3.96)	0.3083
75+	1.55(0.61-3.95)	0.361
Race		
White	Reference	Reference
Black	0.87(0.77-0.98)	0.0165
Hispanic	0.90(0.68-1.18)	0.4481
Missing	0.39(0.22-0.70)	0.0018
Other race	0.91(0.67-1.24)	0.5508
Insurance		
Medicare	1.38(1.22-1.56)	<0.0001
Medicaid	1.69(1.47-1.93)	<0.0001
Other	1.27(0.99-1.64)	0.0622
Private	Reference	Reference
Self	0.87(0.62-1.23)	0.4404
Symptomatic status	1.18(1.02-1.36)	0.0270
Comorbidities		
Alcohol abuse	1.32(1.14-1.53)	0.0002
Deficiency Anemia	1.40(1.27-1.55)	<0.0001
Blood Loss	0.68(0.50-0.92)	0.0113
Congestive Heart Failure	1.72(1.43-2.05)	<0.0001
Chronic Lung Disease	1.26(1.14-1.39)	<0.0001
Diabetes w/ complications	1.34(1.16-1.54)	<0.0001
Drug abuse	1.21(1.08-1.34)	0.0008
Liver disease	1.32(1.15-1.50)	<0.0001
Lymphoma	1.44(1.01-2.07)	0.0458
Electrolyte disorder	1.18(1.08-1.29)	0.0003
Metastatic cancer	2.12(1.45-3.10)	0.0001
Paralysis	1.46(1.16-1.83)	0.0011
Psychoses	1.35(1.15-1.58)	0.0002
Pulmonary circulation disorder	1.70(1.07-2.71)	0.0259
Renal failure	1.66(1.46-1.87)	<0.0001
Tumor	1.81(1.30-2.51)	.0.0004
Weight loss	1.42(1.20-1.68)	<0.0001

Chapter III

Figure 3.1A-C. Age distribution in men living with HIV (MLWH) and their counterparts without HIV with Anal cancer (A), Lymphoma (B), and all other cancer types (C). X-axis: HIV status (0) denotes non-HIV population, HIV (1) denotes men living with HIV. Y-axis: age (years).

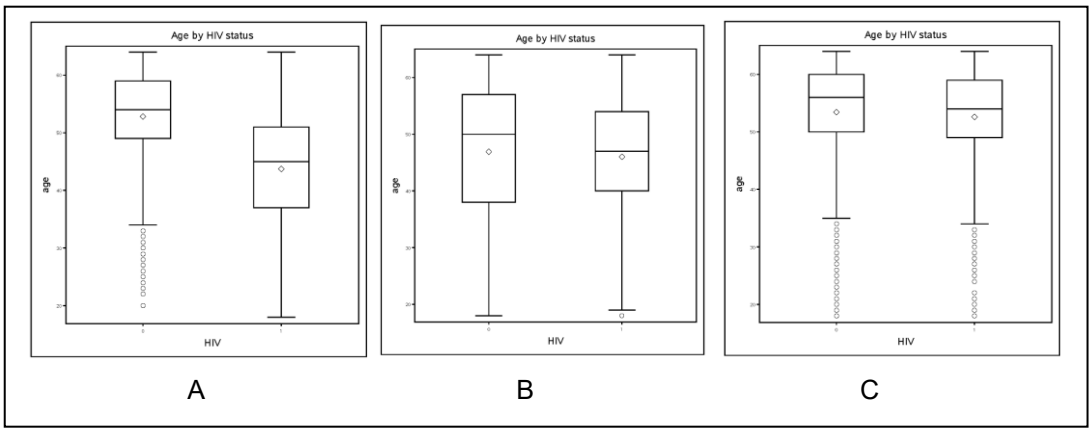


Figure 3.2: Age- and race/ethnicity-adjusted prevalence ratios and 95% CIs are shown for various types of cancer stratified by HIV symptomatic status. The x-axis is on a logarithmic scale. For all adjusted prevalence ratios (APRs), the reference category is men without HIV. APRs for which the 95% confidence interval (CI) crosses 1.0 are not statistically significant at P < .05. Models were adjusted for age, race/ethnicity, US Census Divisions, months of enrollment in Medicaid during 2012, and coinfections for hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV). Models for liver cancer were adjusted for HBV/HCV status, whereas models for head/neck, rectal, and anal cancers were adjusted for HPV status. Models for all other cancers and all cancers combined were adjusted for the presence of any coinfection (HBV/HCV and/or HPV). Models for lymphoma did not adjust for coinfections.

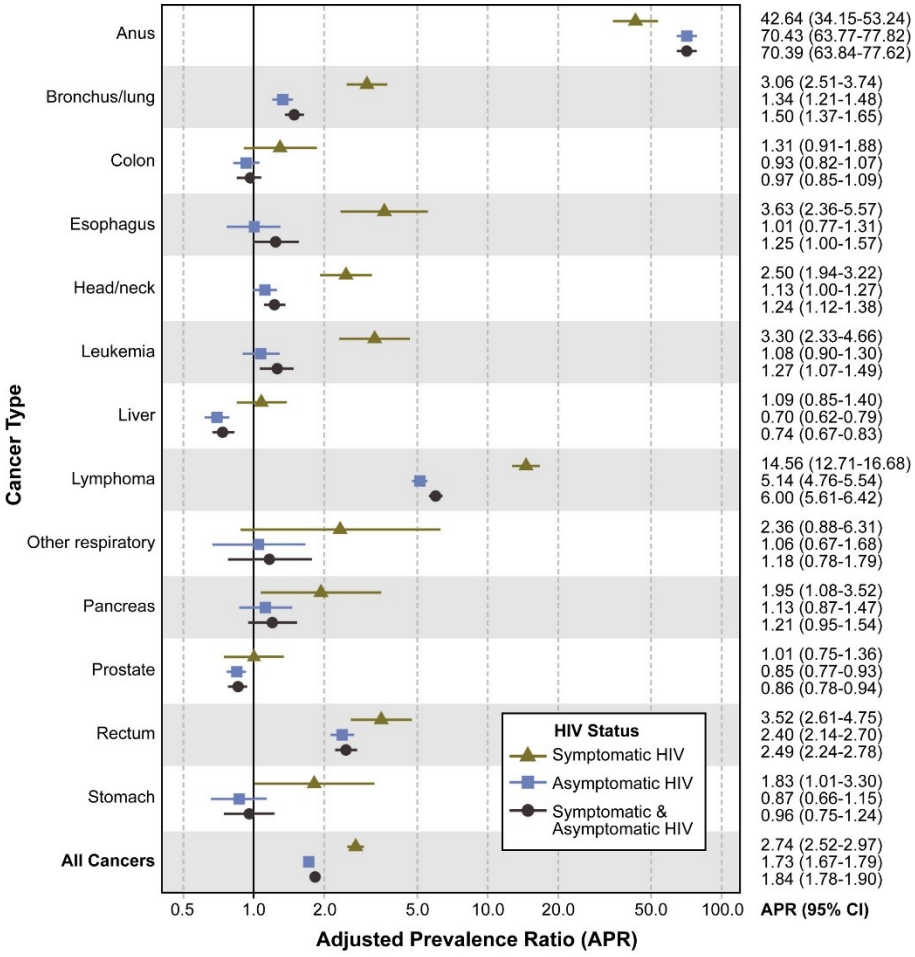


Table 3.1: ICD-9 diagnosis codes to identify men with symptomatic HIV and co-infections

Conditions	Class	ICD-9 diagnosis codes
Candidiasis (pulmonary or esophageal)	Opportunistic infection	'1124' '11284'
Coccidioidomycosis, disseminated or extrapulmonary	Opportunistic infection	'1141' '1142' '1143' '1144'
Cryptococcosis (extrapulmonary)	Opportunistic infection	'1175' '3210'
Cryptosporidiosis, chronic intestinal	Opportunistic infection	'0074'
Cytomegalovirus (other than liver, spleen, or nodes)	Opportunistic infection	0785'
Encephalopathy	Opportunistic infection	'3483' '34830' '34839'
Herpes simplex: chronic ulcers or bronchitis, pneumonitis, or esophagitis	Opportunistic infection	0541' '05410' '05411' '05412' '05413' '05414' '05415' '05416' '05417' '05418' '05419' '05471' '05479'
Histoplasmosis, disseminated or extrapulmonary	Opportunistic infection	'11500' '11501' '11502' '11503' '11504' '11506' '11507' '11508' '11509' '11510' '11511' '11512' '11513' '11514' '11516' '11517' '11518' '11519' '11590' '11591' '11592' '11593' '11594' '11596' '11597' '11598' '11599'
Isosporiasis, chronic intestinal	Opportunistic infection	'0072'
Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary	Opportunistic infection	'0312'
Mycobacterium tuberculosis of any site	Opportunistic infection	'010' '011' '012' '013' '014' '015' '016' '017' '018'
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary	Opportunistic infection	'0318' '0319'
Pneumocystis jirovecii pneumonia	Opportunistic infection	'1363'
Progressive multifocal leukoencephalopathy	Opportunistic infection	'0463'
Salmonella septicemia, recurrent	Opportunistic infection	'0031'
Toxoplasmosis of brain	Opportunistic infection	'1300' '1307' '1309'
Hepatitis C virus	Co-infection	'07041' '07044' '07051' '07054' '07070' '07071' 'V0262'
Hepatitis B virus	Co-infection	'07020' '07021' '07022' '07023' '07030' '07031' '07032' '07033' '07042' '07052' 'V0261'
HPV infection	Co-infection	'79505' '79500' '79501' '79502' '79503' '79504' '79509' '62210' '6230' '2333' '23050' '23890' '7967' '0781' '07810' '07811'
Carcinoma in situ, anal canal or anal unspecified	AIDS-defining symptom	'23060' '23640'
Wasting syndrome attributed to HIV	AIDS-defining symptom	‘78321' '78322' '7837' '260' '261' '262' '263'
Disseminated Herpes simplex virus infection	AIDS-defining symptom	'05479'
Kaposi sarcoma	AIDS-defining cancer	'1760' '1761' '1762' '1763' '1764' '1765' '1766' '1767' '1768' '1769'
Lymphoma, Burkitt	AIDS-defining cancer	'20020' '20021' '20022' '20023' '20024' '20025' '20026' '20027' '20028'
Lymphoma, immunoblastic	AIDS-defining cancer	'20000' '20001' '20002' '20003' '20004' '20005' '20006' '20007' '20008'

Lymphoma, primary, of brain	AIDS-defining cancer	'20050' '20051' '20052' '20053' '20054' '20055' '20056' '20057' '20058'
HPV related cervical cancer	AIDS-defining cancer	'62210' '62211' '62212' '2331' '1801'
Cervical cancer, invasive	AIDS-defining cancer	1800' '1801' '1808' '1809'

Table 3.2: ICD-9 codes and CCS codes used in this study to identify the relevant cancers

Disease	CCS	ICD-9 codes
HIV	5	'042' '0420' '0421' '0422' '0429' '0430' '0431' '0432' '0433' 0'439' '0440' '0449' '07953' '27910' '27919' '79571' '7958' 'V08'
Cancer of head and neck	11	'1400' '1401' '1403' '1404' '1405' '1406' '1408' '1409' '1410' '1411' '1412' '1413' '1414' '1415' '1416' '1418' '1419' '1420' '1421' '1422' '1428' '1429' '1430' '1431' '1438' '1439' '1440' '1441' '1448' '1449' '1450' '1451' '1452' '1453' '1454' '1455' '1456' '1458' '1459' '1460' '1461' '1462' '1463' '1464' '1465' '1466' '1467' '1468' '1469' '1470' '1471' '1472' '1473' '1478' '1479' '1480' '1481' '1482' '1483' '1488' '1489' '1490' '1491' '1498' '1499' '1600' '1601' '1602' '1603' '1604' '1605' '1608' '1609' '1610' '1611' '1612' '1613' '1618' '1619' '1950 2300' '2310' 'V1001' 'V1002' 'V1021'
Cancer of esophagus	12	'1500' '1501' '1502' '1503' '1504' '1505' '1508' '1509' '2301' 'V1003'
Cancer of stomach	13	'1510' '1511' '1512' '1513' '1514' '1515' '1516' '1518' '1519' '20923' '2302' 'V1004'
Cancer of colon	14	'1530' '1531' '1532' '1533' '1534' '1535' '1536' '1537' '1538' '1539' '1590' '20910' '20911' '20912' '20913' '20914' '20915' '20916' '2303' 'V1005'
Cancer of anus	15	'1542' '1543' '2305' '2306' '79670' '79671' '79672' '79673' '79674' '79676'
Cancer of rectum	15	'1540' '1541' '20917' '2304' 'V1006'
Cancer of liver & intrahepatic bile duct	16	'1550' '1551' '1552' '2308' 'V1007'
Cancer of pancreas	17	'1570' '1571' '1572' '1573' '1574' '1578' '1579'
Cancer of bronchus; lung	19	'1622' '1623' '1624' '1625' '1628' '1629' '20921' '2312' 'V1011'
Cancer; other respiratory & intrathoracic	20	'1620' '1630' '1631' '1638' '1639' '1650' '1658' '1659' '2311' '2318' '2319' 'V1012' 'V1020' 'V1022'
Cancer of prostate	29	'185' '2334' 'V1046'
Leukemia	39	'20240' '20241' '20242' '20243' '20244' '20245' '20246' '20247' '20248' '2031' '20310' '20311' '20312' '2040' '20400' '20401' '20402' '2041' '20410' '20411' '20412' '2042' '20420' '20421' '20422' '2048' '20480' '20481' '20482' '2049' '20490' '20491' '20492' '2050' '20500' '20501' '20502' '2051' '20510' '20511' '20512' '2052' '20520' '20521' '20522' '2053' '20530' '20531' '20532' '2058' '20580' '20581' '20582' '2059' '20590' '20591' '20592' '2060' '20600' '20601' '20602' '2061' '20610' '20611' '20612' '2062' '20620' '20621' '20622' '2068' '20680' '20681' '20682' '2069' '20690' '20691' '20692' '2070' '20700' '20701' '20702' '2071' '20710' '20711' '20712' '2072' '20720' '20721' '20722' '2078' '20780' '20781' '20782' '2080' '20800' '20801' '20802' '2081' '20810' '20811' '20812' '2082' '20820' '20821' '20822' '2088' '20880' '20881' '20882' '2089' '20890' '20891' '20892' 'V1060' 'V1061' 'V1062' 'V1063' 'V1069'
Lymphoma*		'20000-20238' '20250-20301' '2386' '2733' '20302-20382'

*https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comformat2012-2015.txt

Table 3.3: Distribution of men living with HIV (MLWH) by symptomatic status and by cancer type

	Symptomatic HIV	Asymptomatic HIV	Symptomatic and Asymptomatic Combined
Non-Hispanic White			
Anus	30 (2.17)	395 (2.25)	425 (2.24)
Rectum	15 (1.09)	116 (0.66)	131 (0.69)
Hodgkin's lymphoma	46 (3.33)	215 (1.22)	261 (1.38)
All Other Cancers	69 (4.99)	463 (2.63)	532 (2.80)
All Cancers Combined	136 (9.84)	1,032 (5.87)	1,168 (6.16)
Non-Hispanic Black			
Anus	45 (1.20)	439 (1.21)	484 (1.21)
Rectum	21 (0.56)	124 (0.34)	145 (0.36)
Hodgkin's lymphoma	97 (2.60)	323 (0.89)	420 (1.05)
All Other Cancers	169 (4.52)	873 (2.40)	1,042 (2.60)
All Cancers Combined	295 (7.90)	1,582 (4.35)	1,877 (4.68)
Hispanic			
Anus	16 (1.21)	216 (1.57)	232 (1.53)
Rectum	<11	**	47 (0.31)
Hodgkin's lymphoma	49 (3.70)	156 (1.13)	205 (1.36)
All Other Cancers	58 (4.38)	245 (1.78)	303 (2.00)
All Cancers Combined	113 (8.53)	605 (4.39)	718 (4.75)
All Others			
Anus	<11	**	150 (1.81)
Rectum	<11	**	33 (0.40)
Hodgkin's lymphoma	17 (2.11)	85 (1.13)	102 (1.23)
All Other Cancers	22 (2.73)	154 (2.06)	176 (2.12)
All Cancers Combined	41 (5.09)	373 (4.98)	414 (4.99)

Cells < 11 masked in accordance with the Centers for Medicare & Medicaid Services Privacy Rules. ** Cells in the corresponding rows and/or columns are modified to prevent the reader from deriving the small cells.

Note: Individuals with more than one cancer were included in each cancer site analysis. Therefore, the cells for *All Cancers Combined* do not represent the sum of the cells for each cancer type.

Table 3.4: The sensitivity analysis of adjusted prevalence ratios (APR) for various types of cancer stratified by HIV symptomatic status. The cohort included AIDS-defining cancers (non-Hodgkin's lymphoma and Kaposi's sarcoma). APRs and the 95% confidence intervals (CI) are shown, and the reference category is men without HIV. Models were adjusted for age, race/ethnicity, US Census Divisions, months of enrollment in Medicaid during 2012, and coinfections for hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV) as described in Figure 3.2.

	Symptomatic	**Asymptomatic**	**All combined**
Cancer type	APR (95% CI)	APR (95% CI)	APR (95% CI)
Head/neck	2.82 (2.19-3.64)	1.26 (1.12-1.41)	1.39 (1.24-1.54)
Esophagus	4.17 (2.72-6.40)	1.13 (0.87-1.48)	1.41 (1.13-1.77)
Stomach	2.11 (1.17-3.81)	0.98 (0.74-1.30)	1.09 (0.84-1.41)
Colon	1.49 (1.04-2.15)	1.05 (0.92-1.20)	1.09 (0.96-1.23)
Rectum	3.98 (2.95-5.37)	2.67 (2.38-3.00)	2.78 (2.49-3.10)
Anus	46.01(36.8-57.52)	79.47 (71.88-87.86)	79.6 (72.14-87.84)
Liver	1.11 (0.86-1.43)	0.71 (0.63-0.80)	0.75 (0.68-0.84)
Pancreas	2.26 (1.25-4.08)	1.28 (0.99-1.67)	1.38 (1.08-1.75)
Bronchus/lung	3.51 (2.88-4.28)	1.51 (1.36-1.67)	1.70 (1.55-1.86)
Other respiratory	2.69 (1.01-7.20)	1.19 (0.76-1.89)	1.32 (0.87-2.01)
Prostate	1.14 (0.84-1.54)	0.95 (0.86-1.04)	0.96 (0.88-1.06)
Leukemia	3.83 (2.71-5.42)	1.23 (1.02-1.48)	1.44 (1.22-1.70)
Lymphoma *	16.86 (14.72-19.31)	5.80 (5.38-6.26)	6.80 (6.36-7.28)
All Cancers	2.96 (2.73-3.21)	1.87 (1.80-1.93)	1.98 (1.92-2.05)

* Including Hodgkin's and non-Hodgkin's lymphoma

Table 3.5: Distribution of the study population by HIV symptomatic status, demographics, and cancer type.

	Men with HIV & symptoms	Men with HIV but without symptoms	Total men with HIV	Men without HIV
	N (% of total)	N (% of total)	N (% of total)	N (% of total)
Age				
18-44	3,274 (45.18)	29,898 (39.73)	33,172 (40.21)	5,123,299 (70.16)
45-64	3,973 (54.82)	45,350 (60.27)	49,323 (59.79)	2,179,224 (29.84)
Race				
Non-Hispanic White	1,382 (19.07)	17,591 (23.38)	18,973 (23.00)	3,013,360 (41.26)
Non-Hispanic Black	3,736 (51.55)	36,373 (48.34)	40,109 (48.62)	1,413,808 (19.36)
Hispanic	1,324 (18.27)	13,791 (18.33)	15,115 (18.32)	1,752,108 (23.99)
Asian	79 (1.09)	851 (1.13)	930 (1.13)	356,002 (4.88)
American Indian or Alaskan native	27 (0.37)	368 (0.49)	395 (0.48)	89,728 (1.23)
Native Hawaiian or other Pacific Islander	26 (0.36)	247 (0.33)	273 (0.33)	66,780 (0.91)
More than one race	32 (0.44)	376 (0.50)	408 (0.49)	30,395 (0.42)
Unknown or missing	641 (8.85)	5,651 (7.51)	6,292 (7.63)	580,342 (7.95)
Total	7,247 (100)	75,248 (100)	82,495 (100)	7,302,523 (100)
Co-Infections				
Hepatitis B Virus (HBV)	458 (6.32)	2,561 (3.40)	3,019 (3.66)	24,492 (0.34)
Hepatitis C Virus (HCV)	1,400 (19.32)	12,004 (15.95)	13,404 (16.25)	108,895 (1.49)
Human Papilloma Virus (HPV)	306 (4.22)	2,738 (3.64)	3,044 (3.69)	35,638 (0.49)
Cancer types				
Head/neck	59 (0.81)	288 (0.38)	347 (0.42)	15,400 (0.21)
Esophagus	21 (0.29)	56 (0.07)	77 (0.09)	3,804 (0.05)
Stomach	11 (0.15)	50 (0.07)	61 (0.07)	3,661 (0.05)
Colon	29 (0.40)	221 (0.29)	250 (0.30)	13,342 (0.18)
Rectum	43 (0.59)	313 (0.42)	356 (0.43)	7,752 (0.11)
Anus	98 (1.35)	1,193 (1.59)	1,291 (1.56)	908 (0.01)
Liver & intrahepatic bile duct	58 (0.80)	282 (0.37)	340 (0.41)	8,352 (0.11)
Pancreas	11 (0.15)	58 (0.08)	69 (0.08)	3,396 (0.05)
Bronchus/lung	94 (1.30)	388 (0.52)	482 (0.58)	19,320 (0.26)
Other respiratory & intrathoracic	*	*	23 (0.03)	1,073 (0.01)
Prostate	42 (0.58)	424 (0.56)	466 (0.56)	18,164 (0.25)
Leukemia	32 (0.44)	114 (0.15)	146 (0.18)	8,254 (0.11)
Hodgkin's lymphoma	209 (2.88)	779 (1.04)	988 (1.20)	9,460 (0.13)
All cancers	585 (8.07)	3,592 (4.77)	4,177 (5.06)	96,096 (1.32)

Table 3.6: Adjusted Prevalence Ratios and 95% Confidence Intervals for select cancers, by HIV symptomatic status and age

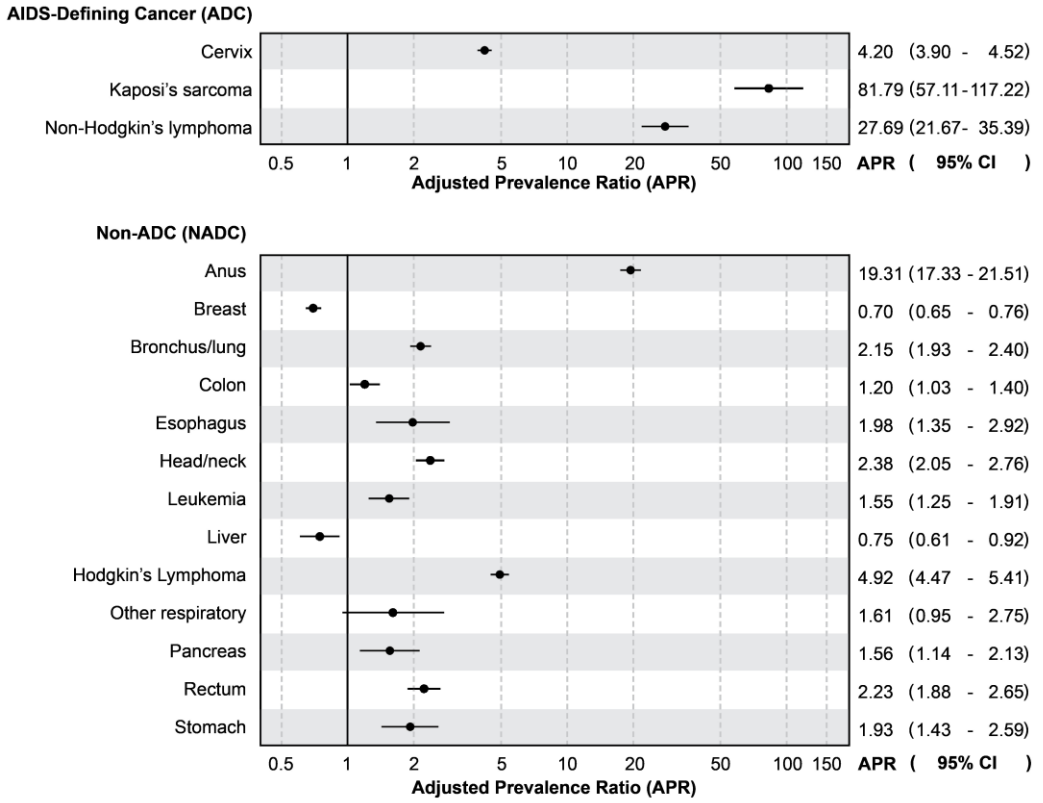
	Symptomatic HIV	**Asymptomatic HIV**	**Symptomatic and Asymptomatic Combined**
Younger Age Group (18-44 years of age)			
Anus	312.97 (210.27-465.84)	482.26 (390.67-595.32)	480.28 (390.27-591.04)
Rectum	16.78 (9.67-29.11)	11.55 (9.04-14.77)	12.10 (9.63-15.21)
Hodgkin's lymphoma	31.73 (25.64-39.26)	13.85 (12.27-15.63)	16.42 (14.75-18.29)
All Other Cancers	4.98 (3.82-6.48)	1.97 (1.70-2.30)	2.30 (2.02-2.63)
All Cancers Combined	13.28 (11.45-15.42)	8.82 (8.23-9.45)	9.38 (8.80-10.01)
Older Age Group (45-64 years of age)			
Anus	24.08 (17.70-32.76)	36.71 (32.66-41.25)	36.18 (32.27-40.57)
Rectum	2.57 (1.80-3.68)	1.90 (1.67-2.17)	1.95 (1.73-2.21)
Hodgkin's lymphoma	6.82 (5.67-8.21)	3.74 (3.41-4.12)	4.29 (3.93-4.67)
All Other Cancers	1.31 (1.16-1.47)	0.81 (0.77-0.85)	0.85 (0.81-0.89)
All Cancers Combined	1.83 (1.66-2.02)	1.24 (1.19-1.29)	1.30 (1.25-1.35)

Table 3.7: Age-adjusted prevalence ratios (APRs) and 95% Confidence Intervals for select cancers, by HIV symptomatic status and race/ethnicity

	Symptomatic HIV	Asymptomatic HIV	Symptomatic and Asymptomatic Combined
Non-Hispanic White			
Anus	37.37 (26.31-53.10)	54.92 (47.63-63.33)	55.36 (48.17-63.61)
Rectum	4.76 (2.88-7.87)	2.89 (2.40-3.48)	3.03 (2.54-3.60)
Hodgkin's lymphoma	14.92 (11.22-19.83)	5.27 (4.60-6.05)	5.96 (5.26-6.76)
All Other Cancers	1.76 (1.39-2.23)	1.03 (0.94-1.13)	1.09 (1.00-1.19)
All Cancers Combined	3.11 (2.63-3.69)	2.04 (1.92-2.17)	2.13 (2.01-2.26)
Non-Hispanic Black			
Anus	44.02 (29.92-64.77)	62.72 (51.10-76.98)	63.65 (52.04-77.86)
Rectum	3.35 (2.17-5.16)	2.02 (1.67-2.44)	2.13 (1.79-2.54)
Hodgkin's lymphoma	12.05 (9.85-14.75)	4.12 (3.65-4.64)	4.92 (4.42-5.48)
All Other Cancers	1.66 (1.42-1.93)	0.89 (0.83-0.96)	0.97 (0.91-1.04)
All Cancers Combined	2.61 (2.32-2.93)	1.47 (1.40-1.56)	1.59 (1.51-1.67)
Hispanic			
Anus	87.38 (48.22-158.35)	207.37 (149.91-286.85)	198.53 (144.54-272.68)
Rectum	4.05 (1.82-9.02)	2.50 (1.82-3.44)	2.63 (1.95-3.55)
Hodgkin's lymphoma	26.03 (19.67-34.45)	7.43 (6.24-8.83)	9.10 (7.80-10.63)
All Other Cancers	2.10 (1.62-2.73)	0.88 (0.77-1.01)	0.99 (0.88-1.12)
All Cancers Combined	3.78 (3.13-4.56)	2.06 (1.89-2.25)	2.25 (2.07-2.44)
All Others			
Anus	28.97 (13.32-62.99)	91.78 (70.75-119.06)	87.32 (67.48-112.99)
Rectum	0.65 (0.09-4.60)	2.23 (1.57-3.18)	2.07 (1.47-2.94)
Lymphoma	11.08 (6.90-17.79)	6.34 (5.08-7.91)	6.86 (5.59-8.41)
All Other Cancers	1.05 (0.69-1.60)	0.85 (0.73-1.00)	0.87 (0.75-1.02)
All Cancers Combined	1.78 (1.31-2.42)	1.89 (1.70-2.10)	1.89 (1.71-2.08)

Chapter IV

Figure 4.1 Adjusted prevalence ratios (APRs) and 95% confidence interval for various types of cancer stratified by ADC/NADC.



The X-axis is on a logarithmic scale. For all APRs, the reference category is women without HIV. APRs for which the 95% confidence interval crosses 1.0 are not statistically significant at $p < 0.05$.

Models adjusted for age, race/ethnicity, U.S. Census Divisions, months of enrollment in Medicaid during 2012, and co-infections for hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV). Models for liver cancer adjusted for HBV/HCV, models for cervical cancer adjusted for cervical HPV, while models for head/neck, rectal and anal cancers adjusted for any type of HPV.

Table 4.1: ICD-9 and CCS codes used in this study to identify the relevant cancers and co-infections

Disease	CCS	ICD-9 codes
HIV	5	'042' '0420' '0421' '0422' '0429' '0430' '0431' '0432' '0433' 0'439' '0440' '0449' '07953' '27910' '27919' '79571' '7958' 'V08'
Cancer of head and neck	11	‘1400' '1401' '1403' '1404' '1405' '1406' '1408' '1409' '1410' '1411' '1412' '1413' '1414' '1415' '1416' '1418' '1419' '1420' '1421' '1422' '1428' '1429' '1430' '1431' '1438' '1439' '1440' '1441' '1448' '1449' '1450' '1451' '1452' '1453' '1454' '1455' '1456' '1458' '1459' '1460' '1461' '1462' '1463' '1464' '1465' '1466' '1467' '1468' '1469' '1470' '1471' '1472' '1473' '1478' '1479' '1480' '1481' '1482' '1483' '1488' '1489' '1490' '1491' '1498' '1499' '1600' '1601' '1602' '1603' '1604' '1605' '1608' '1609' '1610' '1611' '1612' '1613' '1618' '1619' '1950 2300' '2310' 'V1001' 'V1002' 'V1021'
Cancer of esophagus	12	'1500' '1501' '1502' '1503' '1504' '1505' '1508' '1509' '2301' 'V1003'
Cancer of stomach	13	'1510' '1511' '1512' '1513' '1514' '1515' '1516' '1518' '1519' '20923' '2302' 'V1004'
Cancer of colon	14	'1530' '1531' '1532' '1533' '1534' '1535' '1536' '1537' '1538' '1539' '1590' '20910' '20911' '20912' '20913' '20914' '20915' '20916' '2303' 'V1005'
Cancer of anus		'1542' '1543' '2305' '2306' '79670' '79671' '79672' '79673' '79674' '79676'
Cancer of rectum		'1540' '1541' '20917' '2304' 'V1006'
Cancer of liver & intrahepatic bile duct	16	'1550' '1551' '1552' '2308' 'V1007'
Cancer of pancreas	17	‘1570' '1571' '1572' '1573' '1574' '1578' '1579'
Cancer of bronchus; lung	19	'1622' '1623' '1624' '1625' '1628' '1629' '20921' '2312' 'V1011'
Cancer; other respiratory and intrathoracic	20	'1620' '1630' '1631' '1638' '1639' '1650' '1658' '1659' '2311' '2318' '2319' 'V1012' 'V1020' 'V1022'

Cancer of breast	24	'1740' '1741' '1742' '1743' '1744' '1745' '1746' '1748' '1749' '1750' '1759' '2330' 'V103'
Cancer of Cervical		'1800' '1801' '1808' '1809' '2331'
Leukemia	39	'20240' '20241' '20242' '20243' '20244' '20245' '20246' '20247' '20248' '2031' '20310' '20311' '20312' '2040' '20400' '20401' '20402' '2041' '20410' '20411' '20412' '2042' '20420' '20421' '20422' '2048' '20480' '20481' '20482' '2049' '20490' '20491' '20492' '2050' '20500' '20501' '20502' '2051' '20510' '20511' '20512' '2052' '20520' '20521' '20522' '2053' '20530' '20531' '20532' '2058' '20580' '20581' '20582' '2059' '20590' '20591' '20592' '2060' '20600' '20601' '20602' '2061' '20610' '20611' '20612' '2062' '20620' '20621' '20622' '2068' '20680' '20681' '20682' '2069' '20690' '20691' '20692' '2070' '20700' '20701' '20702' '2071' '20710' '20711' '20712' '2072' '20720' '20721' '20722' '2078' '20780' '20781' '20782' '2080' '20800' '20801' '20802' '2081' '20810' '20811' '20812' '2082' '20820' '20821' '20822' '2088' '20880' '20881' '20882' '2089' '20890' '20891' '20892' 'V1060' 'V1061' 'V1062' 'V1063' 'V1069'
Hodgkin's lymphoma		'20100-20238' '20250-20301' '2386' '2733' '20302-20382'
Non-Hodgkin's lymphoma		'20000' '20001' '20002' '20003' '20004' '20005' '20006' '20007' '20008' '20020' '20021' '20022' '20023' '20024' '20025' '20026' '20027' '20028' '20050' '20051' '20052' '20053' '20054' '20055' '20056' '20057' '20058'
Kaposi's sarcoma		'1760' '1761' '1762' '1763' '1764' '1765' '1766' '1767' '1768' '1769'
Hepatitis C virus		'07041' '07044' '07051' '07054' '07070' '07071' 'V0262'
Hepatitis B virus		'07020' '07021' '07022' '07023' '07030' '07031' '07032' '07033' '07042' '07052' 'V0261'
Cervical HPV infection		'79505'
Any types of HPV infection		'79505' '79500' '79501' '79502' '79503' '79504' '79509' '62210' '6230' '2333' '23050' '23890' '7967' '0781' '07810' '07811'

Table 4.2: Distribution of the study population by HIV status, demographics, and cancer type

	Women with HIV	**Women without HIV**
	N (% of total)	**N (% of total)**
Age		
18-44	38,760 (53.46)	14,320,901 (82.52)
45-64	33,748 (46.54)	3,033,062 (17.48)
Race		
White	12,358 (17.04)	6,858,472 (39.52)
Black	42,450 (58.55)	3,675,929 (21.18)
Hispanic	12,245 (16.88)	4,658,134 (26.84)
Asian	711 (0.98)	652,457 (3.76)
American Indian or Alaskan Native	380 (0.52)	209,965 (1.21)
Native Hawaiian or other Pacific Islander	169 (0.23)	158,629 (0.91)
More than one race	293 (0.40)	66,414 (0.38)
Unknown or missing	3,902 (5.38)	1,073,963 (6.19)
Total	72,508 (100)	17,353,963 (100)
Co-Infections		
Hepatitis B Virus (HBV)	1,609 (2.22)	29,022 (0.17)
Hepatitis C Virus (HCV)	8,032 (11.08)	100,762 (0.58)
Human Papilloma Virus (HPV)	8,040 (11.09)	553,646 (3.19)
AIDS-defining cancers	1027 (1.42)	39,067 (0.23)
Cervix	837 (1.15)	37,898 (0.22)
Non-Hodgkin's Lymphoma	127 (0.18)	955 (<0.01)
Kaposi’s Sarcoma	73 (0.10)	223 (<0.01)
Non-AIDS-defining cancers	2,560 (3.53)	167,224 (0.96)
Head/neck	206 (0.28)	8,574 (0.05)
Esophagus	29 (0.04)	1,457 (0.01)
Stomach	48 (0.07)	2,676 (0.02)
Colon	183 (0.25)	14,710 (0.08)
Rectum	153 (0.21)	7,090 (0.04)
Anus	595 (0.82)	2,337 (0.01)
Liver & intrahepatic bile duct	112 (0.15)	4,292 (0.02)
Pancreas	42 (0.06)	3,031 (0.02)
Bronchus/lung	358 (0.49)	19,419 (0.11)
Other respiratory & intrathoracic	14 (0.02)	1,052 (0.01)
Breast	705 (0.97)	99,810 (0.58)
Leukemia	105 (0.14)	8,564 (0.05)
Hodgkin's lymphoma	475 (0.66)	10,886 (0.06)
Total	3,471 (4.79%)	204,145 (1.18)

Table 4.3: Adjusted prevalence ratios and 95% confidence intervals for select cancers by age group from WLWH. For the APRs of older age group (45–64 years), the reference category is younger age group (18–44 years). APRs for which the 95% CI crosses 1.0 are not statistically significant at $p < 0.05$. Models are adjusted for race/ethnicity, US Census divisions, and months of enrollment in Medicaid during 2012. The model for cervical cancer is adjusted for cervical HPV, and models for rectal and anal cancers adjusted for any type of HPV. Models for All Other Cancers and All Cancers Combined are adjusted for the presence of any co-infection (HBV/HCV and/or HPV). Models for non-Hodgkin's and Hodgkin's lymphoma and breast cancer are not adjusted for co-infections. APR: adjusted prevalence ratio; CI: confidence interval; WLWH: women living with HIV; HPV: human papillomavirus; HBV: hepatitis B virus; HCV: hepatitis C virus.

	45-64 group
AIDS-defining cancers	APR (95%CI) Reference Group: WLWH 18-44 years of age
Cervix	1.02 (0.89-1.17)
Non-Hodgkin's Lymphoma	0.81 (0.56-1.18)
Kaposi's Sarcoma	0.98 (0.61-1.56)
Non-AIDS-defining cancers	
Anus	1.93 (1.63-2.29)
Rectum	2.68 (1.89-3.80)
Hodgkin's Lymphoma	1.52 (1.26-1.82)
Breast	5.13 (4.23-6.22)
Other cancer	3.88 (3.32-4.54)
All cancer types	1.99 (1.86-2.14)

Table 4.4: Distribution of women living with HIV by select cancer types and age. The crude prevalence percentages in the parenthesis were calculated from the total number of cancers divided by the population of the age group.

	18-44 group	**45-64 group**
AIDS-defining cancers		
Cervix	446 (1.15)	391 (1.16)
Non-Hodgkin Lymphoma	78 (0.20)	49 (0.15)
Kaposi Sarcoma	40 (0.10)	33 (0.10)
Non-AIDS-defining cancers		
Anus	207 (0.53)	388 (1.15)
Rectum	47 (0.12)	106 (0.31)
Hodgkin Lymphoma	213 (0.55)	262 (0.78)
Breast	128 (0.33)	577 (1.71)
Other cancer	208 (0.54)	728 (2.16)
All cancer types combined	1,211 (3.12)	2,260 (6.70)
Total Women with HIV	38,760 (53.46)	33,748 (46.54)

Table 4.5: Distribution of women living with HIV for select cancers by select cancer types and race/ethnicity. The crude prevalence percentages in the parenthesis were calculated from the total number of cancer divided by the population of the race/ethnicity.

	Non-Hispanic White	Non-Hispanic Black	Hispanic	All Others
AIDS-defining cancers				
Cervix	144 (1.17)	522 (1.23)	113 (0.92)	58 (1.06)
Non-Hodgkin's Lymphoma	<30 (<0.20) [1]	56 (0.13)	34 (0.28)	<15 (<0.30) [1]
Kaposi Sarcoma	<11 (<0.10) [1]	46 (0.11)	11 (0.09)	<11 (<0.30) [1]
Non-AIDS-defining cancers				
Anus	91 (0.74)	297 (0.70)	171 (1.40)	36 (0.66)
Rectum	30 (0.24)	88 (0.21)	<30 (<0.25) [1]	<11 (<0.30) [1]
Hodgkin's Lymphoma	67 (0.54)	285 (0.67)	78 (0.64)	45 (0.82)
Breast	111 (0.90)	459 (1.08)	91 (0.74)	44 (0.81)
All Other Cancers	161 (1.30)	582 (1.37)	124 (1.01)	58 (1.06)
All cancer types combined	556 (4.50)	2,074 (4.89)	581 (4.74)	260 (4.77)
Total Women with HIV	12,358 (17.04)	42,450 (58.55)	12,245 (16.88)	5,455 (22.53)

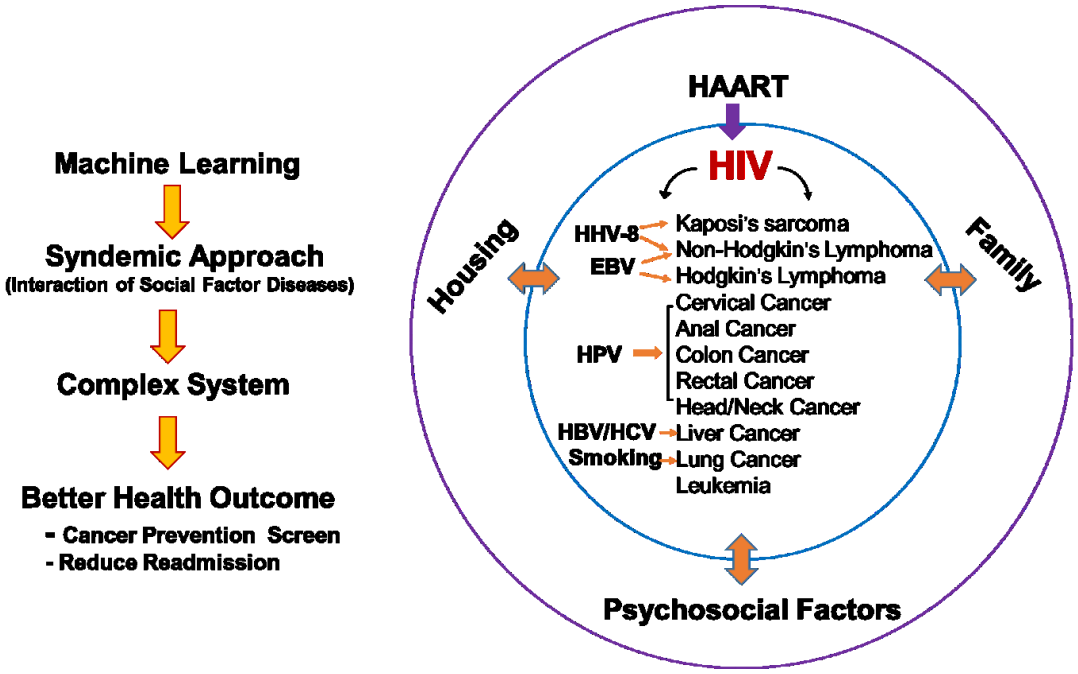
Footnote 1: Cells with frequency <11 or another smallest number in the same raw/column were suppressed due to requirements in the CMS data use agreement.

Table 4.6: Adjusted prevalence ratios and 95% confidence intervals for select cancers by race/ethnicity from WLWH. For the APRs of each race/ethnicity strata, the reference category is the all the other women except the race/ethnicity strata, the reference category is all the other women except the race/ethnicity examined (i.e. non-Hispanic White vs all other race/ethnicities (reference), non-Hispanic Black vs all other race/ethnicities (reference), Hispanic vs all other race/ethnicities (reference), all other race vs non-Hispanic White/non-Hispanic Black/Hispanic (reference)). All models were adjusted for age, US Census divisions, and months of enrollment in Medicaid during 2012. Models for cervical cancer were adjusted for cervical HPV, and models for rectal and anal cancers were adjusted for any type of HPV. Models for All Other Cancers and All Cancers Combined were adjusted for the presence of any co-infection (HBV/HCV and/or HPV). Models for non-Hodgkin's and Hodgkin's lymphoma and breast cancer were not adjusted for co-infections. APRs: adjusted prevalence ratios; CI: confidence interval; WLWH: women living with HIV; HPV: human papillomavirus; HBV: hepatitis B virus; HCV: hepatitis C virus.

	Non-Hispanic White	**Non-Hispanic Black**	**Hispanic**	**All Others**
AIDS-defining cancers	APR (95%CI)	APR (95%CI)	APR (95%CI)	APR (95%CI)
Cervix	0.99 (0.82-1.18)	1.07 (0.93-1.24)	0.93 (0.76-1.15)	0.91 (0.70-1.20)
Non-Hodgkin's lymphoma	1.12 (0.71-1.78)	0.59 (0.41-0.86)	2.00 (1.30-3.07)	0.93 (0.47-1.84)
Kaposi's sarcoma	0.58 (0.27-1.21)	1.27 (0.77-2.08)	0.86 (0.44-1.68)	1.47 (0.70-3.10)
Non-AIDS-defining cancers				
Anus	0.98 (0.78-1.23)	0.78 (0.66-0.91)	1.42 (1.18-1.70)	0.99 (0.71-1.39)
Rectum	1.37 (0.91-2.06)	0.85 (0.61-1.19)	0.99 (0.63-1.56)	0.90 (0.47-1.72)
Hodgkin's Lymphoma	0.78 (0.60-1.02)	1.00 (0.82-1.21)	1.14 (0.88-1.47)	1.24 (0.91-1.69)
Breast	1.02 (0.83-1.26)	1.22 (1.04-1.43)	0.73 (0.58-0.92)	0.86 (0.63-1.17)
All Other Cancers	1.14 (0.96-1.35)	1.07 (0.93-1.22)	0.76 (0.63-0.93)	0.99 (0.78-1.27)
All cancer types	0.93 (0.85-1.02)	1.03 (0.96-1.11)	1.00 (0.92-1.10)	1.00 (0.92-1.10)

Chapter V

Figure 5.1: The illustration provides the insights into the implications and future directions for study. The syndemic effect of social needs and cancer burden is not fully understood. Future studies employing machine learning approaches to dissect this complex system could be the desired goal for achieving better health outcomes in HIV population.



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