DISPARITIES IN HOSPITALIZATION RATES AMONG PERSONS WITH HIV IN THE UNITED STATES AND CANADA BETWEEN 2005 AND 2015

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ABSTRACT

Thibaut Davy-Mendez: Disparities in Hospitalization Rates among Persons with HIV in the United States and Canada between 2005 and 2015
(Under the direction of Sonia Napravnik)

Increased antiretroviral therapy (ART) use with potent regimens has increased virologic suppression and life expectancy among persons with HIV (PWH) and might have affected hospitalization rates among different sub-groups of PWH. Among PWH in care in six clinical cohorts in the United States (US) and Canada 2005–2015, we examined (1) racial/ethnic and gender disparities in hospitalization rates, and (2) associations between CD4 cell count and hospitalizations across years of virologic suppression. We used Poisson regression models with robust variances to estimate incidence rate ratios (IRR).

Of 27,085 patients (122,566 person-years), 80% were cisgender men, 1% transgender, 43% White, 33% Black, 17% Hispanic, and 1% Indigenous. Unadjusted all-cause hospitalization rates were higher for Black (IRR 1.46, 95% CI 1.32-1.61) and Indigenous (1.99, 1.44-2.74) versus White cisgender men, and for Indigenous versus White cisgender women (2.55, 1.68-3.89). Unadjusted AIDS-related hospitalization rates were also higher for Black, Hispanic, and Indigenous versus White cisgender men (all $P<0.05$). Transgender patients had 1.50 times (1.05-2.14) and cisgender women 1.37 times (1.26-1.48) the unadjusted hospitalization rate of cisgender men. In adjusted analyses, among cisgender men and women, Black patients had higher rates of cardiovascular and renal/genitourinary hospitalizations compared to Whites (all $P<0.05$).

Among 6997 patients (19,980 person-years) with virologic suppression for at least a year, among those whose lowest pre-suppression CD4 count was <200 cells/μL (44%), patients

with a current CD4 count 200–350 versus >500 had an adjusted IRR of hospitalization of 1.44 during suppression years 2–5 (95% CI 1.01, 2.06), and 1.67 (1.03, 2.72) during years 6–11. Among patients whose lowest pre-suppression CD4 was ≥200 (56%), during suppression years 6–11, for patients whose current CD4 count 351–500 versus >500, the adjusted hospitalization IRR was 2.09 (1.18, 3.70).

Black, Indigenous, women, and transgender PWH in the US and Canada experienced substantially higher hospitalization rates than White patients and cisgender men. Contributors likely include differences in virologic suppression and chronic conditions (e.g. diabetes and renal disease). Among PWH on ART for up to 11 years, patients whose CD4 counts remained lower experienced higher hospitalization rates, even without a history of severe immunodeficiency.

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A journey of a thousand miles begins with a single step. This one began when I stepped into Maison d'Hérelle in Montreal, Quebec in 2011, with little more knowledge about HIV than what its letters stood for. I am grateful to Aurélie Bernard and the staff and residents of Maison d'Hérelle for the lessons in solidarity, selflessness, patience, and acceptance that I received as a volunteer.

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LIST OF ABBREVIATIONS

ACA	Patient Protection and Affordable Care Act
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
CCS	Clinical Classifications Software
ESLD	End-stage liver disease
ESRD	End-stage renal disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
MI	Myocardial infarction
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
PWH	Person(s) with HIV
US	United States

CHAPTER I: SPECIFIC AIMS

Clinical management of persons with HIV (PWH) has changed substantially in the past 25 years. The introduction of combination antiretroviral therapy (ART) in 1996 led to drastic decreases in AIDS morbidity and mortality in the United States (US) and Canada [1, 2]. ART initiation early in HIV infection, which prevents AIDS and non-AIDS morbidity and mortality, and the use of safer, more potent ART regimens, which has resulted in improvements in virologic suppression rates, together have contributed to further reductions in mortality [3-12]. Meanwhile, PWH in the US and Canada are aging, with almost half over 50 years of age, and experiencing an increasing burden of comorbidities [13-18].

Hospitalization rates among PWH also decreased with the introduction of ART [19, 20]. However, after 2000, evidence has been mixed as to whether hospitalization rates might be decreasing, plateauing, or even increasing for some causes, possibly due to cumulative exposure to HIV or ART [19-22]. Studies also showed a shift in hospitalization causes from AIDS-defining illnesses to non-AIDS infections and chronic conditions [19, 21]. It is not well-known how hospitalization rates may differ according to race, ethnicity, gender, and the extent of CD4 recovery after viral suppression.

Hospitalization rates might differ across subgroups of race, ethnicity, and gender because of disparities in timing of HIV diagnosis, engagement in care, virologic suppression, and incidence of comorbidities [6, 7, 14-17, 23-26]. Among patients with sustained virologic suppression, those with poor CD4 count recovery might have higher hospitalization rates due to late ART initiation or to end-organ damage from chronic inflammation and immune activation [27, 28]. Low CD4 counts prior to and during ART are associated with greater incidence of

comorbidities [8, 12, 29, 30]. Studies from the 2000s showed hospitalization rate differences across demographic and clinical characteristics [19, 21, 22]. Recent studies have suggested that disparities persist, but these have been limited to particular geographic areas or populations such as veterans [31-33]. In addition, few studies have focused on virologically suppressed PWH [34, 35]. Up-to-date evidence identifying patients at highest risk of hospitalization could inform clinical management strategies to prevent disease progression requiring inpatient care.

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a large consortium of HIV cohorts in North America [36]. Five US and one Canadian cohort have collected hospitalization records including discharge diagnoses for the period 2005–2015. In this study, we used NA-ACCORD data to investigate differences in hospitalization rates by gender, race/ethnicity, and CD4 count recovery. Specifically, we pursued the following aims.

Aim 1: Among PWH in care in the US and Canada, assess changes in racial/ethnic and gender disparities in all-cause and cause-specific hospitalization rates across calendar years 2005–2015. For all-cause hospitalizations, we estimated annual hospitalization rates and trends over time, stratified by race/ethnicity and gender. For all-cause hospitalizations and the ten most frequent diagnostic categories, we estimated incidence rate ratios (IRR) comparing rates between racial/ethnic groups, stratified by gender. The racial/ethnic groups examined were Black, White, Hispanic, Asian, Indigenous, and multiracial/other. Additionally, we compared hospitalization rates between cisgender men, cisgender women, and transgender patients. Poisson regression models with generalized estimating equations (GEE) and an independent correlation matrix were used to estimate calendar time trends and incidence rate ratios, accounting for patients contributing more than one hospitalization. We conducted both unadjusted analyses, and analyses adjusted for age, HIV risk factor, CD4 cell count, and HIV viral load.

Aim 2: Among PWH in the US and Canada on virologically suppressive ART, estimate the association between CD4 cell count and hospitalization rates. Among patients who were observed to become and remain virologically suppressed, we estimated all-cause hospitalization rates by current CD4 count, categorized as <200, 201–350, 351–500, and >500 copies/μL. To take into account past immunodeficiency and duration of suppression, we stratified analyses by lowest pre-suppression CD4 count <200 or ≥200 copies/μL, and by duration of suppression 1–4 or ≥5 years. We used Poisson regression models to estimate IRR comparing CD4 count categories, within each stratum.

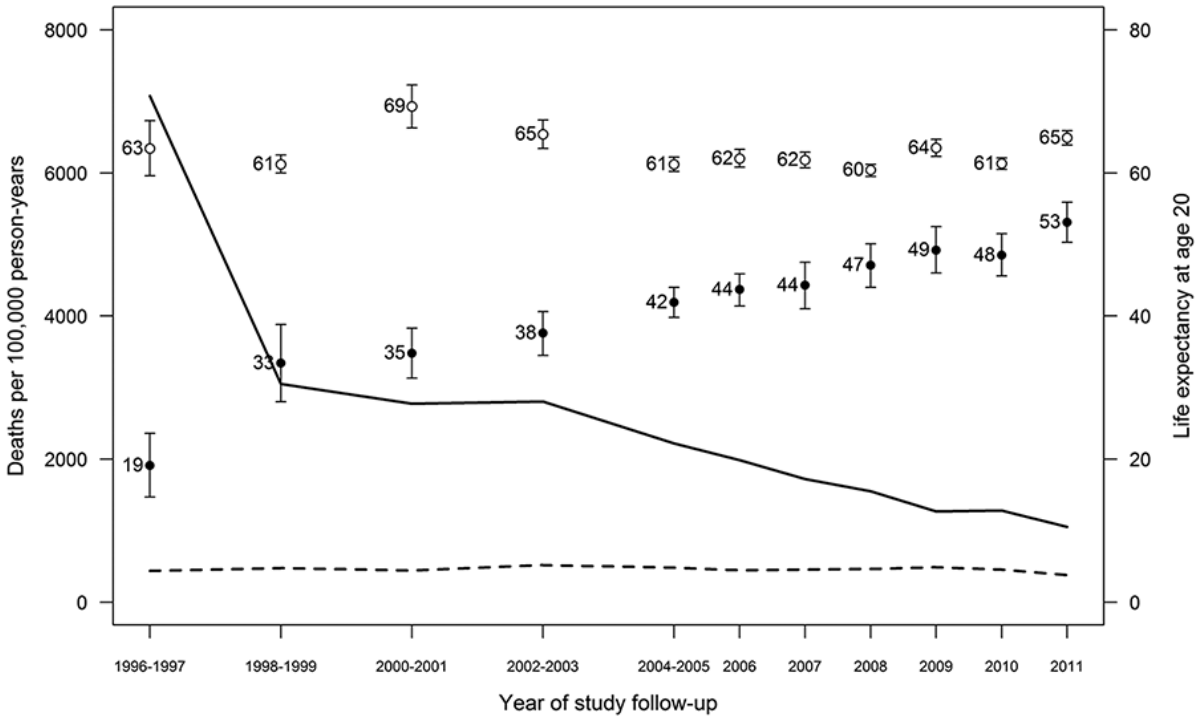
CHAPTER II: BACKGROUND

Mortality among persons with HIV (PWH)

The introduction of combination antiretroviral therapy (ART) in 1996 led to sharp decreases in mortality among PWH in the United States (US) and Canada, from 30 deaths per 100 person-years in 1995 to 10 deaths per 100 person-years in 1997 [1, 37]. With growing evidence of the benefits of earlier ART initiation, treatment guidelines progressively recommended ART at higher CD4 cell counts [38, 39]. In 2012, US treatment guidelines began recommending ART for all PWH irrespective of CD4 cell count [3]. Canadian treatment guidelines have been similar [4]. Guidelines changes led to increased ART use in the US and Canada, with associated improvements in viral suppression and CD4 cell counts [6, 7].

Earlier ART in HIV infection has been shown to decrease the risk of mortality and both AIDS and non-AIDS morbidity [8, 11, 40]. In consequence, PWH are living longer, healthier lives. Mortality rates among PWH in the US and Canada further decreased to 1–2 deaths per 100 person-years through the mid- to late 2000s [9, 10, 41]. Life expectancy for PWH is approaching that of HIV-negative persons, with an estimate of 50 additional years of life for a 20-year old PWH (Fig. 2.1), and half of the HIV population in the US is now over the age of 50 years [9, 10, 13]. In addition, studies have reported a changing burden in causes of death among PWH, notably a decrease in AIDS-related mortality and an increase in deaths due to non-AIDS cancers, liver disease, and cardiovascular disease [37, 41-43]. However, disparities in life expectancy persist, with lower estimates for Black PWH, those with low CD4 cell counts at ART initiation, and those with injection drug use (IDU) as an HIV transmission risk factor [9].

Figure 2.1. Age-adjusted mortality rates and life expectancy at age 20 for HIV-infected and HIV-uninfected individuals, Kaiser Permanente California, 1996–2011. Rates are represented by solid lines for HIV-infected and dotted lines for HIV-uninfected individuals ($P < 0.001$ and $P = 0.43$ for changes over time, respectively). Life expectancies at age 20 are represented by solid circles for HIV-infected and open circles for HIV-uninfected individuals. From Marcus et al. 2016 [9].

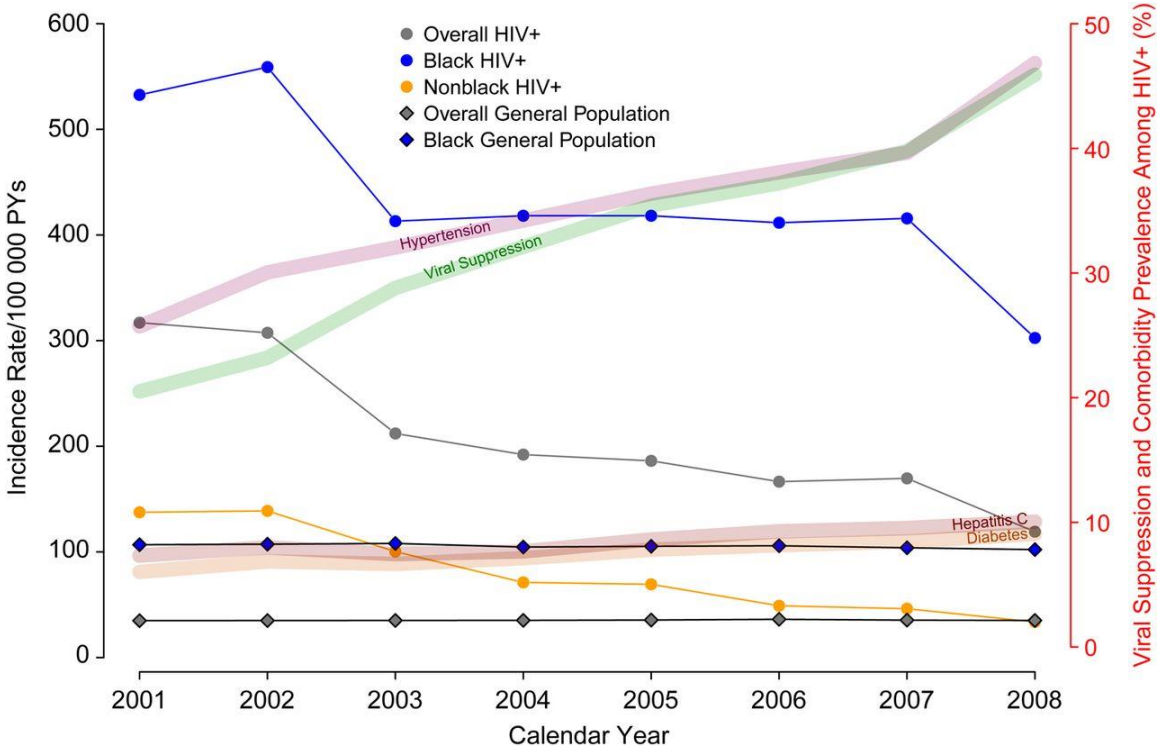


Morbidity among PWH

Reduced mortality, increased use of effective ART, and aging among PWH have led to a shift in the comorbid burden in this population. Improvements in viral suppression and CD4 cell counts after 1996 resulted in a decrease in the incidence of Kaposi sarcoma, non-Hodgkin's lymphoma, and end-stage renal disease (ESRD, Fig. 2.2) [15, 16]. However, incidence of anal, colorectal, and liver cancer has increased in PWH [15]. Lung cancer risk, while stable over time, is high among PWH, with an estimated 4% cumulative incidence by age 75 [15]. Incidence of end-stage liver disease (ESLD) has remained stable but high, especially among persons co-infected with hepatitis B virus (HBV) and hepatitis C virus (HCV) [17]. Importantly, conditions such as hypertension, diabetes mellitus, HCV infection, which are pre-cursors to more severe

conditions, have become more frequent, reaching prevalences of 50%, 10%, and 10% in 2008, respectively (Fig. 2.2) [16]. In parallel, the co-occurrence of morbidity, most commonly hypertension, hypercholesterolemia, and chronic kidney disease, has also increased, with 22% of PWH having more than one comorbidity in 2009 [44]. However, the role of increasing HCV prevalence in liver disease progression is likely to be mitigated by the introduction of direct-acting antiviral agents with high HCV cure rates in both trial and clinical settings, including among PWH [45, 46]. Notably, compared to people with HIV, PWH are at higher risk of myocardial infarction (MI), ESRD, and all types of cancers, including non-AIDS cancers [14-16, 44]. HIV-related risk factors, such as low CD4 counts, uncontrolled viremia, and history of AIDS, and non-HIV risk factors, such as smoking, have both been shown to contribute to morbidity among PWH [47].

Figure 2.2. Age- and sex-standardized incidence of end-stage renal disease among human immunodeficiency virus (HIV)-infected adults stratified by race and compared with age- and sex-standardized rates in the general population (US Renal Database System). Incidence rates are 3-year rolling averages. Abbreviation: PY, person-years. From Abraham et al. 2015 [16].



Comorbid burden is not identical in the entire HIV population. PWH who are Black have a higher incidence of ESRD and are at higher risk of developing hypertension, type 2 diabetes, and chronic kidney disease, which are risk factors for developing more severe morbidity [24]. Women are at higher risk of developing ESRD and type 2 diabetes compared to male PWH [16, 24]. In contrast, PWH who develop ESLD are more likely to be male and white [17]. Those with IDU as a risk factor, compared to men who have sex with men (MSM) or heterosexual transmission, are more likely to experience ESRD and ESLD [16, 17]. Having low CD4 cell counts prior to or during ART or having an unsuppressed viral load both lead to higher incidence of comorbid conditions, including ESRD, ESLD, MI, and several types of cancer [14, 16, 17, 30, 48]. Intuitively, older PWH are also at higher risk of developing severe comorbidities, as well as multimorbidity [14, 16, 17, 44]. These disparities in comorbidities by demographic and clinical characteristics are likely to play a role in the changes of hospitalization rates and causes within different subpopulations of PWH.

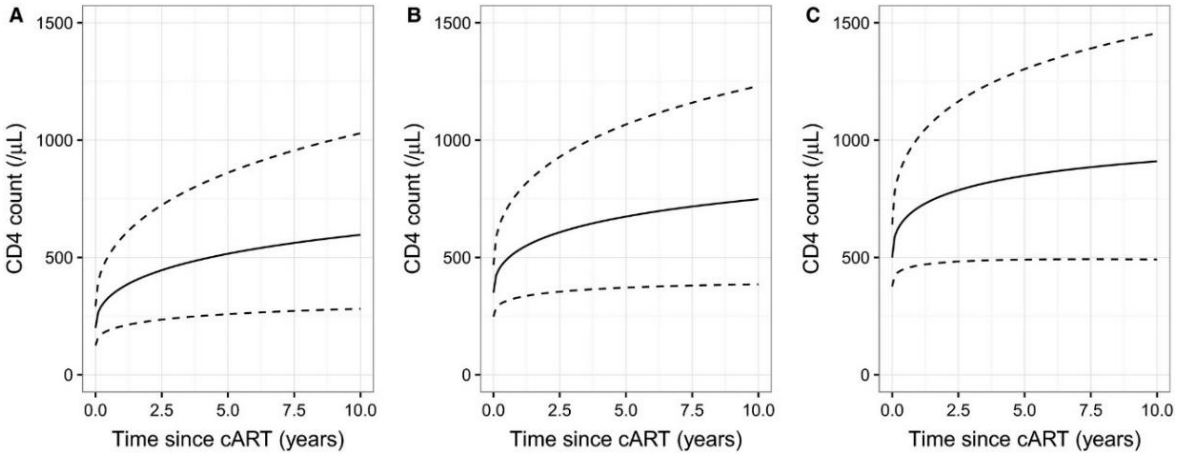
Immune recovery among PWH

Initiating ART at higher CD4 cell counts prevents AIDS, severe non-AIDS outcomes, and mortality [8, 11, 40]. For this reason, HIV treatment guidelines recommend universal ART early in HIV infection [49]. However, CD4 counts at HIV entry to care have not increased substantially over time, and about 25% of PWH continue be diagnosed late in HIV infection, with a low CD4 count or rapid progression to AIDS [25, 26, 50]. Black, Hispanic, and Indigenous PWH continue to experience delayed HIV diagnosis or entry to care compared to White PWH [26, 51-53].

CD4 count increases can occur slowly and have been measured up to 6–7 years after initiation of ART [54-56]. In one study following patients on ART for seven years, less than half of patients who initiated ART with CD4 count <500 cells/μL reached a CD4 count comparable to the HIV-negative population by the end of study [55]. The most important gains in CD4 count were observed in the first few years of ART [55]. Even among patients with CD4 counts >500 at

ART initiation, those who start treatment more than one year after HIV infection are less likely to experience complete CD4 recovery, with approximately 35% reaching CD4 >900 after four years of ART [27].

Figure 2.3. Plots of predicted median (continuous line) and 5th and 95th percentiles (dashed line) for recovery in CD4 counts following initiation of combination antiretroviral therapy (cART). Shown are patients initiating cART with a CD4 of 200 (A), 350 (B), and 500 (C) cells/μL. Adapted from Stirrup et al. 2018 [54]



More severe immunodeficiency at ART initiation leads to lower CD4 count recovery during virologic suppression (Fig. 2.3) and leads to chronic immune activation and inflammation [27, 54, 57, 58]. This immune dysfunction leads to tissue damage and contributes to the development of morbidity [28, 59]. Lower CD4 cell counts prior to and on ART are associated with higher incidence of morbidity, including AIDS-defining opportunistic infections, non-AIDS infections such as bacterial pneumonia, skin and soft tissue infections, and bacteremia, myocardial infarctions, end-stage renal disease, and cancers [8, 12, 16, 29, 30, 60-62].

Socioeconomic factors that lead to delayed HIV diagnosis and ART initiation might also contribute to the incidence of comorbidities among patients with poor CD4 recovery during virologic suppression [63, 64]. For example, patients living in poverty have higher rates of smoking and poor nutrition [47, 65]. In addition, poor insurance coverage can compromise the

management of comorbidities such as hypertension, even adjusting for virologic suppression [66].

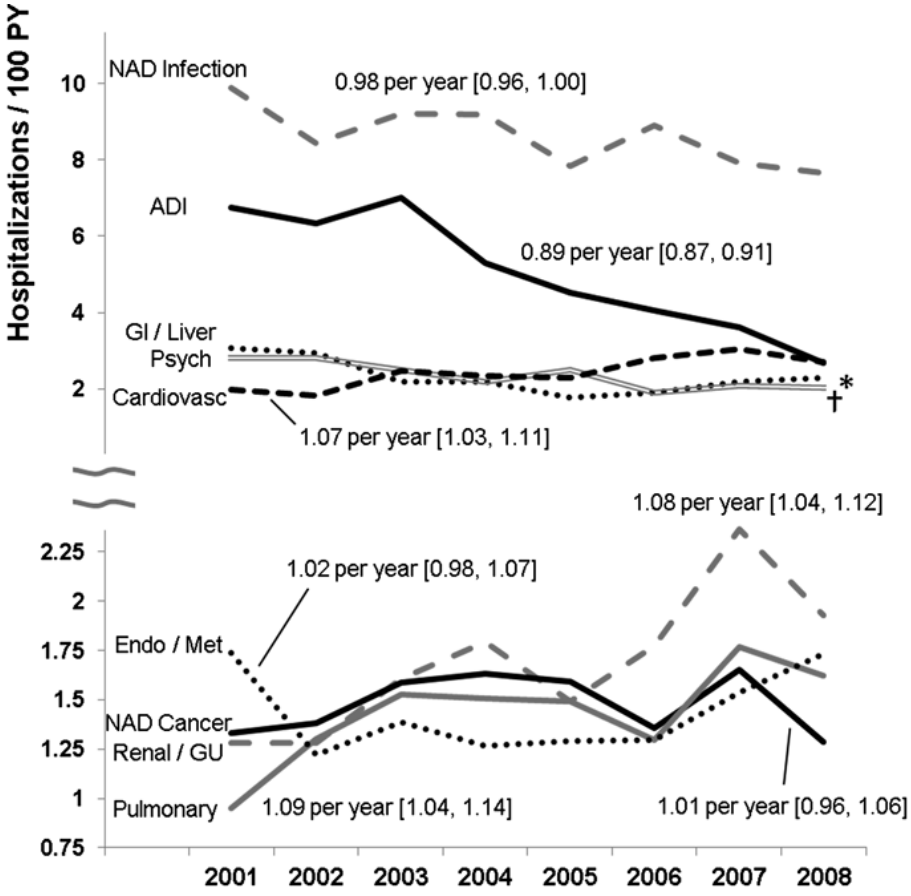
Hospitalizations among PWH

Rates of hospitalization among PWH in the US and Canada decreased sharply after the introduction of combination ART, though rate estimates vary substantially by region and population, ranging 15–40 admissions per 100 person-years around the year 2001 [19-22, 67, 68]. After 2000, studies have generally reported either a plateau or a continued decreased in hospitalization rates through the mid- to late 2000s, with estimates ranging 17–27 admissions per 100 persons-years around the year 2008 [19, 21, 22, 69]. Cause-specific hospitalization rates for AIDS-defining conditions and non-AIDS infections have also decreased over time, but some studies have found increasing rates for hospitalizations due to cardiovascular, renal, and pulmonary disease (Fig. 2.4) [19-21]. Among hospitalized patients, AIDS-defining conditions have made up a decreasing proportion of hospital discharge diagnoses, with increasing proportions due to non-AIDS infections, cardiovascular disease, renal disease, and liver/gastrointestinal disease [21, 70-72].

More recent evidence on hospitalization rates in North America is scarce. One study reported a hospitalization rate of 37 admissions per 100 person-years among PWH in New York City in 2013, with 20% due to non-AIDS infections [33]. One study in North Carolina found a persistent decrease in rates reaching 22 admissions per 100 person-years in 2016 [73]. Among veterans with HIV, rates have decreased through 2011 for hospitalizations due to any cause, AIDS-defining conditions, and non-AIDS infections, and increased for admissions due to cardiovascular and renal disease [32]. Outside of North America, an Italian study has reported all-cause hospitalization rates as low as 13 admissions per 100 person-years in 2013–2016, with decreasing rates for most causes [74]. Additional studies have focused on specific populations, such as perinatally infected individuals, elite controllers, and persons in the military

[34, 35, 75, 76]. One study focusing on PWH with CD4>350 did not report any changes in rates over the period 2005–2011 [35].

Figure 2.4. Unadjusted hospitalization rates by diagnostic categories. *GI/Liver, 0.96 (0.92, 1.00). †Psych, 0.96 (0.93, 1.00). NAD, non–AIDS-defining; GI, gastrointestinal; Psych, psychiatric; Cardiovasc, cardiovascular; Endo/Met, endocrine/metabolic/nutritional/immune; GU, genitourinary. Adapted from Berry et al. 2012 [21].



Disparities in hospitalization rates have been frequently reported. Black PWH, women, and older individuals have higher hospitalization risk, for all-cause admissions as well as specifically for non-AIDS infections, cardiovascular conditions, and renal/genitourinary conditions [19, 21, 22, 77]. Having IDU as a risk factor, compared to MSM or heterosexual transmission, is also associated with higher hospitalization rates [21, 35, 76]. In contrast, PWH with higher CD4 counts are less likely to be hospitalized across all causes of admission, and

having a suppressed viral load is associated with lower all-cause hospitalization, as well as hospitalizations for AIDS-defining illnesses, non-AIDS infections, and cardiovascular disease [19, 21, 22]. Several studies have previously reported higher hospitalization rates with CD4 counts below <500 cells/μL, often with progressively higher rates as CD4 counts decrease [19, 21, 22, 31, 35, 78]. However, few studies have examined CD4 counts among patients who are virologically suppressed, and these were limited by shorter follow-up or restricted to special populations, such as young members of the military [34, 76].

In the US, another factor that may have impacted hospitalization rates among PWH is the Patient Protection and Affordable Care Act (ACA), passed in 2010, which included several reforms related to hospitalization. The expansion of Medicaid eligibility in some states led to a drastic increase in Medicaid coverage among PWH from 23% to 38%, and a decrease in the proportion without insurance, from 28% to 13% [79]. The ACA promotes care coordination aiming to prevent hospital admission and readmission, and it instituted Medicare/Medicaid payment penalties for hospitals with excess readmissions [80]. Medicare and Medicaid together insure over half of PWH and reimburse approximately 70% of hospitalizations among PWH [69, 79, 81]. In addition, quality metrics developed by the Centers for Medicare and Medicaid Services (CMS) also impact health care practices for recipients of other insurance types [82]. The ACA is therefore likely to have affected hospitalization rates among PWH, with potential differences for Black PWH, women, and those with IDU risk factor, who are more likely to be uninsured or receiving Medicaid coverage [22, 79].

Summary

In the last 25 years, ART has been increasingly used and effective at achieving viral suppression, leading to decreases in mortality, hospitalization rates, AIDS morbidity, and some non-AIDS morbidity. However, the aging population of PWH experiences a high burden of comorbidities. These factors are likely to have impacted hospitalization rates. In addition,

disparities in morbidity between demographic groups and according to clinical history could lead to differences in hospitalization rates among PWH. In the US, changes in health policy might have affected health care access and efforts to prevent hospitalizations, but not equally among all groups of PWH. Yet little is known about hospitalizations among PWH in more recent years, including about causes of hospitalizations and rates in different patient subgroups. This dissertation work investigated whether, among PWH in care in the US and Canada between 2005 and 2015, disparities in all-cause and cause-specific hospitalization rates by race/ethnicity and gender continue to exist, and whether differences in CD4 cell count recovery on ART are associated with differences in hospitalization rates.

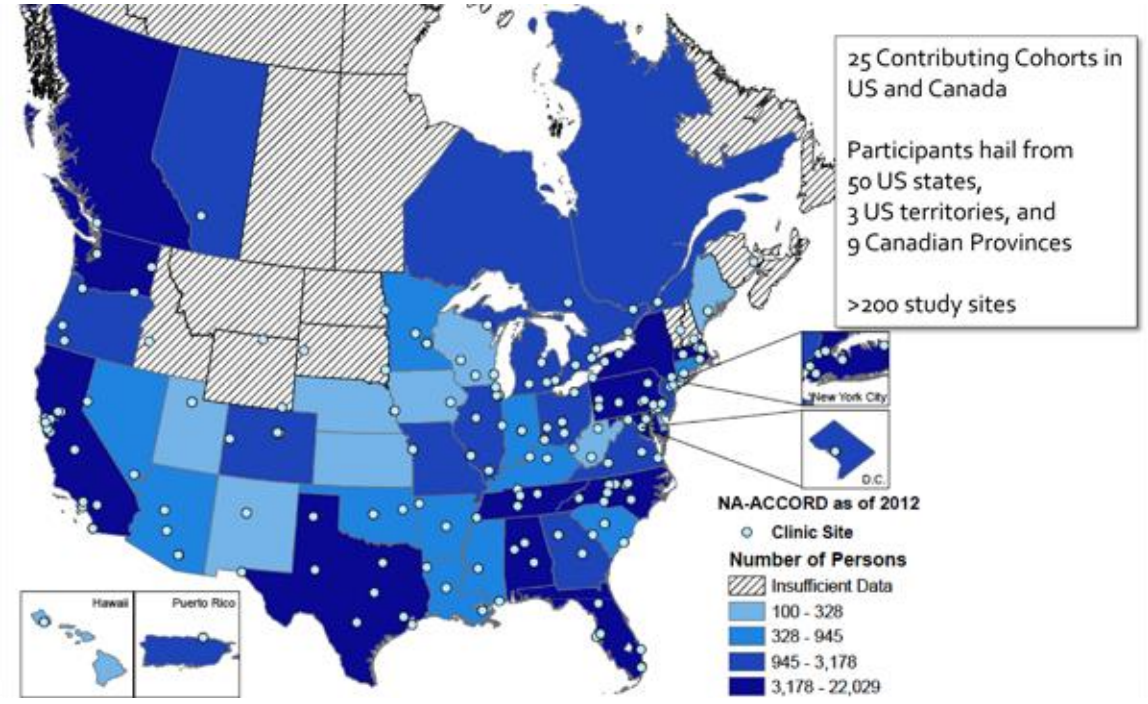
CHAPTER III: RESEARCH DESIGN AND METHODS

Study population

This dissertation work was based in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [36]. NA-ACCORD is part of the International epidemiologic Databases to Evaluate AIDS (IeDEA), a global consortium of data centers funded by the National Institutes of Health to collect and harmonize data on the HIV epidemic [83]. NA-ACCORD comprises 25 prospective clinical and interval cohorts of 190,000 persons with HIV (PWH) in the United States (US) and Canada, including over 200 separate study sites (Fig. 3.1). The granular data of these observational cohorts stem from a combination of electronic medical records, manual review and abstraction of medical information, protocol-adjudicated clinical endpoints, and linked records from state and national death indices. Collected variables include, with variability by site: demographic data, HIV risk factors, laboratory measurements (both HIV- and non-HIV-related), medication history (antiretroviral drugs as well as treatment for other conditions), drug resistance testing, diagnostic history, inpatient services utilization, and geocoded residence data [36, 84, 85].

Overall, participants in NA-ACCORD are approximately 30% women, 45% White, 45% Black, and 10% Hispanic, with a median age close to 50 years [36]. NA-ACCORD is representative of the population of PWH in the US and Canada [6, 13]. In addition, the Institute of Medicine has recognized the value of NA-ACCORD in assessing quality of care measures, including inpatient health care utilization, in the context of evaluating the National HIV/AIDS Strategy and the Patient Protection and Affordable Care Act [23, 86].

Figure 3.1. Map showing the location and contribution of sites participating in NA-ACCORD. From https://statepiaps7.jhsph.edu/naaccord/



This study was conducted in six NA-ACCORD clinical cohorts, five in the US and one in Canada, that have collected hospitalization data for the period 2005–2015, including hospital admission and discharge dates and International Classification of Diseases (ICD) codes for discharge diagnoses. Local institutional review boards (IRBs) approved data collection for each cohort, and the University of North Carolina IRB approved these secondary data analyses. Each cohort either obtained written, informed consent from cohort participants, or received a waiver of informed consent from their local IRB.

Hospitalization data

Data quality control

The NA-ACCORD Data Management Core (DMC) performs routine quality control of annual data submissions from participating cohorts. For this study, the DMC performed

additional quality control of hospitalization data by examining discharge diagnoses and crude annual hospitalization rates by cohort. The following exclusion criteria were applied:

- Cohorts considered to have substantial data completeness issues were excluded. This included cohorts with >50% annual hospitalization rate change and <1000 participants in care annually; cohorts with >40% annual rate change and 1000–2999 annual participants; cohorts with >30% annual rate change and >3000 annual participants; cohorts with an annual rate <5 per 100 person-years, irrespective of number of participants in care.
- Cohorts that did not capture ICD codes for hospital discharge diagnoses were excluded.
- Cohorts that recorded discharge diagnoses without a ranking order were excluded.

Hospitalizations with identical or overlapping dates were de-duplicated to keep only the hospitalization record with the longest duration. Hospitalizations with same-day discharge were not included as outcomes in any analyses. These are rare events, and for some cohorts these were indistinguishable from outpatient procedures, such as endoscopies.

Hospitalization diagnostic codes

For cause-specific analyses, we assigned the primary discharge diagnosis of hospitalization into diagnostic categories. We used the Clinical Classifications Software (CCS) to assign ICD, Ninth Revision, Clinical Modification (ICD-9-CM) codes into 19 categories. We modified the CCS to create separate category for AIDS-defining illnesses, using Centers for Disease Control and Prevention criteria, and to reassign all other infections from organ system categories to a “Non-AIDS-defining infection” category [21, 87, 88]. Using a previously validated approach, if HIV or Hepatitis C Virus infection was ranked as the top discharge diagnosis, the subsequent diagnosis code was assigned as the primary diagnosis [70]. For cohorts using ICD, Tenth Revision (ICD-10), we first converted codes to ICD-9 using General Equivalence

Mappings (GEMs) from the Centers for Medicare and Medicaid Services, with additional manual review by a physician [89]. In order to describe frequent diagnoses within each diagnostic category, a physician combined ICD-9-CM codes into meaningful groups, e.g. cellulitis/cutaneous abscess. Table 3.1 displays 10 common diagnostic categories and some representative diagnoses they include, adapted from a prior study using this algorithm [90].

For hospitalizations that had more than one ICD code ranked as the top discharge diagnosis, the cause of hospitalization was deemed missing, unless all top-ranked ICD codes were categorized similarly by the CCS program. Hospitalizations with missing causes were included in all-cause analyses but excluded from cause-specific analyses.

Other study variables

Mortality was captured from health records, death certificates, and state and national death indices. Sex, race/ethnicity, and year of birth were collected from electronic health records at cohort entry. Transgender status and HIV risk group were collected from cohort-specific processes including manual chart reviews. CD4 cell count and HIV viral load measurements were captured from electronic health records as they were performed.

Table 3.1. Diagnostic categories and representative diagnoses for hospital discharge diagnoses. Adapted from Berry et al. 2013 [90].

Diagnostic Category	Representative Diagnoses
Oncologic	Lymphoma, liver cancer, lung cancer
AIDS-defining illness	*Pneumocystis* pneumonia, recurrent bacterial pneumonia, candida esophagitis
Liver/gastrointestinal	Pancreatitis, non-infectious gastroenteritis, cirrhosis
Renal/genitourinary	Acute kidney injury, chronic kidney injury, nephrolithiasis
Endocrine/metabolic	Hypovolemia, diabetic ketoacidosis, hyponatremia
Pulmonary	Asthma, chronic obstructive pulmonary disease
Cardiovascular	Chest pain, congestive heart disease, coronary heart disease
Injury/poisoning	Stimulant overdose, vascular device complication, angioedema
Non-AIDS infection	Bacterial pneumonia, cellulitis, sepsis
Psychiatric	Major depression, alcohol withdrawal

Analysis

Aim 1

Patient inclusion and follow-up: We included patients in care at the six eligible cohorts between 2005 and 2015, defined as having at least one HIV RNA or CD4 cell count measurement in that period. Patients contributed person-time from either NA-ACCORD cohort entry or January 1, 2005, whichever occurred later, and until death, December 31, 2015, or loss to follow-up (LTFU), whichever occurred earlier. LTFU was defined as 12 months without an outpatient HIV RNA or CD4 cell count measurement in primary analyses. Patients who re-entered HIV care could contribute additional person-time. Days spent in the hospital were not counted as person-time at risk. Person-time was then divided into calendar years for analysis, allowing patients to contribute partially to a calendar year.

Study measures: The variables included in this analysis were gender, race/ethnicity, injection drug use (IDU) as HIV risk factor, and time-updated age, CD4 count, and HIV viral load (VL). Age was categorized as <40, 41–50, 51–60, and >60 years. CD4 count was categorized as <50, 51–200, 201–350, 351–500, and >500 cells/μL. VL was dichotomized as <400 or ≥ copies/mL, as that was the lowest level of quantification used by some assays in the study period. Patients missing race/ethnicity were excluded. Person-years missing CD4 count or VL were included in unadjusted analyses but excluded in adjusted analyses.

Statistical analysis: We calculated and plotted annual all-cause hospitalization rates stratified by gender and race/ethnicity. We then plotted rates standardized to the age, CD4 count, and VL distribution of the entire sample in 2010, adjusting for both changes over time period and differences between groups. For all-cause hospitalizations, we used Poisson regression models to estimate calendar time trends in rates stratified by race/ethnicity and gender, using year as a linear variable. For all-cause hospitalizations and the ten most frequent diagnostic categories, we used Poisson regression models to estimate incidence rate ratios (IRRs) comparing racial/ethnic groups, stratified by gender. Generalized estimating equations

with an independent correlation matrix were used in all models to account for patients contributing to more than one hospitalization to analysis. Unadjusted models included only NA-ACCORD cohort as a covariate. Adjusted models also included age, IDU risk factor, CD4 count, and VL. SAS software version 9.4 (SAS Inc., Cary, NC) was used for all analyses. *P* values were two-sided.

Aim 2

Patient inclusion and follow-up: We included patients who entered NA-ACCORD with a VL >1000 copies/mL and were observed to have a first virologic suppression between 2005 and 2014, defined as two consecutive VL <400 copies/mL at least 30 days apart within 12 months. We excluded patients if they had any VL ≥400 copies/mL or died before experiencing a complete year of virologic suppression, and patients with no CD4 count prior to suppression.

To avoid including immortal person-time, the person-time for analysis began one year after the start of virologic suppression. Person-time was then censored at death, loss to follow-up, virologic failure, or December 31, 2015, whichever occurred first. Loss to follow-up was defined as 12 months without an outpatient CD4 count or VL. Virologic failure was defined as the first of two VL ≥400 copies/mL at least two weeks apart within 90 days, or one VL ≥400 copies/mL with no confirmatory VL in the next 90 days. Person-time was then divided into six-month time intervals from the start of virologic suppression.

CD4 cell count: We categorized CD4 cell count as <200, 201–350, 351–500, or >500 cells/μL. We used fewer categories in this Aim's analyses as CD4 counts <50 cells/μL in patients with sustained suppression were very rare. To account for individual variability in CD4 counts [91], for each six-month time interval, for each patient, we calculated a weighted moving average of up to three CD4 outpatient counts measured at least 30 days apart in the prior 24 months. We excluded CD4 counts measured during a known hospitalization to avoid capturing immune changes related to acute illness. We restricted averages to CD4 counts measured at

least 30 days apart to avoid overweighing CD4 counts measured closely together. We restricted each moving average to three measurements to limit variability in CD4 count frequency. Without this restriction, each moving average calculation would have used a median of five CD4 count measurements (interquartile range 4, 7; range 1, 18). We excluded person-years in time intervals that did not have any CD4 count measured in the prior 24 months.

Statistical analysis: We estimated hospitalization rates by current CD4 count category. Analyses were stratified by lowest CD4 count prior to the start of suppression <200 or ≥200 cells/μL, and by early suppression (Years 2–5) versus long-term suppression (Years 6–11). This approach allowed us to compare patients according to their CD4 cell count trajectories over the duration of suppression. For example, among patients with severe immunodeficiency, i.e. a lowest pre-suppression CD4 count <200 cells/μL, we could compare patients who during years of suppression 6–11 had a CD4 count 351–500 versus >500 cells/μL.

We used Poisson regression models to estimate IRR comparing CD4 count categories within each strata, excluding strata with less than 100 person-years. Unadjusted models included only NA-ACCORD cohort as a covariate. Adjusted models also included age, gender, calendar year, and duration of virologic suppression. Age, calendar year, and duration of virologic suppression were updated for each six-month time interval and included in models as continuous variables. Parametrization approaches such as use of splines were examined. SAS software version 9.4 (SAS Inc., Cary, NC) was used for all analyses. *P* values were two-sided.

Sensitivity analyses: We examined the impact of censoring patients if they experienced non-HIV-related immunosuppression, defined as a hospitalization for chemotherapy, identified using ICD-9-CM codes, or a persistent decline in CD4 count while on ART. CD4 decline was defined as the first of two consecutive declines ≥15% in an unweighted moving average of up to three CD4 outpatient counts measured at least 30 days apart in the prior 24 months [92]. In another sensitivity analysis, we allowed patients to contribute only one hospitalization per six-month interval, to account for the possible impact of patients who were repeatedly hospitalized.

CHAPTER IV: RACIAL, ETHNIC, AND GENDER DISPARITIES IN HOSPITALIZATION RATES AMONG PERSONS WITH HIV IN THE UNITED STATES AND CANADA, 2005–2015

Introduction

Effective combination antiretroviral therapy (ART) use has decreased AIDS-related morbidity, mortality, and hospitalizations among persons with HIV (PWH) in the United States (US) and Canada [1, 19, 20, 37]. Despite these improvements, disparities in hospitalization rates emerged between different sub-populations of PWH. Studies showed that, through the mid-2000s, women and Black PWH continued to be hospitalized 30–40% more frequently than men and White PWH, respectively, overall and for hospitalizations due to non-AIDS-defining infections, cardiovascular, and renal conditions [19, 21, 22].

Changes in HIV care in the last decade might have affected gender, racial, and ethnic disparities in hospitalization rates. PWH are now diagnosed and initiate ART earlier in HIV infection, and are more likely to be virologically suppressed, partly due to more effective ART, with notable reductions in morbidity and mortality [7, 8]. Yet Black, Hispanic, and Indigenous (including Native American, Alaska Native, and Aboriginal individuals) PWH still frequently enter HIV care with a CD4 count <350 cells/μL or an AIDS-defining illness [26, 51, 53]. Women, Black, and Indigenous PWH are more likely to experience viral rebound or unsuppressed viral loads [7, 93], and Black and Indigenous PWH experience worse retention in HIV care [23, 94]. Uncontrolled viremia and resulting immunocompromised status put these patients at continued risk of AIDS and non-AIDS morbidity.

Non-HIV clinical characteristics might have affected hospitalization disparities as well. Rates of end-stage renal disease among PWH have decreased since 2000, but women and Black PWH have substantially higher rates than men and White PWH, respectively [16]. Black

PWH are at higher risk of developing hypertension and type 2 diabetes mellitus, risk factors for cardiovascular events [24]. Women are at higher risk of developing type 2 diabetes mellitus compared to men with HIV [24]. In contrast, PWH who develop end-stage liver disease are more likely to be men and White [17].

It is not known how these trends have affected racial, ethnic, and gender differences in hospitalizations among PWH in the US and Canada, though some studies suggest that disparities persist [31, 33, 95]. In addition, there is sparse evidence on hospitalization rates among smaller sub-groups of PWH, such as Asian, Hispanic, Indigenous, and transgender individuals. Therefore, we aimed to describe hospitalization rates stratified by racial, ethnic, and gender groups among PWH in clinical care between 2005 and 2015 in the US and Canada.

Methods

Study population and follow-up

This study was based in six clinical cohorts (five in the US, one in Canada) in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) that collect data on hospitalizations including International Classification of Disease (ICD) codes for discharge diagnoses [36]. This secondary data analysis was approved by the University of North Carolina Institutional Review Board. Patients aged ≥18 years contributed person-time at risk from cohort entry or 1 January 2005, whichever occurred later, and until death or 31 December 2015, whichever occurred first. Person-time was censored at loss to follow-up (LTFU), defined as 12 months with no outpatient CD4 count or HIV viral load (VL) measurement, but patients who re-entered HIV care, defined as an outpatient CD4 count or VL, contributed additional person-time. A sensitivity analysis used 18 months to define LTFU. Inpatient days were not counted as person-time.

Study measures

Annual hospitalization rates were calculated as the number of hospitalizations divided by the person-time in a calendar year, allowing more than one hospitalization per patient. Hospitalizations with same-day discharge were not counted as outcomes, as these are rare events and could not be distinguished from outpatient procedures (e.g. endoscopies). We used modified Clinical Classifications Software to categorize International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes for the primary discharge diagnosis [21, 87]. Using a validated approach, if the top-ranked diagnosis was HIV or chronic hepatitis C infection, we used the next diagnosis [77]. ICD, Tenth Revision codes (11% of hospitalizations) were converted to ICD-9-CM. Primary analyses examined all-cause hospitalizations, and secondary analyses examined cause-specific hospitalizations for the ten most frequent categories.

Race, ethnicity, and gender were combined into a composite variable. Transgender patients were identified from locally collected data (n=149), or as individuals with female birth sex reported as being men who have sex with men (MSM) [n=8]. We did not have data on whether transgender patients identified as transfeminine, transmasculine, or non-binary. Because of small numbers, we examined transgender patients in a secondary analysis comparing gender groups. We excluded 972 patients with unknown race and ethnicity.

Covariates included NA-ACCORD cohort, calendar year, injection drug use (IDU) as HIV acquisition risk factor, and annually-updated age, CD4 count, and VL. Categories were created for age (<40, 40–49, 50–59, ≥60 years), CD4 count (<50, 50–200, 201–350, 351–500, >500 cells/μL), and VL (<400, ≥400 copies/mL; the lowest assay quantification limit used during the study period). For each calendar year, we used the earliest CD4 count and VL measurement. If none was available, we used the earliest measurement in the last six months of the previous year or first six months of the following year.

Statistical analysis

We examined trends in clinical covariates by plotting the proportion of patients with a VL<400 copies/mL and the median CD4 count across calendar years, stratified by race, ethnicity, and gender. For all-cause hospitalizations, we plotted unadjusted and standardized annual rates, stratified by race, ethnicity, and gender. Rates were standardized to the entire sample's distribution of covariates in 2010, adjusting for changes over time and differences between groups.

We estimated incidence rate ratios (IRR) using Poisson regression models with generalized estimating equations with an independent correlation matrix to account for patients contributing more than one hospitalization. We fit separate models to estimate calendar time trends stratified by race, ethnicity, and gender, and to compare rates between racial and ethnic groups stratified by gender. Unadjusted models included only NA-ACCORD cohort as a covariate. Adjusted models included all covariates. IRR for trends were reported as a mean percentage change, e.g. an IRR of 0.95 per one-year increase was reported as a -5% annual rate change. Because of small group sizes, we did not estimate trends and annual rates for Asian, Indigenous, and multiracial/other cisgender women, or for transgender patients. *P* values were two-sided. Analyses were conducted in SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Study sample

The 27,085 included patients contributed 122,566 person-years of follow-up and were 80% cisgender men, 19% cisgender women, and 1% transgender adults. Patients were 43% White, 33% Black, 17% Hispanic of any race, 4% Asian, 1% Indigenous, and 2% multiracial/other. Gender distribution differed by race and ethnicity, with 8% of White and 35% of Black patients being cisgender women (Table 4.1). Twenty-eight percent of Indigenous patients were enrolled in a US-based cohort, whereas 88–99% of the other groups were enrolled in a

US-based cohort. White patients had higher CD4 counts at cohort entry than other groups (median 425 vs 350–396 cells/μL). Among cisgender men, cisgender women, and transgender patients, respectively, 13, 15, and 18% had a history of IDU, and the median CD4 count at cohort entry was 389, 374, and 369 (not shown). From 2005 to 2015, the proportion of patients with VL<400 copies/mL and median CD4 counts increased in all groups (Figure 4.2).

Of 21,036 included hospitalizations, the most frequent diagnostic category was non-AIDS-defining infection (25%) followed by cardiovascular (10%) [Table 4.5]. Stratified by race, ethnicity, and gender (Tables 4.6 and 4.7), non-AIDS-defining infection was the most common category across all groups. The second most frequent category was psychiatric for Black and multiracial/other cisgender women, and pregnancy for Asian and Indigenous cisgender women.

All-cause hospitalization rates over time

Among all patients, unadjusted all-cause hospitalization rates per 100 person-years were 22.6 in 2005 (95% confidence interval [CI] 20.9-24.4) and 13.2 in 2015 (95% CI 12.3-14.2). Annual unadjusted rates were generally lowest among White and Asian cisgender men and highest among Black and Hispanic cisgender women (Fig. 4.1A–B). Unadjusted all-cause rates decreased for most groups over time, with a mean annual change of -3% (95% CI -4, -2) for White cisgender men, -6% (95% CI -7, -4) for Black cisgender men, -7% (95% CI -10, -3) for White cisgender women, and -5% (95% CI -7, -3) for Black cisgender women (Table 4.2). In 2015, unadjusted hospitalization rates per 100 person-years were 11.7 for White cisgender men (95% CI 10.4-13.2), 15.5 (95% CI 13.3-18.0) for Black cisgender men, 13.5 (95% CI 9.7-18.8) for White cisgender women, and 18.4 (95% CI 15.4-22.1) for Black cisgender women (Table 4.8). The 2015 unadjusted rates per 100 person-years among all cisgender men and women were 12.2 (95% CI 11.3-13.3) and 17.2 (95% CI 15.0-19.8), respectively. Standardized rates appeared stable over time in each racial, ethnic, and gender group (Fig. 4.1C–D). In adjusted models, there was no significant decrease in rates in any group (Table 4.2). Over the entire

study period, unadjusted hospitalizations rates were 24.7 per 100 person-years (95% CI 18.0-33.8) for Indigenous cisgender men, 42.0 (95% CI 29.7-59.3) for Indigenous cisgender women, and 24.8 (95% CI 17.4-35.5) for transgender patients.

Hospitalization rates by gender, race, and ethnicity

In unadjusted analyses, Black cisgender men had 1.46 times (95% CI 1.32-1.61) and Indigenous cisgender men 1.99 times (95% CI 1.44-2.74) the all-cause hospitalization rates of White cisgender men (Table 4.2). All-cause hospitalization rates were lower for Asian compared to White cisgender men, with an unadjusted IRR of 0.62 (95% CI 0.50-0.75). There was no association between rates and Hispanic ethnicity or multiracial/other race. Estimates were similar in adjusted models. Indigenous cisgender women experienced 2.55 times (95% CI 1.68-3.89) the all-cause hospitalization rate of White cisgender women in unadjusted analyses, and 1.82 times (95% CI 1.27-2.59) in adjusted analyses. Cisgender women in the remaining race and ethnicity groups did not have different hospitalization rates compared to White cisgender women, in unadjusted or adjusted analyses. Using 18 months to define LTFU, IRR estimates were similar to the main findings (Table 4.9).

When examining cause-specific hospitalizations, in unadjusted analyses (Table 4.3), Black patients had higher rates for cardiovascular hospitalizations, with an IRR of 1.58 (95% CI 1.23-2.01) comparing Black to White cisgender men, and a similar estimate among cisgender women. Black cisgender men also had higher hospitalization rates than White cisgender men for renal/genitourinary and endocrine/metabolic conditions, with IRRs of 3.35 (95% CI 2.66-4.21) and 2.02 (95% CI 1.51-2.70), respectively for each category. Compared to White cisgender men, hospitalization rates for AIDS-defining illness (ADI) were higher for Black, Hispanic, and Indigenous cisgender men. For most categories, hospitalization rates were lower for Asian compared to White cisgender men. Among cisgender women, Black and Hispanic patients had approximately twice the rate of White patients in the category of neoplasms

excluding AIDS-defining cancer. In adjusted analyses (Table 4.4), hospitalization rates for ADI did not differ by race or ethnicity for cisgender men or women, while IRR for other categories were similar to unadjusted estimates.

In analyses comparing gender groups (Table 4.10), cisgender women had higher rates compared to cisgender men for all-cause hospitalization and several diagnostic categories including non-AIDS-defining infection, in both unadjusted and adjusted analyses. In addition, transgender patients had 1.50 times (95% CI 1.05-2.14) the rate of cisgender men for all-cause hospitalizations, and 2.51 times (95% CI 1.35-4.66) for ADI in unadjusted analyses, with similar adjusted estimates.

Discussion

Among US and Canadian PWH in care 2005–2015, unadjusted all-cause hospitalization rates decreased for most racial, ethnic, and gender groups and were highest among Black cisgender women. In adjusted analyses, Black and Indigenous cisgender men were approximately 1.5 times more likely to be hospitalized than White cisgender men, and transgender patients 1.4 times more likely than cisgender men. Indigenous cisgender women had 1.8 times the adjusted rate of White cisgender women. Adjusted rates were lower for Asian than White cisgender men. In cause-specific analyses, unadjusted hospitalization rates for ADI were higher for Black, Hispanic, and Indigenous versus White cisgender men, and for transgender patients versus cisgender men. Black cisgender men and women also experienced higher adjusted rates than White counterparts for cardiovascular and renal/genitourinary conditions.

Our findings extend prior studies from the mid-2000s showing higher hospitalization rates among Black PWH and women for all-cause admissions, non-AIDS-defining infections, cardiovascular conditions, and renal/genitourinary conditions [19, 21, 22]. More recently, studies in Illinois, North Carolina, and New York City also reported higher hospitalization rates for

women compared to men and Black compared to White PWH [31, 33, 95]. A previous NA-ACCORD analysis found a small decrease in adjusted rates over time overall [96]. In this study, there was no change in adjusted rates stratified by race, ethnicity, and gender, possibly from reduced sample size when examining individual groups.

Differences in HIV treatment outcomes likely contributed to the hospitalization disparities we observed. Prior studies have shown that women and transgender patients, compared to men, and Black and Indigenous PWH, compared to White PWH, are more likely to experience unsuppressed viral loads or viral rebound [7, 93, 97]. HIV care interruptions occur more frequently among Black and Indigenous than White PWH [23, 94]. Although earlier initiation of ART can prevent AIDS and non-AIDS morbidity, Black, Hispanic, and Indigenous PWH continue to experience delayed HIV diagnosis or entry to care compared to White PWH, with a low CD4 count or an ADI diagnosis [8, 26, 51-53]. Ongoing viral replication and severe immunodeficiency also contribute to end-organ damage, immune dysregulation, and inflammation, which can lead to further non-AIDS morbidity, including myocardial infarction and HIV-associated nephropathy [30, 98]. In our study, while median CD4 counts and viral suppression rates increased for all patients, they were lowest for Black and Hispanic cisgender women. These clinical differences can therefore partly explain the higher unadjusted hospitalization rates experienced by some racial, ethnic, and gender groups, for all-cause but also ADI and other hospitalization causes.

Adjusting for CD4 count and VL, some hospitalization differences by racial, ethnic, and gender groups persisted. One potential explanation is the differences in chronic conditions and risk factors for morbidity between these groups in this region. Rates of type 2 diabetes and chronic kidney disease are higher among women than men, and Black than White PWH [16, 24]. Hypertension rates are higher among Black than White PWH [16, 24]. Hispanic PWH are also more likely than non-Hispanic White PWH to have cardiovascular conditions, hypertension, and diabetes [99]. These comorbidities put patients at risk of developing cardiovascular, renal, and endocrine/metabolic complications and might have contributed to higher hospitalization

rates in these categories and overall. In addition, PWH with IDU as an HIV risk factor, as opposed to sexual transmission, are more likely to develop end-stage renal and liver diseases, partly due to hepatitis C virus co-infection [16, 17]. Ongoing IDU can also cause non-AIDS-defining infections, including sepsis/bacteremia and cellulitis/cutaneous abscesses. Over 30% of indigenous patients in our study had IDU history and potentially ongoing use, which might explain higher rates for hospitalizations for liver/gastrointestinal conditions and non-AIDS-defining infections. Obesity might also have contributed to hospitalization differences, as it is more common among women, Black, and Hispanic PWH and is a risk factor for cellulitis/cutaneous abscesses and progression of infections to sepsis [99, 100].

In addition to differences in HIV care outcomes and chronic conditions, unmet social needs might contribute to disparities in hospitalization rates. Out-of-pocket health expenses, difficulty finding transportation to clinic, or lapses in insurance coverage can prevent PWH from accessing both HIV and non-HIV care [101, 102]. Caregivers, frequently women, might be unable to seek outpatient care for themselves because of their care responsibilities to others [103]. Vulnerable populations, such as people who use drugs and Indigenous, transgender, and immigrant PWH, might delay accessing care because of discrimination or stigma [104-108]. Other barriers, including mental illness, homelessness, and food insecurity, have been associated with poorer health outcomes among PWH and could lead to more frequent hospitalizations [109, 110]. Some PWH might also lack a support network to assist with outpatient management of illness, requiring inpatient admission. Efforts should continue to be made to provide safe environments and culturally competent care, as well as resources to mitigate structural factors leading to poorer health outcomes. For example, interventions providing medication-assisted treatment for opioid use disorder in an HIV clinic and culturally competent care to Hispanic PWH can improve visit attendance [111, 112].

This study's strengths include 11 years of data on longitudinal HIV care and hospitalizations from six cohorts across the US and Canada. The study period includes

important changes in HIV care, such as expansion of ART to all PWH and the introduction of integrase inhibitors, and provides the most recent evidence on racial, ethnic, and gender hospitalization disparities among PWH in this region. Patients in this study were engaged in HIV care, therefore our findings may not be generalizable to all PWH. Nonetheless, our study sample included a racially diverse population, in different geographic areas, receiving care coverage through integrated health systems, private insurers, US Medicaid and Medicare, and Canadian provincial health systems.

To our knowledge, this is the first large study to report that Indigenous and transgender PWH bear a particularly high burden of hospitalizations. However, it is likely that not all transgender patients in our sample were identified, and we were not able to examine transgender men, women, and non-binary individuals separately. In addition, race and ethnicity do not fully capture the lived experiences of PWH, especially across different parts of the US and Canada. We did not capture data on immigration status, which could lead to heterogeneity in health outcomes within a racial or ethnic group. Data on important barriers to care and hospitalization risk factors, such as socioeconomic status and mental health disorders were not available in this study. Future studies should continue to examine drivers of racial, ethnic, and gender disparities in hospitalizations among PWH and evaluate interventions addressing them.

Overall, hospitalization rates decreased among PWH between 2005 and 2015, but several groups remain at higher risk of hospitalization, including cisgender women and Black and Indigenous patients. These disparities persist for all-cause hospitalizations as well as hospitalizations for several causes including ADI, non-AIDS-defining infections, cardiovascular, and renal/genitourinary conditions. Efforts to reduce hospitalization rates and disparities among PWH should focus on identifying and addressing medical and socioeconomic conditions that drive disparately high rates.

Tables

Table 4.1. Characteristics of 27,085 patients in care in six NA-ACCORD cohorts between 2005 and 2015, stratified by race/ethnicity.

Characteristic	White N=11,526	Black N=8947	Hispanic, any race N=4611	Asian N=1052	Indigenous N=320	Multiracial or other N=629
	No. (%) or median (IQR)	No. (%) or median (IQR)	No. (%) or median (IQR)	No. (%) or median (IQR)	No. (%) or median (IQR)	No. (%) or median (IQR)
Gender						
Cisgender men	10,507 (91%)	5803 (65%)	3786 (82%)	925 (88%)	225 (70%)	515 (82%)
Cisgender women	975 (8%)	3095 (35%)	782 (17%)	115 (11%)	91 (28%)	109 (17%)
Transgender [a]	44 (<1%)	49 (<1%)	43 (1%)	12 (1%)	4 (1%)	5 (<1%)
HIV acquisition risk factor						
MSM	7942 (69%)	2556 (29%)	2530 (55%)	722 (69%)	90 (28%)	362 (58%)
IDU	1506 (13%)	1450 (16%)	449 (10%)	52 (5%)	114 (36%)	45 (7%)
Heterosexual or other	2078 (18%)	4941 (55%)	1632 (35%)	278 (26%)	116 (36%)	222 (35%)
Enrolled in a United States based cohort	10,119 (88%)	8395 (94%)	4543 (99%)	925 (88%)	91 (28%)	602 (96%)
Age at study start, years	42 (35, 50)	41 (32, 48)	39 (32, 47)	37 (31, 44)	36 (30, 43)	38 (30, 46)
CD4 count at cohort entry, [b] cells/μl	425 (233, 628)	350 (158, 548)	372 (184, 573)	372 (210, 550)	307 (177, 510)	396 (231, 607)

Abbreviations: IDU, injection drug use; MSM, men who have sex with men; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

[a] Includes 149 patients identified either from locally collected data, and 8 patients having female birth sex and MSM as HIV risk factor.

[b] CD4 count at enrollment was the closest measurement a year before and 30 days after enrollment date and was missing for 2334 patients.

Table 4.2. Annual percentage change in rates and incidence rate ratios for all-cause hospitalizations, stratified by gender, among 26,928 cisgender patients in HIV care in six NA-ACCORD cohorts between 2005 and 2015.

Gender [a] & Race/ethnicity	Annual Percentage Change (95% CI)		Incidence Rate Ratio (95% CI)	
	Unadjusted [b]	Adjusted [c]	Unadjusted [d]	Adjusted [e]
Cisgender men				
White	-3 (-4, -2)	-1 (-2, 1)	1 (ref.)	1 (ref.)
Black	-6 (-7, -4)	-2 (-4, 0)	1.46 (1.32, 1.61)	1.27 (1.14, 1.41)
Hispanic, any race	-5 (-7, -3)	-2 (-4, 1)	1.01 (0.90, 1.13)	0.98 (0.87, 1.10)
Asian	-2 (-8, 4)	0 (-6, 7)	0.62 (0.50, 0.75)	0.64 (0.53, 0.78)
Indigenous	1 (-7, 9)	4 (-5, 14)	1.99 (1.44, 2.74)	1.62 (1.18, 2.22)
Multiracial or other	4 (-3, 11)	6 (-1, 14)	0.82 (0.53, 1.28)	0.88 (0.57, 1.38)
Cisgender women				
White	-7 (-10, -3)	-2 (-6, 2)	1 (ref.)	1 (ref.)
Black	-5 (-7, -3)	-2 (-5, 0)	1.13 (0.94, 1.35)	1.15 (0.97, 1.37)
Hispanic, any race	-5 (-8, -1)	-2 (-6, 2)	1.10 (0.88, 1.38)	1.11 (0.89, 1.38)
Asian [f]			0.68 (0.43, 1.08)	0.74 (0.47, 1.15)
Indigenous [f]			2.55 (1.68, 3.89)	1.88 (1.31, 2.68)
Multiracial or other [f]			0.70 (0.35, 1.39)	0.80 (0.41, 1.56)

Abbreviations: CI, confidence interval; IDU, injection drug use; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; ref., referent.

[a] Transgender patients were identified from locally collected data or as individuals with reported female sex and being men who have sex with men.

[b] Estimates and 95% confidence intervals from separate Poisson regression models with generalized estimating equations to account for patients contributing more than one hospitalization to the analysis. Models are adjusted for NA-ACCORD cohort only.

[c] Estimates and 95% confidence intervals from separate Poisson regression models with generalized estimating equations, adjusted for NA-ACCORD cohort, calendar year, IDU risk factor, and annually-updated age, CD4 cell count, and HIV viral load.

[d] Estimates and 95% confidence intervals from two Poisson regression models with generalized estimating equations, stratified by gender, adjusted for NA-ACCORD cohort only.

[e] Estimates and 95% confidence intervals from two Poisson regression models with generalized estimating equations, stratified by gender, adjusted for NA-ACCORD cohort, calendar year, IDU risk factor, and annually-updated age, CD4 cell count, and HIV viral load.

[f] Trends were not estimated due to small group sizes.

Table 4.3. Unadjusted incidence rate ratios (IRR) with 95% confidence intervals for cause-specific hospitalizations. IRR were not estimated for Asian, Indigenous, or multiracial/other cisgender women due to small group sizes.

	Cisgender men (compared to White cisgender men) [a]					Cisgender women (compared to White cisgender women) [a]	
Diagnostic category [b]	Black	Hispanic, any race	Asian	Indigenous	Multiracial or other	Black	Hispanic, any race
Non-AIDS-defining infection	1.35 (1.19, 1.54)	1.01 (0.86, 1.19)	0.69 (0.52, 0.93)	3.03 (2.02, 4.56)	0.90 (0.55, 1.49)	1.04 (0.81, 1.35)	0.99 (0.72, 1.37)
Cardiovascular	1.58 (1.23, 2.01)	0.88 (0.67, 1.15)	0.43 (0.26, 0.71)	1.25 (0.47, 3.35)	1.04 (0.36, 3.00)	1.84 (1.10, 3.08)	1.45 (0.89, 2.37)
Liver/ gastrointestinal	1.15 (0.92, 1.45)	1.20 (0.95, 1.52)	0.44 (0.26, 0.74)	2.17 (1.16, 4.08)	1.13 (0.61, 2.09)	1.15 (0.76, 1.72)	1.60 (1.01, 2.53)
Psychiatric	1.24 (0.92, 1.67)	0.82 (0.58, 1.14)	0.83 (0.48, 1.43)	1.16 (0.52, 2.59)	0.89 (0.40, 1.99)	0.52 (0.34, 0.78)	0.69 (0.26, 1.82)
AIDS-defining illness	1.90 (1.43, 2.51)	1.77 (1.33, 2.35)	1.17 (0.50, 2.76)	2.79 (1.50, 5.22)	1.00 (0.39, 2.55)	0.89 (0.57, 1.37)	0.93 (0.54, 1.61)
Neoplasms excluding AIDS-defining cancer	0.98 (0.75, 1.28)	0.92 (0.66, 1.27)	0.43 (0.20, 0.95)	1.51 (0.46, 4.99)	0.12 (0.03, 0.47)	1.80 (1.13, 2.87)	2.09 (1.14, 3.84)
Injury/poisoning/ complications of therapy	1.21 (0.98, 1.49)	0.75 (0.59, 0.97)	0.56 (0.34, 0.92)	1.49 (0.84, 2.62)	0.65 (0.31, 1.36)	0.70 (0.47, 1.05)	0.64 (0.38, 1.09)
Renal/genitourinary	3.35 (2.66, 4.21)	1.65 (1.17, 2.32)	0.68 (0.31, 1.49)	1.73 (0.59, 5.09)	0.58 (0.22, 1.55)	1.97 (1.28, 3.04)	0.96 (0.52, 1.75)
Endocrine/metabolic [c]	2.02 (1.51, 2.70)	1.11 (0.79, 1.56)	0.52 (0.26, 1.03)	0.30 (0.04, 2.10)	0.54 (0.22, 1.33)	1.15 (0.71, 1.87)	0.68 (0.36, 1.29)
Pulmonary	1.75 (1.22, 2.49)	0.85 (0.55, 1.31)	0.28 (0.12, 0.70)	1.60 (0.74, 3.48)	0.67 (0.26, 1.72)	1.84 (1.03, 3.29)	1.93 (1.02, 3.66)

Abbreviations: ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; IDU, injection drug use; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

[a] Transgender patients were identified from locally collected data or as individuals with reported female sex and being men who have sex with men. Estimates and 95% confidence intervals from separate Poisson regression models, stratified by gender, with generalized estimating equations to account for patients contributing more than one hospitalization to the analysis. Models are adjusted for NA-ACCORD cohort only.

[b] Shown are the ten most frequent diagnostic categories, ordered by frequency. We used modified Clinical Classifications Software to categorize ICD-9-CM codes for primary discharge diagnoses. Discharge diagnosis was missing for 204 hospitalizations.

[c] Includes diabetes-related hospitalizations.

Table 4.4. Adjusted incidence rate ratios with 95% confidence intervals for cause-specific hospitalizations. White cisgender men are the referent category. IRR were not estimated for Asian, Indigenous, or multiracial/other cisgender women due to small group sizes.

	Cisgender Men (compared to White cisgender men) [a]					Cisgender Women (compared to White cisgender women) [a]	
Diagnostic category [b]	Black	Hispanic, any race	Asian	Indigenous	Multiracial or Other	Black	Hispanic
Non-AIDS-defining infection	1.14 (0.99, 1.30)	0.92 (0.79, 1.08)	0.67 (0.50, 0.88)	2.12 (1.46, 3.10)	0.92 (0.56, 1.50)	1.07 (0.83, 1.37)	1.01 (0.74, 1.39)
Cardiovascular	1.61 (1.23, 2.10)	1.07 (0.81, 1.40)	0.58 (0.35, 0.94)	1.46 (0.51, 4.19)	1.40 (0.49, 4.01)	1.92 (1.13, 3.25)	1.51 (0.92, 2.48)
Liver/ gastrointestinal	1.04 (0.80, 1.34)	1.19 (0.94, 1.51)	0.47 (0.28, 0.78)	1.98 (1.05, 3.76)	1.25 (0.68, 2.33)	1.09 (0.73, 1.62)	1.52 (0.96, 2.41)
Psychiatric	1.17 (0.86, 1.58)	0.75 (0.53, 1.05)	0.74 (0.43, 1.29)	0.93 (0.40, 2.15)	0.83 (0.37, 1.87)	0.64 (0.43, 0.95)	0.86 (0.31, 2.35)
AIDS-defining illness	1.17 (0.87, 1.59)	1.29 (0.98, 1.70)	1.01 (0.42, 2.42)	1.43 (0.80, 2.57)	0.86 (0.35, 2.11)	0.86 (0.58, 1.27)	0.89 (0.53, 1.51)
Neoplasms excluding AIDS-defining cancer	0.82 (0.61, 1.11)	0.92 (0.65, 1.31)	0.49 (0.23, 1.08)	1.50 (0.45, 4.97)	0.14 (0.03, 0.56)	1.78 (1.11, 2.85)	2.04 (1.11, 3.76)
Injury/poisoning/ complications of therapy	1.22 (0.98, 1.52)	0.81 (0.63, 1.04)	0.64 (0.38, 1.05)	1.52 (0.86, 2.68)	0.77 (0.37, 1.59)	0.72 (0.48, 1.09)	0.65 (0.38, 1.12)
Renal/ genitourinary	2.89 (2.24, 3.72)	1.66 (1.17, 2.35)	0.74 (0.34, 1.64)	1.55 (0.52, 4.58)	0.67 (0.25, 1.79)	2.03 (1.31, 3.16)	0.99 (0.53, 1.83)
Endocrine/Metabolic [c]	1.79 (1.33, 2.42)	1.09 (0.76, 1.55)	0.56 (0.28, 1.10)	0.29 (0.04, 1.99)	0.60 (0.25, 1.49)	1.07 (0.65, 1.77)	0.63 (0.33, 1.22)
Pulmonary	1.67 (1.11, 2.51)	0.91 (0.58, 1.43)	0.33 (0.13, 0.82)	1.39 (0.62, 3.12)	0.84 (0.33, 2.14)	1.87 (1.06, 3.32)	1.81 (0.95, 3.43)

Abbreviations: ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; IDU, injection drug use; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

[a] Transgender patients were identified from locally collected data or as individuals with reported female sex and being men who have sex with men. Estimates and 95% confidence intervals from separate Poisson regression models, stratified by gender, with generalized estimating equations to account for patients contributing more than one hospitalization to the analysis. Models are adjusted for NA-ACCORD cohort, calendar year, IDU risk factor, and annually-updated age, CD4 cell count, and HIV viral load.

[b] Shown are the ten most frequent diagnostic categories, ordered by frequency. We used modified Clinical Classifications Software to categorize ICD-9-CM codes for primary discharge diagnoses. Discharge diagnosis was missing for 204 hospitalizations.

[c] Includes diabetes-related hospitalizations.

Table 4.5. Distribution of diagnostic categories and most frequent diagnoses for 21,036 hospitalizations taking place among 27,085 patients in care in six NA-ACCORD cohorts between 2005 and 2015.

Diagnostic category (italic) or diagnosis (Roman)	No. (% of hospitalizations or of category)	ICD-9 codes
Non-AIDS-defining infection	*5274 (25%)*	
Sepsis and bacteremia	1179 (22%)	003.1, 038.0–038.9, 788.52, 790.7, 995.91, 995.92
Bacterial pneumonia	956 (18%)	481–486
Cellulitis and cutaneous abscess	658 (12%)	035, 680.0–686.9
Cardiovascular	*2132 (10%)*	
Congestive heart failure	441 (21%)	398.91, 402.00–404.93, 428.0–428.9
Acute ischemic events including myocardial infarction and unstable angina	265 (12%)	410.00–411.89
Chest pain	224 (11%)	413.9, 786.50–786.59
Liver/gastrointestinal	*1841 (9%)*	
Acute or chronic pancreatitis	295 (16%)	577.0–577.2
Gastrointestinal bleed, upper or lower tract	168 (9%)	456.0, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61, 537.83, 562.03, 562.12, 562.13, 569.85, 569.3, 578.0–578.9
Appendicitis	129 (7%)	540.0–542
Psychiatric	*1675 (8%)*	
Major depressive disorder, single or recurrent episode	316 (19%)	296.20–296.36
Bipolar disorder	200 (12%)	296.40–296.89
Depressive disorder, not elsewhere classified	151 (9%)	311

AIDS-defining illness	*1373 (7%)*	
Pneumocystis jirovecii pneumonia	247 (18%)	136.3
Burkitt lymphoma	161 (12%)	200.20–200.28
Bacterial pneumonia, recurrent [a]	153 (11%)	481–486
Neoplasms excluding AIDS-defining cancer	*1270 (6%)*	
Non-Hodgkin's lymphoma	296 (23%)	153.5, 153.9, 202.80–202.88
Leiomyoma of the uterus	73 (6%)	218.0–218.9
Lung Cancer	70 (6%)	162.2–162.9, V10.11
Injury/poisoning/complication of therapy	*1112 (5%)*	
Femoral neck fracture	49 (4%)	820.03, 820.20, 820.21
Poisoning by cocaine, amphetamine, or other stimulant	47 (4%)	969.7, 969.72, 970.1, 970.8, 970.81, 970.89
Ankle fracture	42 (4%)	824.0–824.8
Renal/genitourinary	*1078 (5%)*	
Acute renal failure	523 (49%)	584.9
Chronic (including end-stage) renal disease	202 (19%)	403.00–403.91, 585–585.9
Calculus of kidney or ureter	82 (8%)	592.0–592.9
Endocrine/metabolic	*992 (5%)*	
Diabetes mellitus, not diabetic ketoacidosis or hyperosmolar state	334 (34%)	249.00–250.93
Hypovolemia	73 (7%)	276.50–276.52
Hyperkalemia	64 (6%)	276.7
Pulmonary	*953 (4%)*	
COPD exacerbation	231 (24%)	491.0–492.8
Asthma exacerbation	213 (22%)	493.00–493.92
Acute respiratory failure	187 (20%)	518.81–518.89, 786.09
Musculoskeletal	*710 (3%)*	
Aseptic necrosis of head and neck of femur	106 (15%)	733.42

Osteoarthritis of the lower leg	90 (13%)	715.16, 715.26, 715.36, 715.96, 715.97
Osteoarthritis of the pelvis and/or thigh	70 (10%)	715.15, 715.25, 715.35, 715.95
Symptoms	*620 (3%)*	
Fever	120 (19%)	780.6, 780.60, 780.61
Abdominal pain	91 (15%)	789.00–789.09
Rehabilitative care	64 (10%)	V57.89, V57.9
Pregnancy	*569 (3%)*	
Delivery in the setting of other viral disease	86 (15%)	647.61
Delivery in the setting of previous cesarean delivery	69 (12%)	654.21
Delivery in the setting of abnormal fetal heart rate or rhythm	32 (6%)	659.71
Neurological	*504 (2%)*	
Epilepsy	96 (19%)	345.00–345.91
Other convulsions	52 (10%)	780.39
Headache	47 (9%)	784.0
Hematological	*453 (2%)*	
Neutropenia	65 (14%)	288.00
Immune thrombocytopenic purpura	46 (7%)	287.31
Anemia, unspecified	43 (9%)	285.9
Dermatological	*84 (<1%)*	
Lower extremity (non-pressure) ulcer	22 (26%)	707.10–707.19
Pressure ulcer	14 (17%)	707.00–707.05, 707.23
Stevens-Johnson Syndrome/toxic epidermal necrolysis	7 (8%)	693.13–693.15
Congenital	*24 (<1%)*	
Anomalies of cerebrovascular system	3 (13%)	747.81
Cystic kidney disease, unspecified	3 (13%)	753.10

Congenital insufficiency of aortic valve	2 (8%)	746.4
Other residual codes	*360 (2%)*	
Accidents occurring in residential institution	76 (21%)	E849.7
Personal history of noncompliance with medical treatment, presenting hazards to health	67 (19%)	V15.81
Home accidents	57 (16%)	E849.0

Abbreviations: AIDS, acquired immunodeficiency syndrome; COPD, Chronic Obstructive Pulmonary Disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

[a] Second hospitalization for bacterial pneumonia within 12 months.

Table 4.6. Distribution of diagnostic categories among cisgender men stratified by race and ethnicity.

Diagnostic category [a]	Cisgender Men					
	White N=6639	Black N=5252	Hispanic N=2320	Asian N=298	Indigenous N=246	Multiracial/ Other N=182
Non-AIDS-defining infection	24%	26%	27%	28%	35%	30%
Cardiovascular	11%	11%	9%	8%	6%	13%
Liver/gastrointestinal	8%	10%	12%	7%	10%	13%
Psychiatric	8%	9%	6%	12%	7%	8%
AIDS-defining illness	7%	5%	9%	8%	9%	7%
Neoplasms excluding AIDS-defining cancer	5%	7%	7%	5%	5%	1%
Injury/poisoning/ complication of therapy	5%	7%	5%	6%	6%	5%
Renal/genitourinary	8%	3%	5%	3%	2%	2%
Metabolic/endocrine	6%	4%	5%	3%	<1%	3%
Pulmonary	5%	4%	3%	2%	4%	3%
Musculoskeletal	3%	5%	2%	2%	3%	4%
Symptoms	3%	3%	2%	5%	4%	3%
Pregnancy	<1%	<1%	0	0	0	0
Neurological	3%	2%	2%	3%	2%	4%
Hematological	2%	2%	3%	2%	2%	1%
Dermatological	1%	<1%	<1%	0	2%	0
Congenital	<1%	<1%	<1%	<1%	0	1%
Other	1%	2%	2%	5%	1%	2%

Abbreviations: ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.
[a] Diagnostic categories are ordered by frequency. We used modified Clinical Classifications Software to categorize ICD-9-CM codes for primary discharge diagnoses. Discharge diagnosis was missing for 204 hospitalizations.

Table 4.7. Distribution of diagnostic categories among cisgender women stratified by race and ethnicity, and among transgender adults.

Diagnostic category [a]	Cisgender Women						Trans-gender, Any race N=144
	White N=994	Black N=3743	Hispanic N=930	Asian N=74	Indigenous N=152	Multiracial/ Other N=62	
Non-AIDS-defining infection	24%	23%	23%	23%	35%	29%	25%
Cardiovascular	6%	10%	9%	9%	1%	0	6%
Liver/ gastrointestinal	6%	7%	8%	9%	7%	10%	2%
Psychiatric	14%	6%	5%	7%	13%	18%	10%
AIDS-defining illness	7%	6%	7%	3%	3%	3%	12%
Neoplasms excluding AIDS-defining cancer	3%	6%	7%	1%	1%	10%	5%
Injury/poisoning/ complication of therapy	6%	4%	3%	0	5%	0	6%
Renal/ genitourinary	4%	6%	3%	3%	3%	3%	8%
Metabolic/ endocrine	4%	5%	4%	5%	0	3%	8%
Pulmonary	3%	6%	8%	0	4%	5%	8%
Musculoskeletal	3%	2%	3%	3%	1%	2%	3%
Symptoms	2%	3%	3%	1%	3%	2%	2%
Pregnancy	8%	9%	9%	22%	18%	15%	0
Neurological	3%	2%	4%	0	1%	0	1%
Hematological	2%	3%	3%	5%	2%	0	1%
Dermatological	<1%	<1%	<1%	0	0	0	1%
Congenital	<1%	0	<1%	0	0	0	0
Other	2%	1%	1%	7%	2%	2%	2%

Abbreviations: ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.
[a] Diagnostic categories are ordered by frequency. We used modified Clinical Classifications Software to categorize ICD-9-CM codes for primary discharge diagnoses. Discharge diagnosis was missing for 204 hospitalizations.

Table 4.8. Unadjusted all-cause hospitalization rates over 2005–2015, in 2005, and in 2015, among 27,085 patients in care in six NA-ACCORD cohorts, stratified by gender and race/ethnicity.

	Unadjusted All-cause Hospitalization Rates (95% CI)		
Gender [a] & Race/ethnicity	2005–2015	2005	2015
Cisgender men			
Any race/ethnicity	15.3 (14.7, 15.9)	19.8 (18.2, 21.7)	12.2 (11.3, 13.3)
White	13.1 (12.5, 13.9)	16.0 (14.8, 19.2)	11.7 (10.4, 13.2)
Black	21.8 (20.4, 23.4)	28.1 (24.3, 32.5)	15.5 (13.3, 18.0)
Hispanic, any race	14.2 (12.8, 15.8)	21.7 (17.4, 26.9)	10.5 (8.6, 12.9)
Asian	7.3 (6.0, 8.8)	10.0 (4.8, 21.0)	5.5 (3.5, 8.5)
Indigenous [b]	24.7 (18.0, 33.8)		
Multiracial/other [b]	12.0 (7.7, 18.6)		
Cisgender women			
Any race/ethnicity	24.3 (22.8, 26.0)	33.2 (28.4, 38.8)	17.2 (15.0, 19.8)
White	20.7 (17.7, 24.3)	31.4 (20.9, 47.2)	13.5 (9.7, 18.8)
Black	25.8 (23.8, 28.1)	37.3 (30.9, 45.1)	18.4 (15.4, 22.1)
Hispanic, any race	24.4 (20.9, 28.3)	28.7 (20.0, 41.3)	17.2 (12.0, 24.6)
Asian [b]	12.2 (8.0, 18.6)		
Indigenous [b]	42.0 (29.7, 59.3)		
Multiracial/other [b]	15.3 (7.8, 29.8)		
Transgender, any race/ethnicity [b]	24.8 (17.4, 35.5)		

Abbreviations: CI, confidence interval; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.
[a] Transgender patients were identified from locally collected data or as individuals with reported female sex and being men who have sex with men.
[b] Annual rates were not estimated due to small group sizes.

Table 4.9. Incidence rate ratios for all-cause hospitalizations, in a sensitivity analysis using 18 months to define loss to follow-up.

	Incidence Rate Ratio (95% CI)	
Gender [a] & Race/ethnicity	Unadjusted [b]	Adjusted [c]
Cisgender men		
White	1 (ref.)	1 (ref.)
Black	1.46 (1.32, 1.62)	1.27 (1.14, 1.41)
Hispanic, any race	1.01 (0.90, 1.14)	0.98 (0.87, 1.09)
Asian	0.62 (0.51, 0.76)	0.64 (0.53, 0.78)
Indigenous	1.96 (1.43, 2.69)	1.61 (1.18, 2.20)
Multiracial or other	0.83 (0.53, 1.30)	0.91 (0.59, 1.42)
Cisgender women		
White	1 (ref.)	1 (ref.)
Black	1.14 (0.95, 1.37)	1.17 (0.98, 1.38)
Hispanic, any race	1.12 (0.90, 1.41)	1.13 (0.91, 1.40)
Asian	0.70 (0.44, 1.13)	0.74 (0.47, 1.15)
Indigenous	2.54 (1.68, 3.85)	1.87 (1.32, 2.66)
Multiracial or other	0.68 (0.35, 1.35)	0.79 (0.40, 1.55)

Abbreviations: CI, confidence interval; IDU, injection drug use; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; ref., referent.

[a] Transgender patients were identified from locally collected data or as individuals with reported female sex and being men who have sex with men.

[b] Estimates and 95% confidence intervals from two Poisson regression models with generalized estimating equations, stratified by gender, adjusted for NA-ACCORD cohort only.

[c] Estimates and 95% confidence intervals from two Poisson regression models with generalized estimating equations, stratified by gender, adjusted for NA-ACCORD cohort, calendar year, IDU risk factor, and annually-updated age, CD4 cell count, and HIV viral load.

Table 4.10. Incidence rate ratios and 95% confidence intervals for all-cause and cause-specific hospitalizations comparing cisgender women and transgender patients to cisgender men.

Diagnostic category [b]	Cisgender women		Transgender patients [a]	
	Unadjusted [c]	Adjusted [d]	Unadjusted [c]	Adjusted [d]
All-cause	1.37 (1.26, 1.48)	1.43 (1.30, 1.57)	1.50 (1.05, 2.14)	1.41 (0.98, 2.02)
Non-AIDS-defining infection	1.27 (1.14, 1.42)	1.44 (1.27, 1.63)	1.39 (0.91, 2.14)	1.26 (0.87, 1.84)
Cardiovascular	1.17 (0.94, 1.45)	1.20 (0.96, 1.49)	0.97 (0.40, 2.34)	1.01 (0.41, 2.48)
Liver/ gastrointestinal	1.14 (0.93, 1.39)	1.18 (0.96, 1.45)	0.32 (0.07, 1.41)	0.31 (0.07, 1.37)
Psychiatric	1.34 (1.04, 1.73)	1.83 (1.24, 2.68)	1.98 (1.00, 3.91)	2.02 (1.02, 4.01)
AIDS-defining illness	1.19 (0.98, 1.44)	1.12 (0.90, 1.39)	2.51 (1.35, 4.66)	1.84 (0.98, 3.47)
Neoplasms excluding AIDS-defining cancer	1.26 (1.03, 1.53)	1.26 (1.01, 1.57)	1.06 (0.32, 3.54)	1.14 (0.34, 3.79)
Injury/ poisoning/ complications of therapy	1.03 (0.85, 1.25)	1.18 (0.94, 1.49)	1.46 (0.59, 3.61)	1.59 (0.64, 3.95)
Renal/ genitourinary	1.15 (0.95, 1.39)	1.13 (0.90, 1.41)	2.11 (0.82, 5.42)	1.77 (0.69, 4.59)
Endocrine/ metabolic [e]	1.15 (0.92, 1.44)	1.08 (0.84, 1.38)	3.19 (0.62, 16.47)	2.96 (0.56, 15.65)
Pulmonary	1.61 (1.28, 2.03)	1.90 (1.44, 2.50)	2.86 (1.18, 6.97)	2.75 (1.10, 6.90)

Abbreviations: ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; IDU, injection drug use; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

[a] Transgender patients were identified from locally collected data (n=149) or as individuals with reported female sex and being men who have sex with men (n=8). We could not differentiate patients who identified as transfeminine, transmasculine, or non-binary.

[b] Shown are the ten most frequent diagnostic categories, ordered by frequency. We used modified Clinical Classifications Software to categorize ICD-9-CM codes for primary discharge diagnoses. Discharge diagnosis was missing for 204 hospitalizations.

[c] Estimates and 95% confidence intervals from separate Poisson regression models with generalized estimating equations with an independent correlation matrix to account for patients contributing more than one hospitalization to the analysis. Models are adjusted for NA-ACCORD cohort only.

[d] Estimates and 95% confidence intervals from separate Poisson regressions model with generalized estimating equations. Models are adjusted for NA-ACCORD cohort, calendar year, race/ethnicity, IDU risk factor, and annually-updated age, CD4 cell count, and HIV viral load.

[e] Includes diabetes-related hospitalizations.

Figures

Figure 4.1. Annual all-cause hospitalization rates stratified by race/ethnicity and gender. Panel A shows unadjusted rates. Panel B shows rates standardized to the distribution in 2010 in the entire study sample of age, CD4 cell count, HIV viral load, and injection drug use (IDU) as HIV risk factor. Standardization strata were defined according to the following categories: age <40, 40–49, 50–59, and ≥60 years; CD4 count <50, 50–200, 201–350, 351–500, and >500 cells/μL; HIV viral load <400 and ≥400 copies/mL; IDU risk factor, yes or no. Due to small group sizes, annual rates were not estimated for Asian cisgender women, Indigenous, multiracial/other, or transgender patients.

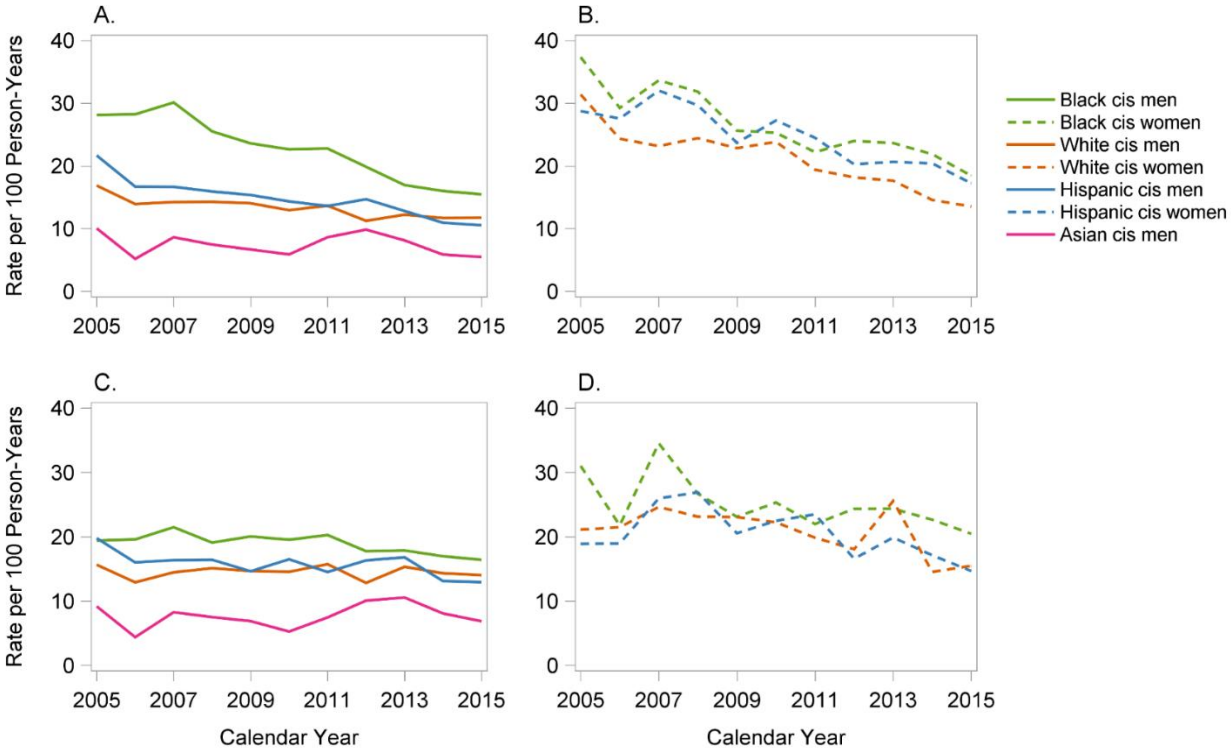
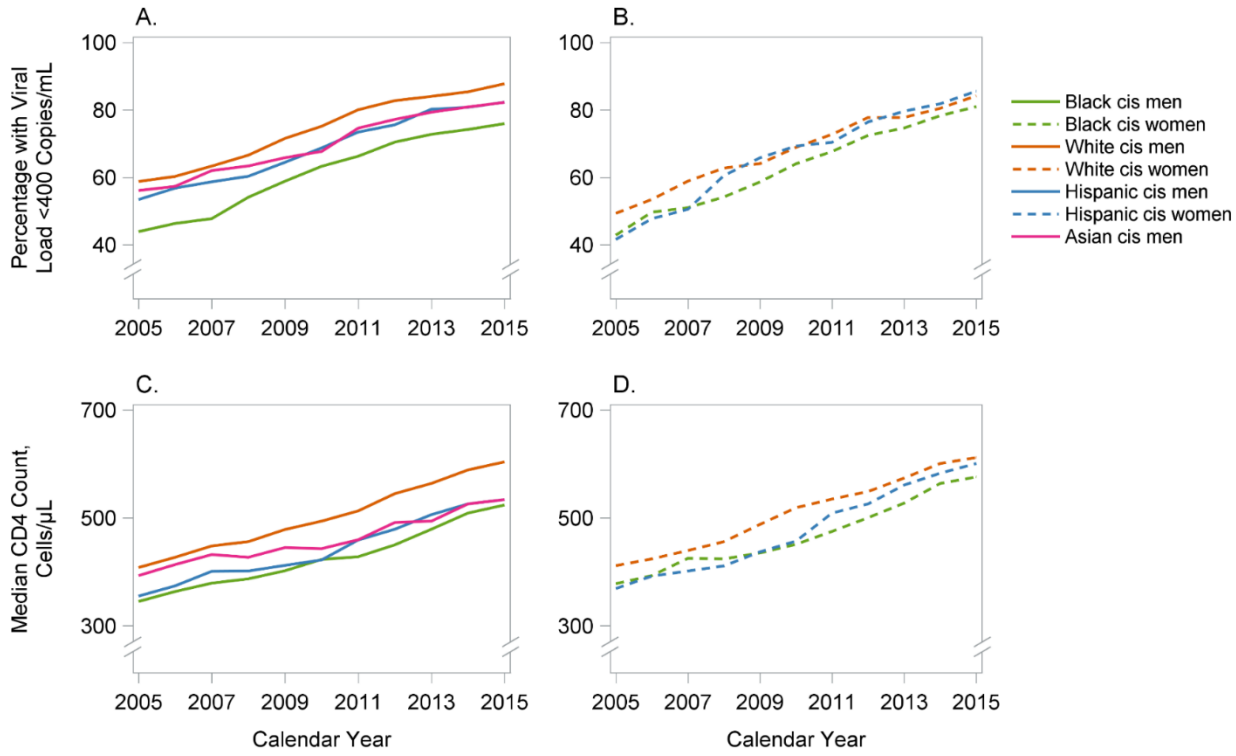


Figure 4.2. Percentage of patients in care with HIV RNA viral load <400 copies/mL (A) and median CD4 cell count/µL (B), stratified by race/ethnicity and gender. Due to small group sizes, estimates are not displayed for Asian cisgender women, Indigenous, multiracial/other, or transgender patients.



CHAPTER V: CURRENT AND PAST IMMUNODEFICIENCY ARE ASSOCIATED WITH HIGHER HOSPITALIZATION RATES AMONG PERSONS ON VIROLOGICALLY SUPPRESSIVE ANTIRETROVIRAL THERAPY FOR UP TO ELEVEN YEARS

Introduction

Among persons with HIV (PWH) in the United States (US) and Canada, hospitalization rates have decreased in recent years but remain elevated compared to the general population [21, 78, 96, 113, 114]. Given improved antiretroviral therapy (ART) efficacy and safety, and greater rates of sustained virologic suppression, work is needed to identify clinical risk factors for hospitalization among persons with well-controlled HIV infection [7]. One patient population that merits attention are PWH with incomplete CD4 cell count recovery in spite of long-term virologic suppression. Initiating ART early in HIV infection improves CD4 count recovery [8, 27]. In the US and Canada approximately 25% of persons are first diagnosed with HIV at CD4 counts <200 cells/μL or with an AIDS-defining condition [25, 26]. Even with early ART, the CD4 counts of many PWH do not increase to levels comparable to the general population [27].

PWH with poor CD4 count recovery on ART might have higher hospitalization rates for several reasons. First, lower CD4 counts are associated with higher incidence of both AIDS- and non-AIDS-defining infections [12, 60]. Patients with delayed ART initiation or lower CD4 count recovery also experience a greater burden of chronic inflammation and immune activation, and are at higher risk of severe non-AIDS outcomes, including myocardial infarction, end-stage renal disease, and cancer [16, 28-30, 57, 58]. Finally, patients with delays in HIV diagnosis and care engagement might have a higher prevalence of smoking, substance use, and comorbidities such as dyslipidemia and hypertension, which could affect clinical outcomes after ART initiation [63, 65, 115].

Prior studies have shown associations between lower CD4 counts and higher hospitalization rates [19, 21, 22, 34]. However, few studies have focused on virologically suppressed PWH or taken into account duration of ART [34, 35]. In this study, we examined hospitalization rates by history of immunodeficiency and current CD4 count among PWH on ART with sustained virologic suppression.

Methods

Data source

This study relied on data available through the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a consortium of HIV cohorts in the US and Canada [36]. We included six clinical cohorts with complete hospital admission and discharge data for the period 2005–2015, including International Classification of Diseases (ICD) codes for discharge diagnoses. Local Institutional Review Boards (IRBs) approved prospective data collection, and the University of North Carolina IRB approved this secondary data analysis.

Patient inclusion and follow-up

Eligible patients met both of the following criteria: (1) HIV RNA viral load (VL) >1000 copies/mL at entry into NA-ACCORD; and (2) first virologic suppression between January 1, 2005 and December 31, 2014 (Fig. 5.1, N=7806). Virologic suppression was defined as at least two consecutive VL measurements <400 copies/mL at least 30 days apart within 12 months. We excluded patients who did not experience a complete year of suppression (N=716 became unsuppressed; N=85 died). Additionally, patients without a CD4 count prior to the start of suppression were excluded (N=8). We included patients who had evidence of prior ART exposure, defined as any prior VL <1000 copies/mL, as long as they had not previously met our definition of virologic suppression (13% of final sample).

Patients were followed from the first VL <400 copies/mL until death, loss to follow-up, virologic failure, or December 31, 2015, whichever occurred first. Loss to follow-up was defined as 12 months with no CD4 count or VL measured in the outpatient setting. Virologic failure was defined as the first of at least two consecutive VL ≥400 copies/mL at least two weeks apart within 90 days, or one VL ≥400 with no confirmatory VL within 90 days.

Patients could not re-enter the analysis after meeting censoring criteria. Person-time was divided into six-month intervals for analysis, using virologically suppressed years as the time scale. Days spent in the hospital were not counted as person-time at risk.

Study measures

The exposure of interest was time-updated CD4 cell count, categorized as <200, 200–350, 351–500, >500 cells/μL. For each six-month interval of analysis, for each patient, we calculated a weighted moving average using the three most recent CD4 cell counts measured in the prior 24 months. Moving averages have previously been used in studies of CD4 counts [92]. Ninety-two percent of average calculations had three measurements available, 7% two measurements, and 2% one measurement. Weights were calculated as one divided by the number of days from the CD4 count measurement to the interval start date. We excluded CD4 counts measured during a known hospitalization to avoid capturing immune changes related to acute illness. We only used CD4 counts measured at least 30 days apart to avoid overweighting measurements taken close together. We excluded 48 person-years (<1%) without any CD4 count in the prior 24 months.

The primary outcome of interest was all-cause hospitalization, allowing patients to contribute more than one hospitalization. We did not count hospitalizations with same-day discharge, which are rare events and could not be distinguished from outpatient procedures (e.g. endoscopies). To examine reasons for hospitalization, we used Clinical Classifications Software (CCS) to categorize the ICD Ninth Revision code (ICD-9) of the primary discharge

diagnosis [21, 87]. We modified the CCS to create an “AIDS-defining illness” category and to include all other infections in a “non-AIDS-defining infection” category. ICD, Tenth Revision codes, when used, were first converted to ICD-9 using General Equivalence Mappings from the Centers for Medicare and Medicaid Studies.

The covariates used in the analysis were NA-ACCORD cohort, age, gender, calendar year, duration of virologic suppression, and lowest known CD4 count measured prior to the first VL <400 copies/mL. Age, calendar year, suppression duration, and lowest CD4 count were included in models as linear variables. In a sensitivity analysis, we adjusted for age using restricted quadratic splines with four knots.

Statistical analysis

We estimated rates of hospitalization per 100 person-years by CD4 count category, stratified by lowest pre-suppression CD4 count <200 or ≥200 cells/μL. To avoid immortal person-time, we did not compare CD4 count categories during the first year of virologic suppression. We stratified analyses into an early suppression period (2–5 years) and long-term suppression period (6–11 years) [Fig. 5.1]. This approach allowed us to compare patients according to CD4 count trajectories over time, e.g. among patients whose lowest pre-suppression CD4 was <200 cells/μL, compare patients with a current CD4 count 200–350 versus >500 during long-term suppression.

We used Poisson regression models to estimate incidence rate ratios (IRR) of hospitalization comparing patients according to current CD4 count categories, in each stratum, using generalized estimating equations with an independent correlation matrix to account for patients contributing more than one outcome to the analysis. Unadjusted models only included NA-ACCORD cohort as a covariate. Adjusted models included all covariates. For rate and IRR estimation, we excluded patients in strata with less than 100 person-years to avoid unstable estimates. In adjusted analyses, we also excluded 35 transgender patients to allow gender-

adjusted models to converge. Analyses were conducted using SAS, versions 9.4 (Cary, NC). *P* values were two-sided.

Sensitivity analyses

We conducted five sets of sensitivity analyses. First, we examined the impact of censoring the person-time of patients with potential non-HIV-related immunodeficiency, defined as either (1) a hospitalization for chemotherapy, or (2) a persistent CD4 count decline after the start of virologic suppression (Fig. 5.4) [92, 116]. We identified chemotherapy hospitalizations using ICD-9 code of V58.11 for the primary discharge diagnosis. A persistent CD4 count decline was defined as the first of two consecutive decreases ≥15% in unweighted moving averages, updated at each CD4 count, using up to three measurements in the past 24 months [92]. In a second sensitivity analysis, we counted only the first hospitalization in each six-month interval, to evaluate the possible impact of a small number of patients contributing many hospitalizations. In this approach, person-time for each six-month interval was censored after the start of the first hospitalization. Thirdly, we excluded ART-experienced patients, defined as having a history of VL <1000 copies/mL without meeting study criteria for virologic suppression. Fourth, we used restricted quadratic splines to adjust for age. And finally, because patients with a lowest pre-suppression CD4 count >200 could be a heterogeneous group, we examined hospitalization rates by current CD4 count among patients whose lowest pre-suppression CD4 count was 200–350 cells/μL.

Results

Study sample

We included 6997 patients who were 81% cisgender men, 40% White, and 33% Black. The median time from NA-ACCORD cohort enrollment to the start of virologic suppression was 5.3 months (interquartile range [IQR] 2.5, 20.9). At the start of virologic suppression, the median

patient age was 42 years (IQR 33, 49), and the median lowest prior CD4 count was 228 cells/μL (IQR 93, 342; range 0, 1227; 44% <200). Demographic characteristics varied in patients with lowest pre-suppression CD4 <200 versus ≥200 cells/μL (Table 5.1). Overall, during the first year of virologic suppression, the hospitalization rate was 17.3 per 100 person-years (95% confidence interval [CI] 15.7, 19.0).

For these analyses, patients contributed a total of 19,980 virologically suppressed person-years of analysis, 15 612 during early suppression (Years 2–5) and 4368 during long-term suppression (Years 6–11). The median person-time contributed per patient in Years 2–11 was 2.1 years (IQR 0.8, 4.4; range 0.0, 10.0), with 12% of patients censored at virologic failure and 2% at death (Fig. 5.1). During Years 2–11, 1231 (18%) patients were hospitalized at least once. Among these, 73% were hospitalized once, 18% twice, 5% three times, 3% four times, and 1% five or more times, for a total of 2035 hospitalizations. The three most frequent diagnostic categories of hospitalization were non-AIDS-defining infection (24% of hospitalizations; most frequent diagnosis, sepsis/bacteremia), cardiovascular (13%; acute cardiac ischemic event), and liver/gastrointestinal (10%; acute or chronic pancreatitis) [Table 5.3].

From the first VL<400 copies/mL to Year 10 of sustained suppression, median (IQR) CD4 counts increased from 191 (110, 285) to 596 cells/μL (457, 805) among patients whose lowest pre-suppression CD4 count was <200, and from 467 (361, 607) to 816 cells/μL (680, 927) among patients whose lowest pre-suppression CD4 count was ≥200 (Fig. 5.2A–B). By the fifth year of virologic suppression, 46% had a CD4 count >500 cells/μL among patients whose lowest pre-suppression CD4 count was <200, and 86% among those whose lowest pre-suppression CD4 was ≥200.

CD4 cell count and hospitalization rates

During Years 2–11, the overall hospitalization rate was 10.2 per 100 person-years (95% CI 9.3, 11.1). Hospitalization rates were highest during early suppression among patients in the lowest current and pre-suppression CD4 group, with an estimate of 21.4 per 100 person-years (95% CI 16.8, 27.3), and lowest among patients during long-term suppression among patients in the highest current and pre-suppression CD4 group, with an estimate of 6.0 per 100 person-years (95% CI 4.6, 7.9) [Fig. 5.3, Table 5.4].

Among patients whose lowest pre-suppression CD4 count was <200 cells/μL (Table 5.2), having a lower current CD4 count during early suppression was associated with higher hospitalization rates, with an unadjusted IRR of 2.03 (95% CI 1.42, 2.89) for a current CD4 count <200 versus >500, and 1.44 (95% CI 1.05, 1.97) for a current CD4 count 200–350 versus >500. Patients with a current CD4 count 351–500 did not have lower rates than those with a CD4 count >500. During long-term suppression, compared to patients with a current CD4 count >500, the unadjusted IRR was 1.84 (1.17, 2.89) for patients with a CD4 count 200–350, and 1.50 (95% CI 1.01, 2.24) for patients with a CD4 count 351–500. In adjusted models, estimates were similar but less precise, with an IRR of 1.40 (0.93, 2.10) for patients with a current CD4 count 351–500 versus >500 during long-term suppression.

Among patients whose lowest pre-suppression CD4 count was ≥200 cells/μL (Table 5.2), we observed similar patterns. During early suppression, compared to patients with a current CD4 >500, patients with a current CD4 count of 200–350 had an unadjusted IRR of 2.58 (1.69, 3.93), and patients with a CD4 count 351–500 had an unadjusted IRR of 1.18 (0.92, 1.53). Adjusted estimates were comparable. During long-term suppression, patients with a CD4 count 351–500 had an unadjusted IRR of 2.15 (1.20, 3.83) and adjusted IRR of 2.09 (1.18, 3.70) compared to those with a CD4 count >500.

Sensitivity analyses

When censoring person-time after patients experienced a chemotherapy hospitalization or a persistent CD4 decline (<1% and 1%, respectively, Fig. 5.4), results were similar to the main findings (Table 5.5). When counting only one hospitalization per six-month interval, hospitalization rates were lower, particularly for patients with lower CD4 counts, and effect estimates were attenuated and less precise; however, comparable trends with increasing hospitalization rates with decreasing CD4 cell count were observed (Tables 5.6 and 5.7). For example, among patients whose lowest pre-suppression CD4 count was <200 cells/μL, the adjusted IRR was 1.32 (0.99, 1.74) for a CD4 count 200–350 versus >500 during early suppression, and 1.25 (0.85, 1.83) for a CD4 count 351–500 versus >500 during long-term suppression. Among patients whose lowest pre-suppression CD4 count was ≥200 cells/μL, the adjusted IRR was 1.83 (1.06, 3.16) for a CD4 count 351–500 versus >500 during long-term suppression. Results for the remaining sensitivity analyses were also similar to the main findings (Tables 5.8–5.10).

Discussion

In this study, among patients on sustained virologically suppressive ART up to 11 years, lower CD4 cell counts were consistently associated with higher hospitalization rates. These disparities were most pronounced during the long-term suppression period. During early suppression (Years 2–5), patients with a current CD4 count 200–350 had 1.5–2.5 times the adjusted hospitalization rates of those with a CD4 count >500 cells/μL. During long-term suppression (Years 6–11), patients with a current CD4 count 351–500 had 1.4–2.1 times the hospitalization rate of patients with a CD4 count >500 cells/μL. These trends were similar for patients with and without a history of CD4 count <200 cells/μL prior to virologic suppression, though patients whose lowest pre-suppression CD4 was <200 cells/μL continued to have the highest hospitalization rates during the long-term suppression period.

In populations of patients with and without virologic suppression, several studies have previously reported higher hospitalization rates in descending CD4 strata below <500 cells/μL [19, 21, 22, 31, 35, 78]. In one study examining ART initiators for a year, patients with sustained virologic suppression and CD4 count increases >100 cells/μL had lower hospitalization rates [76]. In a military cohort, among patients with virologic suppression, having a CD4 count ≤200 versus >750 cells/μL was associated with higher hospitalization rates, but not intermediate categories of CD4 count [34]. However, patients in this study were approximately 12 years younger than our study population, with a short duration of infection, and 20% elite controllers, who may have a different immunologic profile than other PWH.

In our study focusing on patients with sustained virologic suppression for up to eleven years, those with even modestly lower CD4 count recovery had higher rates of hospitalization, including patients who had not been observed to have CD4 counts <200 cells/μL prior to suppression. One possible explanation for our findings is confounding by age. Older patients at ART initiation have poorer CD4 recovery, and older patients are more likely to have multiple comorbidities [44, 54]. Yet estimates adjusted for age were similar to unadjusted results. It is also possible that patients with CD4 count <500 cells/μL after 5 years of ART would continue to experience CD4 recovery and eventually lower hospitalization rates. While CD4 recovery has been shown to occur up to 6–7 years after ART initiation, substantial increases in CD4 count are largely observed in the first three years of virologic suppression [55, 56]. In addition, if lower CD4 count groups included a subset of severely sick and repeatedly hospitalized patients, these individuals could have contributed to the disparities we observed. However, when counting only one hospitalization per patient in each time interval, our estimates, while attenuated, were consistent with the main analysis.

There are several mechanisms through which patients with poor CD4 count recovery could have higher hospitalization rates. First, lower CD4 cell counts put patients at risk of AIDS-defining opportunistic infections and other non-AIDS infections such as bacterial pneumonia,

soft tissues infections, and bacteremia, although this risk is lower with sustained virologic suppression [12, 60-62]. Lower CD4 count recovery could also be a marker for underlying immune dysfunction and more severe comorbid burden. ART initiation at lower CD4 counts leads to poorer CD4 count recovery, chronic inflammation and immune activation, and comorbidities [8, 16, 27-30, 54, 57, 58]. Finally, socioeconomic factors that delay HIV diagnosis and ART initiation might also contribute to the incidence of comorbidities [63, 64]. For example, patients living in poverty have higher rates of smoking and poor nutrition [65, 115]. In addition, poor insurance coverage can result in financial barriers and delays in care, compromise the management of comorbidities such as hypertension, and lead to hospitalization [66, 117].

Our findings of hospitalization disparities by CD4 count recovery on long-term ART raise important questions that future studies should examine. It should be further elucidated if lower CD4 counts on ART are a direct cause of morbidity leading to hospitalization, or if they represent a marker for a larger burden of underlying chronic comorbid conditions. In particular, studies should determine if patients with a similar comorbidity profile but different CD4 trajectories still experience hospitalization disparities. Secondly, studies should evaluate whether different clinical management according to CD4 recovery is appropriate. In our study, the most frequent diagnostic categories of hospitalization were non-AIDS-defining infection, cardiovascular conditions, and liver/gastrointestinal conditions. Patients with CD4 counts below a certain threshold after several years of ART might benefit from earlier screening and treatment or more frequent follow-up for certain conditions, to prevent disease progression leading to hospitalization. They could also receive targeted efforts aimed at smoking cessation and other modifiable risk factors. Infection prevention, including vaccination and harm reduction for people who inject drugs, should be emphasized. Other interventions currently being evaluated in PWH, such as prophylactic statin use, if effective, could potentially be of particular benefit to these patients [118].

A strength of this study is the large sample size and long follow-up allowing us to examine patients with different CD4 count trajectories after more than five years of virologic suppression. Our study included persons with HIV across five cohorts in the US and one in Canada, representing varied patient populations and care settings. However, cisgender women made up a small proportion of the patient sample, and our findings may not be generalizable to all virologically suppressed PWH in this region including cisgender women. In addition, while we restricted our analysis to patients whose viral loads were observed to become suppressed, some patients might have taken ART prior to entering NA-ACCORD cohorts, meaning the lowest pre-suppression CD4 count we observed overestimated their true nadir CD4 count. Finally, we did not have data on important risk factors for morbidity and hospitalization such as smoking and injection drug use.

In conclusion, patients on ART whose CD4 counts remain below 500 cells/μL after several years of virologic suppression have higher hospitalization rates, even if they do not have a history of severe immunodeficiency. Future studies should elucidate the reasons for these disparities and examine if patients with poor CD4 count recovery on ART would benefit from different clinical management to prevent serious acute events requiring inpatient care.

Tables

Table 5.1. Demographic and clinical characteristics of 6997 patients who achieved and maintained virologic suppression for at least a year in six NA-ACCORD cohorts, 2005–2014, stratified by lowest known CD4 count prior to the start of virologic suppression.

Characteristic at first VL<400 copies/mL	Lowest known prior CD4 count <200 cells/μL [a] N=3069	Lowest known prior CD4 count ≥200 cells/μL [a] N=3928
	No. (%) or median (IQR)	No. (%) or median (IQR)
Gender		
Cisgender men	2407 (78%)	3257 (83%)
Cisgender women	643 (21%)	655 (17%)
Transgender [b]	19 (1%)	16 (<1%)
Race/ethnicity		
Black, not Hispanic	1128 (37%)	1167 (30%)
White, not Hispanic	1127 (37%)	1672 (43%)
Hispanic	547 (18%)	544 (16%)
Other or missing	267 (9%)	445 (11%)
HIV acquisition risk factor		
MSM	1450 (47%)	2423 (62%)
Heterosexual or other	1242 (40%)	1155 (29%)
IDU	377 (12%)	350 (9%)
Calendar year	2009 (2007, 2011)	2010 (2008, 2012)
Current age, years	44 (37, 50)	40 (31, 48)
Lowest prior CD4 count, cells/μL	76 (24, 140)	325 (264, 426)
ART experienced [c]	469 (15%)	426 (11%)
Current CD4 count, cells/μL [d]	191 (110, 285)	467 (361, 607)

Abbreviations: IDU, injection drug use; MSM, men who have sex with men; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; VL, HIV viral load.
[a] Lowest observed CD4 count prior to the first VL<400 copies/mL, a proxy for nadir CD4 count.
[b] Transgender adults were identified from local data, or from having female sex and MSM as risk factor.
[c] Defined as having a history of VL <1000 copies/mL.
[d] Based on weighted average of up to three measurements in the prior 24 months. Weights were calculated as one divided by the number of days to the first VL<400 copies/mL. Patients could have a current CD4 count value greater than their lowest prior CD4 count because of previous ART use or because of rapid increases between ART initiation and the first VL<400 copies/mL.

Table 5.2. Incidence rate ratios for all-cause hospitalizations comparing CD4 count categories, stratified by lowest pre-suppression CD4 count, and by duration of virologic suppression.

Current CD4 count, cells/μL [a]	Lowest pre-suppression CD4 count <200 cells/μL		Lowest pre-suppression CD4 count ≥200 cells/μL	
	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]
Early Suppression (Years 2–5)				
<200	2.03 (1.42, 2.89)	2.04 (1.28, 3.27)	[d]	[d]
200–350	1.44 (1.05, 1.97)	1.45 (1.01, 2.06)	2.58 (1.69, 3.93)	2.47 (1.52, 4.02)
351–500	1.00 (0.74, 1.36)	1.01 (0.73, 1.40)	1.18 (0.92, 1.53)	1.22 (0.93, 1.60)
>500	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Long-term Suppression (Years 6–11)				
<200	[d]	[d]	[d]	[d]
200–350	1.84 (1.17, 2.89)	1.67 (1.03, 2.72)	[d]	[d]
351–500	1.50 (1.01, 2.24)	1.40 (0.93, 2.10)	2.15 (1.20, 3.83)	2.09 (1.18, 3.70)
>500	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

[a] Weighted 24-month moving average updated every six months of virologic suppression. Weights are the inverse of the distance to the six-month interval start date.

[b] Estimates and 95% CI two separate Poisson regression models adjusted for NA-ACCORD cohort, with generalized estimating equations to account for patients contributing more than one time interval to the analysis.

[c] Estimates and 95% CI two separate Poisson regression models with generalized estimating equations, adjusted for NA-ACCORD cohort, age, gender, calendar year, years of virologic suppression, and lowest prior CD4 count. We excluded transgender individuals.

[d] Because of small sample size, we did not estimate IRR for this category (see Supplemental Table 1 for distribution of hospitalizations and person-time).

Table 5.3. Distribution of diagnostic categories of 2035 hospitalizations with the three most frequent diagnoses in each category. Diagnosis was missing for 25 (1%) of hospitalizations.

Diagnostic category (italic) or diagnosis (Roman)	No. (% overall or in category)	ICD-9 codes
Non-AIDS-defining infection	*483 (24%)*	
Sepsis and bacteremia	124 (26%)	003.1, 038.0–038.9, 788.52, 790.7, 995.91, 995.92
Bacterial pneumonia	71 (15%)	481–486
Cellulitis and cutaneous abscess	53 (11%)	035, 680.0–686.9
Cardiovascular	*258 (13%)*	
Acute cardiac ischemic events	45 (17%)	398.91, 402.00–404.93, 428.0–428.9
Congestive heart failure	42 (16%)	410.00–411.89
Venous thromboembolism	26 (10%)	415.13, 415.19, 451.0, 453.41, 453.42
Liver/gastrointestinal	*212 (10%)*	
Acute or chronic pancreatitis	30 (14%)	577.0–577.2
Appendicitis	23 (11%)	540.0–542
Gastrointestinal bleed, upper or lower tract	18 (8%)	456.0, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61, 537.83, 562.03, 562.12, 562.13, 569.85, 569.3, 578.0–578.9
Psychiatric	*140 (7%)*	
Major depressive disorder, single or recurrent episode	31 (22%)	296.20–296.36
Substance use disorders, including management of addition, withdrawal, and overdose (alcohol)	20 (14%)	291.0, 291.81, 303.00–303.93, 305.00, 305.01, 980.0, V11.3
Bipolar disorder	16 (11%)	296.40–296.89
Injury/poisoning/complications of therapy	*129 (6%)*	

Ankle fracture	7 (5%)	824.0–824.8
Tibia and/or fibula fracture	7 (5%)	823.00, 823.02, 823.22, 823.80
Foot fracture	5 (4%)	825.0, 825.21, 825.25
Neoplasm excluding AIDS-defining cancer	*111 (5%)*	
Non-Hodgkin's lymphoma	16 (14%)	153.5, 153.9, 202.80–202.88
Hepatic cancer	10 (9%)	155.0
Leiomyoma of the uterus	9 (8%)	218.0–218.9
Renal/genitourinary	*109 (5%)*	
Acute renal failure	55 (50%)	584.9
Chronic (including end-stage) renal disease	19 (17%)	403.00–403.91, 585–585.9
Calculus of kidney or ureter	11 (10%)	592.0–592.9
Pulmonary	*101 (5%)*	
COPD exacerbation	33 (33%)	491.0–492.8
Asthma exacerbation	21 (21%)	493.00–493.92
Acute respiratory failure	18 (18%)	518.81–518.89, 786.09
Musculoskeletal	*95 (5%)*	
Osteoarthritis of the lower leg	19 (20%)	715.16, 715.26, 715.36, 715.96, 715.97
Aseptic necrosis of head and neck of femur	16 (17%)	733.42
Cervical spondylosis	8 (8%)	721.0, 721.1
Endocrine/metabolic	*93 (5%)*	
Diabetes mellitus, not diabetic ketoacidosis or hyperosmolar state	29 (31%)	249.00–250.93
Hyperkalemia	7 (8%)	276.7
Hypovolemia	6 (6%)	276.50–276.52
Pregnancy	*66 (3%)*	
Delivery in the setting of other viral disease	8 (12%)	647.61
Delivery in the setting of previous cesarean delivery	6 (9%)	654.21
Delivery in the setting of abnormal fetal heart rate or rhythm	5 (8%)	659.71

AIDS-definition illness	*59 (3%)*	
Burkitt lymphoma	12 (20%)	200.20–200.28
Bacterial pneumonia, recurrent [a]	9 (15%)	481–486
Herpes simplex: chronic ulcers or bronchitis, pneumonitis, or esophagitis	5 (8%)	054.19
Symptoms	*50 (2%)*	
Fever	13 (26%)	780.6, 780.60, 780.61
Abdominal pain	8 (16%)	789.00–789.09
Syncope and collapse	5 (10%)	780.2
Neurological	*42 (2%)*	
Epilepsy	7 (17%)	345.00–345.91
Other convulsions	7 (17%)	780.39
Neoplasm-related pain, acute, chronic	5 (12%)	338.3
Hematological	*35 (2%)*	
Neutropenia	7 (20%)	288.00
Sickle cell disease	6 (17%)	282.5, 282.60–282.69
Anemia, unspecified	5 (14%)	285.9
Dermatological	*5 (<1%)*	
Pressure ulcer	2 (40%)	707.00–707.05, 707.23
Lower extremity (non-pressure) ulcer	1 (20%)	707.10–707.19
Sunburn of second degree	1 (20%)	692.76
Congenital	*3 (<1%)*	
Congenital insufficiency of aortic valve	1 (33%)	746.4
Congenital cystic lung	1 (33%)	748.4
Other hamartoses, not elsewhere classified	1 (33%)	759.6
Other residual codes	*19 (1%)*	
Altered mental status	4 (21%)	780.97
Do not resuscitate status	3 (16%)	V49.86
Abnormal coagulation profile	2 (11%)	784.2

Abbreviations: AIDS, acquired immunodeficiency syndrome; COPD, Chronic Obstructive Pulmonary Disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.
[a] Second hospitalization for bacterial pneumonia within 12 months.

Table 5.4. Distribution of hospitalizations and person-years, and unadjusted hospitalization rates per 100 person-years for each CD4 count category and stratum of analysis.

Current CD4 count, cells/μL [a]	Lowest pre-suppression CD4 count <200 cells/μL			Lowest pre-suppression CD4 count ≥200 cells/μL		
	Events	Person-years	Rate per 100 PY (95% CI)	Events	Person-years	Rate per 100 PY (95% CI)
Early Suppression (Years 2–5)						
<200	218	1017	21.4 (16.8, 27.3)	8	9	[b]
200–350	346	2297	15.1 (12.5, 18.1)	74	427	17.3 (11.7, 25.6)
351–500	212	2015	10.5 (8.6, 12.9)	145	1834	7.9 (6.3, 9.9)
>500	189	1702	11.1 (8.5, 14.4)	427	6285	6.8 (5.8, 7.9)
Long-term Suppression (Years 6–11)						
<200	13	58	[b]	4	5	[b]
200–350	58	374	15.5 (10.7, 22.6)	12	41	[b]
351–500	79	661	12.0 (8.5, 16.8)	28	221	12.7 (7.4, 21.6)
>500	104	1205	8.6 (6.6, 11.4)	107	1780	6.0 (4.6, 7.9)

Abbreviations: CI, confidence interval; PY, person-years.
[a] Weighted 24-month moving average updated every six months of virologic suppression. Weights are the inverse of the distance to the six-month interval start date.
[b] Rates were not estimated because of small sample size.

Table 5.5. Incidence rate ratios for all-cause hospitalizations, censoring person-time after a chemotherapy hospitalization or CD4 count decline.

Current CD4 count, cells/μL [a]	Lowest pre-suppression CD4 count <200 cells/μL		Lowest pre-suppression CD4 count ≥200 cells/μL	
	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]
Early Suppression (Years 2–5)				
<200	2.08 (1.43, 3.02)	2.19 (1.32, 3.61)	[d]	[d]
200–350	1.46 (1.06, 2.01)	1.50 (1.03, 2.18)	2.00 (1.34, 2.99)	1.81 (1.15, 2.85)
351–500	1.06 (0.77, 1.45)	1.08 (0.77, 1.52)	1.20 (0.93, 1.54)	1.19 (0.90, 1.57)
>500	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Long-term Suppression (Years 6–11)				
<200	[d]	[d]	[d]	[d]
200–350	1.83 (1.13, 2.96)	1.68 (1.00, 2.82)	[d]	[d]
351–500	1.50 (0.98, 2.28)	1.41 (0.92, 2.16)	2.20 (1.19, 4.07)	2.02 (1.10, 3.70)
>500	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref., referent.
[a] Weighted 24-month moving average updated every six months of virologic suppression. Weights are the inverse of the distance to the six-month interval start date.
[b] Estimates and 95% CI separate Poisson regression models adjusted for NA-ACCORD cohort, with generalized estimating equations to account for patients contributing more than one hospitalization to the analysis.
[c] Estimates and 95% CI separate Poisson regression models with generalized estimating equations, adjusted for NA-ACCORD cohort, age, gender, calendar year, years of virologic suppression, and lowest prior CD4 count.
[d] Because of small sample size, we did not estimate IRR for this category.

Table 5.6. Distribution of hospitalizations and person-time, and hospitalization rates per 100 person-years, counting only one hospitalization per six-month interval.

Current CD4 count, cells/μL [a]	Lowest pre-suppression CD4 count <200 cells/μL			Lowest pre-suppression CD4 count ≥200 cells/μL		
	Events	Person-years	Rate per 100 PY (95% CI)	Events	Person-years	Rate per 100 PY (95% CI)
Early Suppression (Years 2–5)						
<200	153	987	15.5 (12.7, 18.9)	6	8	[b]
200–350	237	2251	10.5 (9.0, 12.3)	46	420	11.0 (8.1, 14.9)
351–500	169	1979	8.5 (7.1, 10.2)	112	1810	6.2 (5.0, 7.6)
>500	139	1674	8.3 (6.7, 10.2)	331	6213	5.3 (4.7, 6.1)
Long-term Suppression (Years 6–11)						
<200	11	56	[b]	3	5	[b]
200–350	50	365	13.7 (9.7, 19.3)	8	40	[b]
351–500	59	649	9.1 (6.8, 12.2)	21	216	9.7 (6.0, 15.7)
>500	87	1190	7.3 (5.5, 9.7)	90	1760	5.1 (4.0, 6.5)

Abbreviations: CI, confidence interval; PY, person-years.
[a] Weighted 24-month moving average updated every six months of virologic suppression. Weights are the inverse of the distance to the six-month interval start date.
[b] Rates were not estimated because of small sample size.

Table 5.7. Incidence rate ratios for all-cause hospitalizations, when including only one hospitalization per six-month interval.

Current CD4 count, cells/μL [a]	Lowest pre-suppression CD4 count <200 cells/μL		Lowest pre-suppression CD4 count ≥200 cells/μL	
	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]
Early Suppression (Years 2–5)				
<200	1.95 (1.47, 2.59)	1.88 (1.34, 2.65)	[d]	[d]
200–350	1.34 (1.04, 1.74)	1.32 (0.99, 1.74)	2.05 (1.46, 2.87)	1.98 (1.37, 2.85)
351–500	1.09 (0.84, 1.42)	1.09 (0.83, 1.43)	1.17 (0.92, 1.48)	1.19 (0.92, 1.54)
>500	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Long-term Suppression (Years 6–11)				
<200	[d]	[d]	[d]	[d]
200–350	1.87 (1.20, 2.90)	1.74 (1.10, 2.74)	[d]	[d]
351–500	1.32 (0.91, 1.93)	1.25 (0.85, 1.83)	1.93 (1.13, 3.30)	1.83 (1.06, 3.16)
>500	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref., referent.
[a] Weighted 24-month moving average updated every six months of virologic suppression. Weights are the inverse of the distance to the six-month interval start date.
[b] Estimates and 95% CI separate Poisson regression models adjusted for NA-ACCORD cohort, with generalized estimating equations to account for patients contributing more than one hospitalization to the analysis.
[c] Estimates and 95% CI separate Poisson regression models with generalized estimating equations, adjusted for NA-ACCORD cohort, age, gender, calendar year, years of virologic suppression, and lowest prior CD4 count.
[d] Because of small sample size, we did not estimate IRR for this category.

Table 5.8. Incidence rate ratios for all-cause hospitalizations, when excluding ART-experienced patients.

Current CD4 count, cells/μL [a]	Lowest pre-suppression CD4 count <200 cells/μL		Lowest pre-suppression CD4 count ≥200 cells/μL	
	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]
Early Suppression (Years 2–5)				
<200	2.00 (1.36, 2.95)	1.87 (1.14, 3.05)	[d]	[d]
200–350	1.52 (1.05, 2.19)	1.45 (0.97, 2.18)	2.65 (1.68, 4.18)	2.46 (1.44, 4.18)
351–500	1.06 (0.74, 1.53)	1.05 (0.71, 1.53)	1.22 (0.93, 1.59)	1.22 (0.91, 1.63)
>500	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Long-term Suppression (Years 6–11)				
<200	[d]	[d]	[d]	[d]
200–350	1.72 (1.04, 2.87)	1.47 (0.89, 2.45)	[d]	[d]
351–500	1.78 (1.13, 2.81)	1.58 (1.00, 2.50)	1.93 (1.05, 3.54)	1.85 (0.99, 3.42)
>500	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref., referent.
[a] Weighted 24-month moving average updated every six months of virologic suppression. Weights are the inverse of the distance to the six-month interval start date.
[b] Estimates and 95% CI separate Poisson regression models adjusted for NA-ACCORD cohort, with generalized estimating equations to account for patients contributing more than one hospitalization to the analysis.
[c] Estimates and 95% CI separate Poisson regression models with generalized estimating equations, adjusted for NA-ACCORD cohort, age, gender, calendar year, years of virologic suppression, and lowest prior CD4 count.
[d] Because of small sample size, we did not estimate IRR for this category.

Table 5.9. Incidence rate ratios for all-cause hospitalizations, when adjusting for age using restricted quadratic splines with four equidistant knots.

Current CD4 count, cells/µL [a]	Lowest pre-suppression CD4 count <200 cells/µL	Lowest pre-suppression CD4 count ≥200 cells/µL
	Adjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [b]
Early Suppression (Years 2–5)		
<200	2.02 (1.27, 3.21)	[c]
200–350	1.44 (1.01, 2.06)	2.46 (1.51, 4.02)
351–500	1.01 (0.73, 1.40)	1.22 (0.93, 1.61)
>500	1 (ref.)	1 (ref.)
Long-term Suppression (Years 6–11)		
<200	[c]	[c]
200–350	1.66 (1.02, 2.71)	[c]
351–500	1.38 (0.91, 2.09)	2.07 (1.16, 3.68)
>500	1 (ref.)	1 (ref.)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref., referent.
[a] Weighted 24-month moving average updated every six months of virologic suppression. Weights are the inverse of the distance to the six-month interval start date.
[b] Estimates and 95% CI separate Poisson regression models with generalized estimating equations, adjusted for NA-ACCORD cohort, age, gender, calendar year, years of virologic suppression, and lowest prior CD4 count.
[c] Because of small sample size, we did not estimate IRR for this category.

Table 5.10. Incidence rate ratios for all-cause hospitalizations, among patients whose lowest known prior CD4 count was between 200 and 350 cells/μL.

Current CD4 count, cells/μL [a]	Lowest pre-suppression CD4 count 200–350 cells/μL	
	Unadjusted IRR (95% CI) [b]	Adjusted IRR (95% CI) [c]
Early Suppression (Years 2–5)		
<200	[d]	[d]
200–350	2.01 (1.31, 3.09)	1.75 (1.04, 2.93)
351–500	1.15 (0.86, 1.54)	1.12 (0.81, 1.55)
>500	1 (ref.)	1 (ref.)
Long-term Suppression (Years 6–11)		
<200	[d]	[d]
200–350	[d]	[d]
351–500	2.01 (1.09, 3.71)	1.69 (0.92, 3.12)
>500	1 (ref.)	1 (ref.)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref., referent.
[a] Weighted 24-month moving average updated every six months of virologic suppression. Weights are the inverse of the distance to the six-month interval start date.
[b] Estimates and 95% CI separate Poisson regression models adjusted for NA-ACCORD cohort, with generalized estimating equations to account for patients contributing more than one hospitalization to the analysis.
[c] Estimates and 95% CI separate Poisson regression models with generalized estimating equations, adjusted for NA-ACCORD cohort, age, gender, calendar year, years of virologic suppression, and lowest prior CD4 count.
[d] Because of small sample size, we did not estimate IRR for this category.

Figures

Figure 5.1. Flowchart of patient inclusion and follow-up.

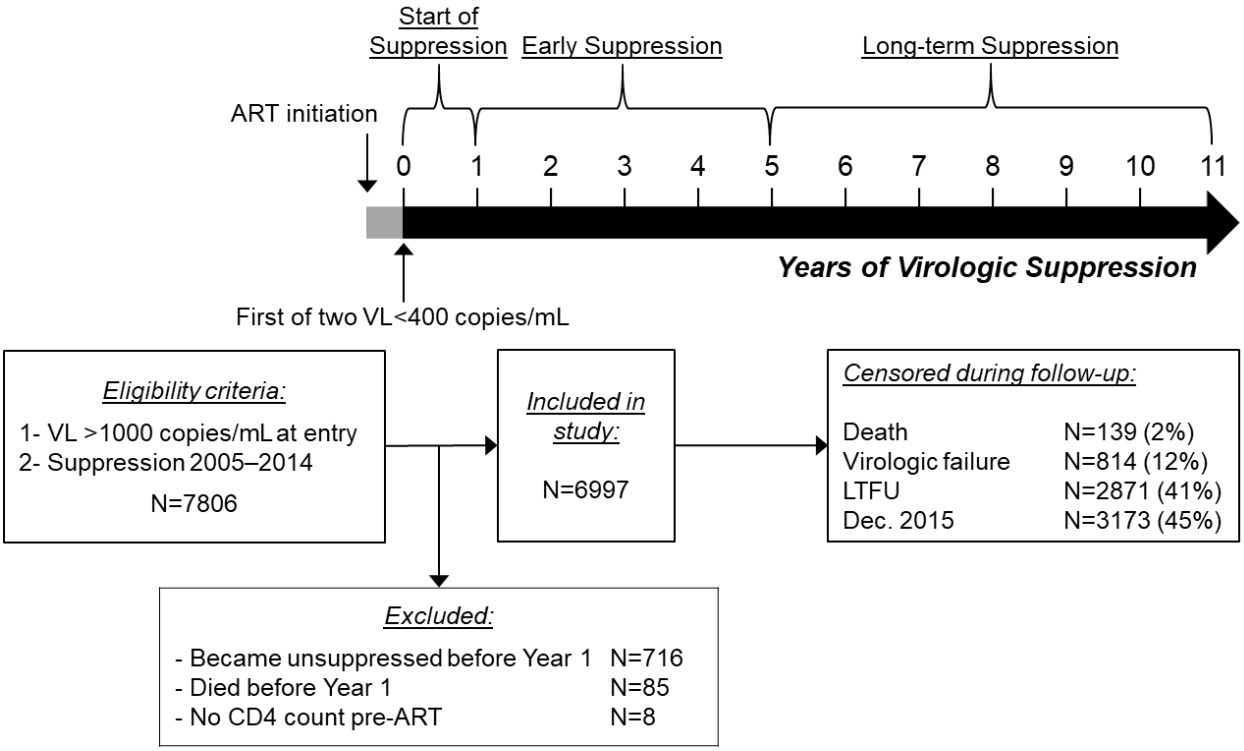


Figure 5.2. CD4 cell count distribution from the first HIV viral load <400 copies/mL to Year 10 of sustained virologic suppression, among patients with a lowest pre-suppression CD4 count <200 (A) and ≥200 cells/μL (B). Shown are the median (solid line), interquartile range (band), and 5th and 95th percentiles (dashed lines). CD4 counts are 24-month weighted moving averages of up to three measurements, updated every six months of virologic suppression. Values for Year 11 are not displayed due to small sample sizes.

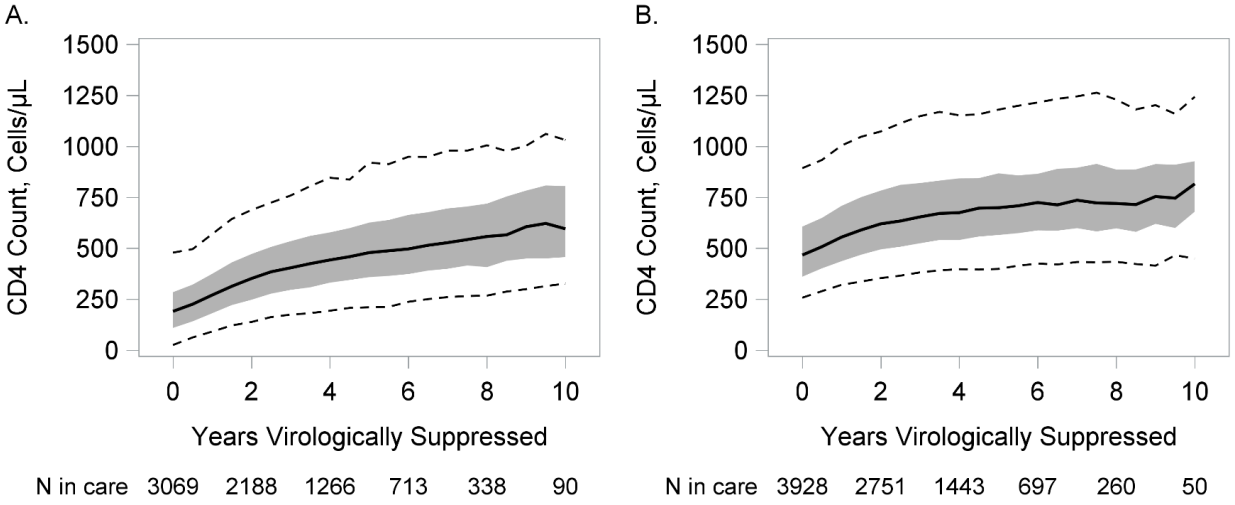


Figure 5.3. Unadjusted all-cause hospitalization rates by CD4 cell count category, stratified by early (Years 2–5) or long-term (Years 6–11) virologic suppression, among patients with a lowest pre-suppression CD4 count <200 (A) and ≥200 cells/μL (B). Error bars are the 95% confidence intervals. Rates were not estimated for categories with less than 100 person-years.

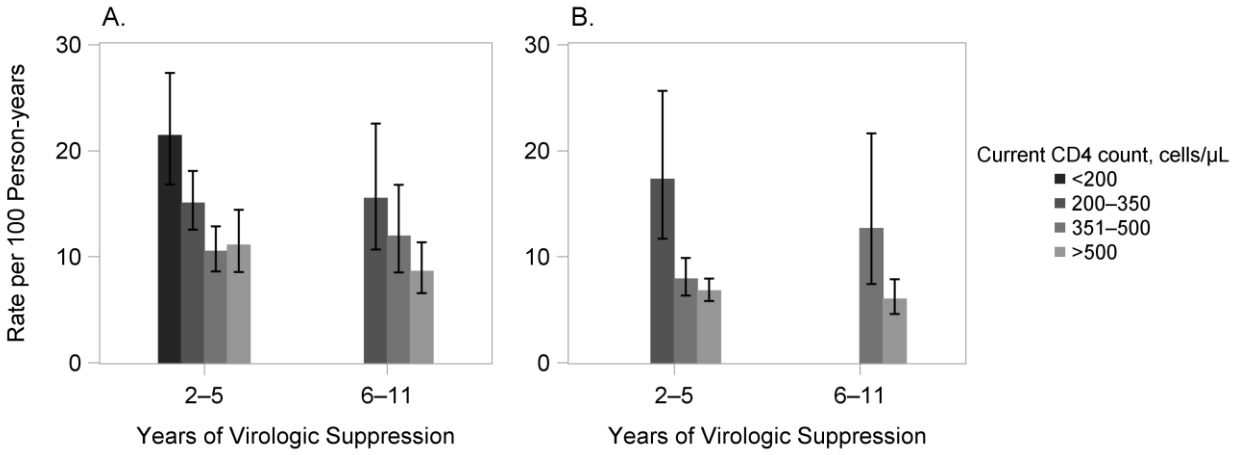
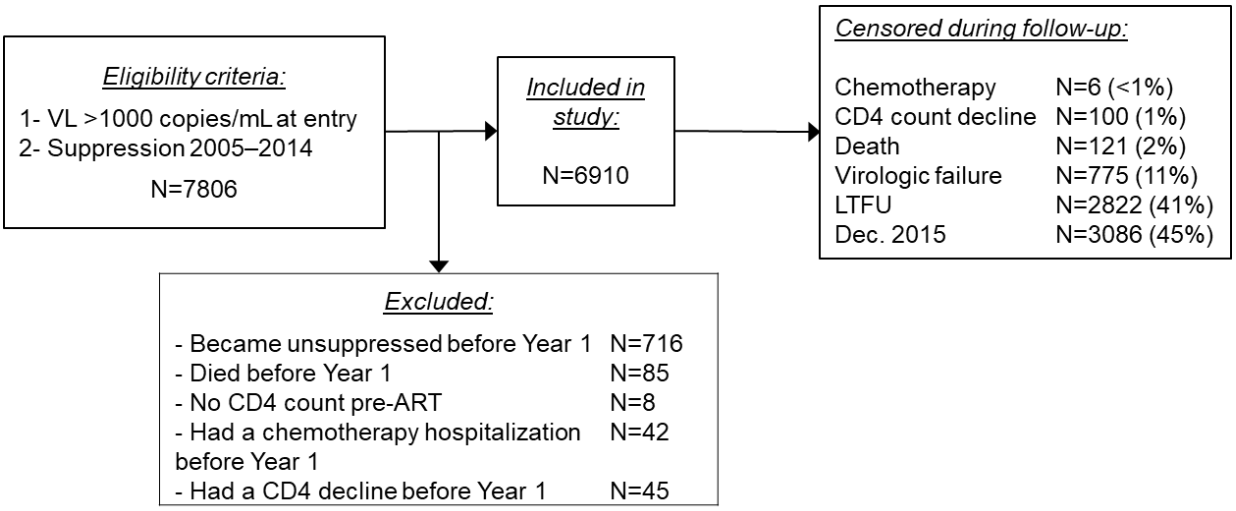


Figure 5.4. Inclusion, exclusion, and censoring criteria when censoring person-time after a chemotherapy hospitalization or CD4 count decline.



CHAPTER VI: CONCLUSIONS

Summary

In this study of persons with HIV in the US and Canada, from 2005 to 2015, all-cause hospitalization rates decreased from 23 to 13 hospitalizations per 100 person-years. Hospitalization rates among PWH remained slighted elevated compared to the general population, with estimates of 11 and 8 per 100 person-years in the US and Canada in 2015, respectively. Among PWH who achieved and maintained virologic suppression, hospitalization rates were low overall and decreased as patients experienced CD4 recovery above 500 cells/μL during long-term suppression, with rates of 9 and 6 per 100 person-years among patients whose lowest pre-suppression CD4 counts were <200 and ≥200 cells/μL, respectively.

In Aim 1, we observed that while hospitalization rates decreased among patients in almost all racial/ethnic and gender groups, notable disparities persisted. In 2015, Black patients continued to experience rates that were approximately 1.1–1.5 times those of White patients depending on their gender. Cisgender women also had rates that were 1.4 times those cisgender men. Over the entire study period, Indigenous cisgender women and transgender patients had some of the highest burden of hospitalizations.

When we examined cause-specific hospitalizations, Black cisgender men had higher rates than White cisgender men for cardiovascular, renal/genitourinary, and endocrine/metabolic conditions. Hospitalizations for AIDS-defining illness were also more frequent among Black, Hispanic, and Indigenous cisgender men. Black and Hispanic cisgender women had approximately twice the rate of White cisgender women in the non-AIDS-defining cancer category.

These hospitalization disparities were explained in part by differences in CD4 count and virologic suppression. CD4 counts and virologic suppression rates increased substantially over time for all patients but remained lower among cisgender women and Black and Hispanic PWH. However, after adjusting for CD4 count and HIV viral load, differences in all-cause and most cause-specific hospitalizations were still present, indicating that other factors contributed to these disparities.

In Aim 2, among patients with virologic suppression for at least one year, those with less robust CD4 count recovery experienced higher hospitalization rates, irrespective of their immunodeficiency prior to virologic suppression. During long-term virologic suppression (Years 6–11), patients with CD4 counts 350–500 cells/μL had 1.5–2.2 times the hospitalization rates of patients with CD4 counts >500 cells/μL. These differences were observed after adjusting for age and other factors and after censoring the person-time of patients with likely immune decline. In addition, when including only one hospitalization per patient per six-month interval, to account for the possible contribution of a subset of sicker patients, the strong association between lower CD4 count and higher hospitalization rates persisted.

Strengths

The strengths of this study include 11 years of data on HIV care and hospitalizations, including discharge diagnoses allowing us to examine cause-specific hospitalization rates. Our data came from six clinical cohorts, one in Canada and five across the US, representing a racially diverse group of PWH receiving health care coverage through the Canadian provincial system, private insurers, integrated health systems, and US public programs such as Medicare and Medicaid.

The large sample size and long follow-up allowed us to examine hospitalizations after up to 11 years of virologic suppression, stratified by both current and past CD4 counts. The number of hospitalizations in our data was sufficiently large to examine in detail rates for all-cause

hospitalizations, and several causes of hospitalization in Aim 1. In addition, we described all-cause hospitalization rates in several smaller patient groups, including Asian, Indigenous, and transgender PWH, for whom hospitalization estimates in the US and Canada are scarce.

Finally, our study spans calendar years 2005 to 2015, a period during which important changes in HIV care occurred. The FDA approved single-table ART regimens and agents in the new class of integrase strand transfer inhibitors [119, 120]. ART became recommended for all PWH irrespective of CD4 count [3]. PWH in this period experienced drastic improvements in virologic suppression rates and a continued decrease in mortality rates, leading to half of PWH in North America being at least 50 years old [7, 9, 10, 13]. The Patient Protection and Affordable Care Act, passed in 2010, included several provisions aiming to reduce hospitalization rates, and substantially changed insurance coverage among PWH in some states [79, 80].

Limitations

Missing data

For clinical cohorts based on the electronic health records of a single academic center, it is likely that hospitalizations taking place at other hospital systems were not captured. Previous analyses conducted in the University of North Carolina Center for AIDS Research HIV Clinical Cohort showed that this missingness could lead to slightly underestimated hospitalization rates but similar findings for calendar time trends [121]. In addition, a substantial proportion of patients in our study received care through an integrated health system or Canadian provincial health care, which might not be affected by this limitation to the same degree.

Missingness for other study variables was negligible. Discharge diagnosis was missing for about 1% of hospitalizations. CD4 count and HIV viral load were missing for small proportions of person-years (Aim 1: 2% of person-years missing CD4 count, 2% missing viral load; Aim 2: <1% of person-years missing CD4 count). Race/ethnicity was missing for 3% of patients in both Aims.

Measurement error

ICD coding for hospital discharge diagnoses is subject to error. However, coding of inpatient services is generally accurate in settings with trained medical coders, such as hospitals, and is incentivized by reimbursement needs and frequent audits [122-125]. Nonetheless, primary discharge diagnoses capture the most proximal cause of hospitalization and may not reflect complex clinical profiles or underlying conditions. For example, a patient with cancer may be hospitalized with a discharge diagnosis of bacterial pneumonia. Analyses of cause-specific hospitalizations should be interpreted with these considerations.

CD4 cell count measurements can vary substantially according to time of day, body mass index, age, sex, and other external factors [91]. In addition, CD4 cell counts and HIV viral loads might change throughout a one-year or six-month interval of analysis. Use of a single measurement in Aim 1 could lead to residual confounding in estimates adjusted for those variables. In Aim 2, this variability is of lesser concern, as we calculated 24-month moving averages to assign patients to a CD4 count category. Aim 2 analyses also used multiple viral load measurements to define virologic suppression and failure. This approach avoids the inclusion of patients with intermittent adherence in our study, or the censoring of patients with viral blips.

Generalizability

To be eligible for observation in the NA-ACCORD, patients must have at least two HIV care visits in a 12-month period. In Aim 1, patients also had to receive HIV care, in the form of a CD4 count or HIV viral load, at least once every 12 months to remain in the analysis. Our findings might therefore not be generalizable to PWH who are not well engaged in HIV care. In particular, factors affecting engagement in care could lead to higher hospitalization rates.

Generalizability of our findings to PWH who are in care (Aim 1) or virologically suppressed (Aim 2) in the US and Canada might be limited for other reasons. While many types

of health care setting and payer are represented in our study, it is likely that patients in integrated health systems were overrepresented compared to PWH in the US. Other patients in our study received HIV care at academic medical centers, which might be different from care received in other settings, for example in access to specialist care or support services. In addition, local factors can affect hospitalization rates. Notably, Medicaid expansion in US states, urban versus rural characteristics, and local support organizations can have an impact on access to health care and other services, such as housing or transportation assistance. The six cohorts in this study might not capture the experiences of all PWH in the US and Canada.

Public health significance

The findings of this study emphasize the importance of early HIV diagnosis, early ART initiation, and sustained engagement in HIV care. Racial/ethnic and gender disparities in hospitalization rates persist alongside differences in CD4 cell count and virologic suppression rates. Ensuring that all patients can remain on virologically suppressive ART will help reduce the disparities in hospitalizations between demographic groups of PWH. In addition, initiating ART with higher CD4 counts will lead to better CD4 count recovery, prevent AIDS and non-AIDS morbidity, and can contribute to lower hospitalization rates over the long term. This is especially important given that CD4 counts even modestly lower than the 500 cells/μL threshold were associated with increased hospitalization rates.

Efforts should target social and clinical factors that challenge ART adherence and care engagement. This includes diagnosing and treating substance use disorders, as well as addressing unstable housing, food insecurity, caregiving responsibilities, lack of transport to clinic, and inadequate health insurance coverage leading to out-of-pocket costs. These factors can contribute to PWH delaying seeking care and can negatively impact both HIV and non-HIV health outcomes. Providers should also ensure that vulnerable populations, including immigrants, racial/ethnic minorities, and transgender PWH, receive culturally competent care

free of stigma and in a welcoming environment. Hospitalizations themselves might be opportunities to link or re-engaged patients who are not in HIV care [126].

With low rates of hospitalization for AIDS-defining illness, our study highlights the importance of preventing, diagnosis, and treating comorbidities among PWH. Approaches to accomplish this could be to integrate HIV and non-HIV care in a single location, to delegate HIV care to other primary care providers, or to improve coordination of care between different providers. Studies have shown that several models of care can produce similar HIV care outcomes [127], and approach selection may ultimately vary according to patient preference, insurance coverage, and clinical complexity. Patients with multiple comorbidities, one-quarter of PWH in the US, might have the highest hospitalization risk and benefit the most from such care strategies [44].

Overall, our findings can inform clinical management strategies aiming to reduce hospitalization burden among PWH, which is important for several reasons. Firstly, hospitalizations might represent a previously missed opportunity for preventing disease progression. Secondly, hospitalizations put patients at risk of adverse health outcomes. Up to 30% of hospitalized PWH experience antiretroviral medication errors [128]. Hospitalized PWH have a high incidence of nosocomial infections, 15 per 1000 hospitalized person-days [129]. Thirdly, hospitalizations are expensive. For the period 2008–2011, annual hospitalization costs among PWH were about $4200 per person, including costs to both patients and other payers [130]. Hospitalizations, which last on average one week for PWH, are also substantial disruptions to caregiving and work responsibilities and might lead to further financial burden.

Future directions

The work raises several questions that merit further study. Understanding of the relationship between CD4 cell counts and hospitalization rates can inform clinical management of patients with incomplete CD4 count recovery. Persistently low CD4 counts despite sustained

virologic suppression could be a marker for a high burden of comorbidities caused by late ART initiation. It is also possible that for a given clinical profile, patients with incomplete CD4 count recovery have worse outcomes due to immune dysfunction. It should be evaluated whether these patients might benefit from more aggressive prevention and treatment of comorbidities.

This study's follow-up ends December 31, 2015. As HIV care evolves, hospitalization rates should continue to be examined. For example, the US and Canada have been affected by epidemics of substance use, including opioid, cocaine, and methamphetamine. Approximately 11% of PWH engaged in HIV care use cocaine, and 13% methamphetamine [131]. Opioid misuse is relatively low among PWH in care, but injection of opioids has led to HIV outbreaks throughout the US [131-134]. Rates of infective endocarditis associated with injection drug use have increased drastically in some areas [135]. Studies examining hospitalizations for overdose, withdrawal, and injection-related infections would provide important information on the evolving burden of substance use among PWH in this region.

Our findings highlighted the preponderance of hospitalizations due to non-AIDS-defining infections, most commonly sepsis/bacteremia, bacterial pneumonia, and cellulitis/cutaneous abscess. Additional work is needed to understand underlying causes and identify risk factors for these infections. Incorporating additional data elements, such as smoking, ongoing injection drug use, and diagnosed comorbidities can shed light on the clinical profile of patients at risk and on possible prevention strategies. Reducing infections among PWH might also prevent other morbidity, as sepsis contributes to type 2 myocardial infarctions in these patients [136].

Finally, studies should determine whether hospital readmission rates have decreased alongside hospitalization rates. Prior studies have shown that 30-day readmission risk is approximately 20% among PWH and 1.5 times that of persons without HIV [90, 137]. Improvements in CD4 count and virologic suppression might have led to decreases in readmissions. However, among patients who are hospitalized, older age, uncontrolled HIV, and comorbidities could still be contributing to frequent readmissions.

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