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Trends and Causes of Hospitalizations among HIV-Infected Persons during the Late HAART Era: What is the Impact of CD4 Counts and HAART Use?

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Abstract

Background—Declining rates of hospitalizations occurred shortly after the availability of HAART. However, trends in the late HAART era are less defined, and data on the impact of CD4 counts and HAART use on hospitalizations are needed.

Methods—We evaluated hospitalization rates from 1999–2007 among HIV-infected persons enrolled in a large U.S. military cohort. Poisson regression was used to compare hospitalization rates per year and to examine factors associated with hospitalization.

Results—Of the 2,429 participants, 822 (34%) were hospitalized at least once with 1,770 separate hospital admissions. The rate of hospitalizations (137 per 1,000 PYs) was constant over the study period (relative rate, RR 1.00 per year change, 95% CI, 0.98–1.02). The hospitalization rates due to skin infections (RR 1.50, p=0.02), MRSA (RR 3.19, p=0.03), liver disease (RR 1.71, p=0.04), and surgery (RR 1.17, p=0.04) significantly increased over time, while psychological causes (RR 0.60, p<0.01) and trauma (RR 0.54, p<0.01) decreased. In the multivariate model, higher nadir CD4 (RR 0.92 per 50 cells, P<0.01) and higher proximal CD4 counts (RR of 0.71 for 350–499 vs. <350 cells/mm^3 and RR 0.67 for >500 vs. <350 cells/mm^3, both P<0.01) were associated with lower risk of hospitalization. Risk of hospitalization was constant for proximal CD4 levels above 350 (RR 0.94 P=0.51, CD4 ≥500 vs. 350–499). HAART was associated with a reduced risk of hospitalization among those with a CD4 <350 (RR 0.72, P=0.02), but had smaller

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estimated and non-significant effects at higher CD4 levels (RR 0.81, P=0.33 and 1.06, P=0.71 for CD4 350–499 and ≥500, respectively).

Conclusions—Hospitalizations continue to occur at high rates among HIV-infected persons with increasing rates for skin infections, MRSA, liver disease, and surgeries. Factors associated with a reduced risk of hospitalization include CD4 counts >350 cells/mm^3 and HAART use among patients with a CD4 count <350 cells/mm^3.

Keywords

HIV; hospitalization; morbidity; complications; MRSA infections; surgery; epidemiology

Background

Declining rates of hospitalizations occurred shortly after the availability of highly active antiretroviral therapy (HAART) [1–8] along with significant reductions in both the length of stay and hospital mortality rates [2,9,10]. These dramatic shifts were largely attributed to the effects of HAART, which decreased the incidence of AIDS events and improved the immune status of HIV-infected persons. Trends in hospitalization rates during the late HAART era are less defined, with some studies suggesting stabilization or increasing rates of hospitalizations [11–13]. The potential reasons for the lack of continued decline in hospitalization rates include aging of the HIV population, development of chronic end organ diseases, toxicity from long-term antiretroviral use, development of multidrug resistant viruses, and high prevalence of lifestyle-related factors such as illicit drug use and smoking.

As HIV-infected persons are surviving and experiencing longer life expectancies, hospitalizations have become an important outcome measure and are an important component of excess healthcare costs among this population. Hence, data on the rates of hospitalizations in the late HAART era are useful for both healthcare planning and the development of strategies to improve the health of HIV patients. Although higher CD4 counts and HAART use are known to decrease AIDS-defining events and death [14], their impact on hospitalizations is less certain, especially since many hospitalizations are now due to non-AIDS-defining comorbidities [6,15]. Further investigation into the effects of current treatment approaches [16] on hospitalization rates are needed [1].

We evaluated prospectively collected data from an observational HIV Natural History Study (NHS) to investigate the trends and causes of hospitalizations among HIV-infected persons during the late HAART era. In addition, we assessed the impact of time-updated CD4 cell counts and antiretroviral medication use on hospitalization events during the late HAART era.

Methods

Study Cohort

We examined data collected from participants in the U.S. Military NHS, an ongoing, multicenter, prospective, observational study of military personnel and beneficiaries with HIV infection, as previously described [17,18]. All active duty U.S. military personnel are confirmed HIV-negative prior to enlistment and undergo routine HIV screening every one to five years. Participants in the NHS are evaluated every six months by an HIV specialist as part of the study, in addition to receiving routine clinical care. Data collected include demographics (age, gender, and self-reported ethnicity), markers of HIV progression, ongoing medical history, and HAART use as previously defined [18]. Chronic hepatitis B was defined as two positive surface antigen tests over time and chronic hepatitis C as a

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positive antibody test. Standardized collection of hospitalization data in the NHS began in 1999. This substudy evaluated data from 1999–2007 among 2,429 HIV-infected persons.

Hospitalization Data Collection

Hospitalizations were defined as a ≥24 hours admission to an inpatient hospital ward and were captured among both discharged patients and those who died during admission. Data on hospitalizations were collected at each six month visit using admission records and discharge summaries. Since participants were military beneficiaries, most admissions were to a military facility, which were collected via computerized medical review. In addition, participants were asked about any other hospitalizations including at civilian facilities and these data were collected to ensure complete hospitalization data. For this study, the primary cause of hospitalization was used and was categorized based on an organ and disease system coding scheme as shown in the appendix. Diseases not within one of these categories or when the diagnosis was unknown were coded as `other'. Each hospitalization was placed into a single category.

In addition to these categories, a review of each discharge diagnosis was performed to assess for other clinically relevant medical diagnoses, and these were assigned an additional non-mutually exclusive reason for hospitalization. These diagnoses included AIDS-defining illnesses excluding solely a CD4 count <200 cells/mm^3 [19], infection, skin/soft tissue infections, culture-confirmed MRSA infection, trauma, drug-related (illicit drug use, alcohol, or overdose), suicide attempt, and chronic end-organ diseases (chronic obstructive lung disease, asthma, congestive heart failure, cardiomyopathy, arrhythmia, coronary artery disease, cerebrovascular disease, hypertension, pancreatitis, chronic liver disease, or chronic renal disease) [6]. We also assessed each hospitalization if a surgical procedure was performed, and if so, whether the procedure was the primary reason for admission.

Statistical Methods

The number of hospitalizations, person years at risk, and rates of hospitalization (per 1,000 person years of follow-up) were calculated for the overall study period, individual study years, and the following *a priori* determined study periods: 1999–2001, 2002–2004, and 2005–2007. Each participant contributed person years at risk from their date of documented HIV diagnosis or January 1, 1999 (whichever was later) to their last follow-up visit or December 31, 2007 (whichever was earlier). Participants could be included in multiple time periods, and could contribute more than one hospitalization per time period. Hospitalization rates per period (year or year interval) were computed as total hospitalizations occurring during the period divided by total person years of follow-up in the period.

Comparisons of rates across periods were assessed using Poisson regression (with offset for person years) with a compound symmetry covariance structure to account for participants contributing to multiple periods. Analyses were done for total hospitalizations and for selected causes. Relative rates (RR) were estimated from the model using calendar year as a continuous variable entered either as a single year (1999–2007) or as an ordinal variable for the three year categories. Thus, RR presented is per year or per period difference (approximately 3 years). We utilized and reported one degree of freedom (DF) tests for linear trends over time; this strategy was chosen to be most clinically relevant and the most powerful test to determine if linear trends existed; however, two DF tests were also examined for differences among any of the three periods.

Poisson regression was also used to assess risk factors for hospitalization. For these analyses, risk factors were updated for each calendar year and the hospitalization rate for the subsequent year was modeled as a function of the current level of covariates. CD4 levels

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used were the last recorded value in the prior year (referred to as “proximal CD4” and categorized in thee levels) and the lowest CD4 recorded up through the prior year (referred to as “nadir CD4”). HAART was examined in the models using time-updated variables accounting for time on and off of antiretroviral medications and was recorded as the status at the beginning of the year. To assess if the effect of HAART use on hospitalization differed by CD4 level an interaction term (CD4 level x HAART use) was added to the model. Longitudinal models were used to compare characteristics of patients hospitalized across time periods. All analyses were conducted using SAS (version 9.1, Cary, NC); PROC GENMOD was used for Poisson regression modeling.

Results

Baseline Characteristics of Study Population

During the study period (1999–2007), 2,429 participants were followed for a total of 12,923 person years. The median length of follow-up during this period was 5.6 years. Mean age of participants at HIV diagnosis was 30 (SD 8) years; 91% were male; 46% reported to be African-American and 41% Caucasian/non-Hispanic. Documented HIV positive date was prior to 1996 for 48% of participants. Median CD4 count at HIV diagnosis was 488 cells/mm^3 (IQR: 344–644 cells/mm^3).

Table 1 shows the characteristics of the population during the overall study period and over the three time periods. The mean age during the study period was 37 (SD 10) years, mean duration of HIV infection was 7 (SD 5) years, and 62% were receiving HAART for a mean duration of 4 (SD 2) years. The mean CD4 count at HAART initiation was 352 cells/mm^3 (SD 207). The mean CD4 count throughout the study period was 554 (SD 286) cells/mm^3 with a nadir of 327 (SD 200) cells/mm^3, and 52% had a suppressed (<400 copies/ml) HIV RNA level. Characteristics of the cohort were similar over the time periods except for duration factors reflecting the aging of the cohort.

Rates and Causes of Hospitalizations

Of the 2,429 participants, 822 (33.8%) were hospitalized at least once during 1999–2007 with 1,770 separate hospital admissions. Of those hospitalized, 53% had one admission, 24% had two, 10% had three, and 13% had four or more admissions. The mean duration of hospitalization was 6.3 (SD 9.2) days and did not significantly vary over the study periods (6.6 (SD 5.6), 7.1 (8.2), and 5.1 (3.6) from earliest to latest periods). The longest hospitalizations were due to drug-related and psychiatric causes with a mean duration of 15 (SD 13.5) and 10 (20.2) days, respectively.

The overall rate of hospitalizations during the study period was 137 (95% CI, 131–143) per 1,000 PYs (Table 2). Rates during the three time periods were 137 (95% CI, 126–148), 148 (95% CI 137–159), and 125 (95% CI 115–137), respectively. The estimated relative rate slope was 1.00 per year (95% CI, 0.98–1.02). Age-adjusted hospitalization rates over the study period also showed no significant change over time (RR 0.98, 95% CI 0.96–1.01).

The unadjusted rates of the primary causes of hospitalization based on organ and disease system categories are shown in Table 3. The most common reason for hospitalization was gastrointestinal (rate 23.8 per 1,000 PYs), followed by bacterial infection (17.8 per 1,000 PYs), respiratory (15.8 per 1,000 PYs), and cardiovascular (12.0 per 1,000 PYs). The most frequent gastrointestinal cause was pancreatitis (appendix). There was 40% reduction (RR 0.60, 95% CI 0.46–0.77) from period to period in the rate of hospitalizations due to psychological causes which was most commonly a major depressive disorder. There were trends for rising rates of hospitalization for cancer (RR 1.50, P=0.06) and cardiovascular disease (RR 1.24, P=0.06), and decreasing trends for neurological disease (RR 0.75,

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P=0.05). We also examined the data using two DF and found no additional categories with significant p-values beyond that found with one DF.

We also examined rates of selected clinically relevant individual causes of hospitalizations (Table 4). AIDS-defining conditions occurred at a rate of 10.3 admissions per 1,000 PYs and did not significantly change over the study period (RR 0.95, 95% CI 0.71–1.27). Infections accounted for the highest rate of hospitalizations (rate 49.2 per 1,000 PYs) and also did not change over time (RR 0.94, 95% CI 0.84, 1.05). However, some non-AIDS-defining infections occurred at higher rates over time: hospitalizations for MRSA infections, although infrequent, increased 300% over time (RR 3.19, 95% 1.10–9.20) and skin/soft tissue infections increased by 50% (RR 1.50, 95% 1.07–2.09). Liver disease due to hepatitis B or C infection, cirrhosis, or other forms of hepatitis also accounted for an increasing rate of admissions (RR 1.71, 95% 1.03–2.83). Surgery as the primary reason for admission occurred at a rate of 21.9 per 1,000 PYs and increased over time (RR 1.17, 95% 1.01–1.35), as did any surgery being performed during admission (RR 1.14, 95% 1.01–1.29). Decreasing rates for trauma-related admissions were noted (RR 0.54, 95% CI 0.35–0.83).

In addition to rates, the proportion of hospitalizations due to specific causes was examined. AIDS-defining conditions accounted for 133 (7.5%) of admissions and did not change from 1999–2007. Infections were the most common cause of admission and accounted for 637 (36%) admissions, but also did not significantly change over time. Of infections, MRSA accounted for an increasing proportion of admissions (0.3%, 0.6%, and 2.9%, respectively). Likewise the proportion of admissions due to skin/soft tissue infections increased from 3.6%, 4.5%, to 8.3%. Surgery as the primary reason for admission accounted for 283 (16%) of hospitalizations, and this proportion increased over time: 12.8%, 16.0%, and 19.6%, respectively. By the last study period, any surgery (as either the primary reason or as a result of another reason) occurred among 28.5% of admissions. The most common type of surgery performed was orthopedic (n=86), followed by appendectomy due to acute appendicitis (n=37), abscess drainage procedure (n=37), human papillomavirus procedure for anal disease including cancer (n=30), hernia repair (n=30), and cardiovascular disease-related procedures (n=29).

Characteristics of Hospitalized HIV-Infected Persons and Trends in the HAART Era

We examined characteristics of HIV-infected persons who were hospitalized (Table 5). The mean age of hospitalized patients was 40.7 (SD 10.2) years, with age steadily increasing over the study period from 39 to 43 years ($p<0.001$). The percentage of hospitalized patients with hepatitis C increased over time from 8 to 14% ($p<0.01$). Hospitalized HIV-infected persons had a mean duration of HIV of 10 (SD 6) years, which progressively increased over the study period (8, 10, 11 years, $p<0.001$). The mean proximal CD4 count of those hospitalized also increased, although this did not reach statistical significance: 409, 437, and 466 cells/mm^3 ($p=0.18$); nadir CD4 counts did significantly increase over time ($p<0.01$). The HIV RNA level was suppressed among 47% of hospitalized patients which did not significantly change over time. While the percentage of patients currently receiving HAART also did not significantly change over time (overall 70%), the cumulative duration of HAART use was higher over time: 3, 5, and 7 years, respectively ($p<0.001$).

Factors Associated with Hospitalization

In a multivariate model, factors associated with a lower risk of hospitalization included higher nadir CD4 count (RR 0.92 per 50 cells, 95% CI 0.89–0.95, $p<0.01$) and higher proximal CD4 count (RR of 0.71 for 350–499 vs. <350 cells/mm^3 and RR 0.67 for >500 vs. <350 cells/mm^3, both $p<0.01$) (Table 6). The risk of hospitalization was further explored for proximal CD4 strata above 350 cells/mm^3 and found to be not significantly different (RR

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0.94, 95% CI 0.88–1.14, p=0.51, CD4 >500 vs. 350–499 cells/mm^3). HAART use among those with a CD4 <350 cells/mm^3 (RR 0.72, 95% CI 0.55–0.94, p=0.02) was associated with a reduced risk of hospitalization, but had a smaller estimated effect at CD4 levels of 350–499 cells/mm^3 (RR of 0.81, 95% CI 0.53–1.24, p=0.33) and no apparent effect at CD4 levels >500 cells/mm^3 (RR of 1.06, 95% CI 0.79–1.41, p=0.71). The test for CD4-HAART interaction was not significant (p=0.13). Chronic hepatitis C infection was associated with a higher risk of hospitalization (RR 1.46, 95% CI 1.05–2.03, p=0.02), with trends for female gender (RR 1.34, 95% CI 0.99–1.80, p=0.05). HIV duration was also examined, but was highly correlated with age. When HIV duration was included instead of age in the multivariate model, it had a borderline statistical significance (RR 1.02 per year, 95% CI 1.0–1.03, p=0.05). We also repeated the multivariate analyses for each of the three time periods; similar results were found, except that female was a risk factor for hospitalization early in the study period (1999–2001), but not significant in more recent years (data not shown). Multivariate analyses were repeated for non-AIDS-defining causes of hospitalizations and similar findings were noted (Table 6).

In addition, multivariate analyses for factors associated with fewer hospitalizations due to an infectious cause were performed. Stronger associations were found for nadir CD4 count (RR 0.86 per 50 cells, p<0.01) and proximal CD4 count (RR of 0.67 for 350–499 vs. <350 cells/mm^3 and RR 0.56 for >500 vs. <350 cells/mm^3, both p<0.01). HAART also appeared beneficial at CD4 counts <350 cells/mm^3 (RR 0.62, 95% CI 0.45–0.84, p<0.01) and at CD4 counts 350–499 cells/mm^3 (RR 0.58, 95% CI 0.34–0.99, p=0.05), but not at CD4 counts >500 cells/mm^3 (RR 1.34, 95% CI 0.85–2.10, p=0.21) (Table 6). Finally, factors associated with hospitalizations primarily due to a surgery procedure included increasing age (RR 1.25, 95% CI 1.06–1.48, p<0.01) and race; African Americans compared to Caucasians had a lower risk for hospitalization for surgery (RR 0.58, 95% CI 0.41–0.81, p<0.01). Neither CD4 counts nor HAART use was associated with admission for a surgical procedure.

Discussion

Our study demonstrates that hospitalizations continue to occur at high rates among HIV-infected persons and that these rates have not changed during the late HAART era. The causes of hospitalizations have diversified with non-AIDS-related comorbidities currently being the most common cause of admission. Our study has shown that CD4 counts >350 cells/mm^3 and the use HAART among persons with a CD4 count <350 cells/mm^3 are associated with reduced rates of hospitalization. These data suggest that HAART use by the current treatment guidelines [16] appears to be protective of hospitalizations due to non-AIDS-related causes.

Our study investigated the rates of hospitalization during the late HAART era and found that rates have stabilized and occurred at 137 per 1,000 PYs, a rate higher than both the in the general and military population [13,20–22]. In fact, one-third of HIV-infected persons required hospitalized at least once during our study period. In addition, the length of stay for hospitalizations also remained constant during the late HAART era. These data suggests that hospitalizations remain an important issue among HIV-infected persons, and provide useful information for planning future resource allocation and providing areas of focus to improve health among HIV-infected persons.

Infections were the most common cause of admission, although most were non-AIDS-defining. We noted increasing hospitalization rates due to skin and soft tissue infections as well as MRSA infections. These increases may reflect trends seen in the general population [23]. Another study also noted the importance of MRSA as a cause for hospitalizations among HIV-infected persons, although that study was among injection drug users [24]. Our

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military population consists mostly of non-drug users, suggesting that hospitalizations due to MRSA infections among these HIV patients are also occurring at increasing rates.

Chronic end organ diseases are an important cause of hospitalizations among HIV-infected persons [6,25]. Our study suggests that liver disease, and perhaps cardiovascular diseases and cancers, are increasingly important reasons for hospitalization. Other studies have demonstrated the increasing impact of chronic viral hepatitis and liver disease on admission rates [2,5,25–28], including one study that showed nearly 10% of admissions and one-third of in-hospital deaths were due to liver disease [29]. Many studies focused on the importance of hepatitis C virus on the increasing hospitalization rates of liver disease [2,28]; of note, we found increasing rates of liver disease despite an overall low prevalence of hepatitis C among our cohort. Together, these data emphasize the importance of the prevention of hepatitis co-infection, treatment of chronic viral hepatitis, and avoidance of other causes of hepatic injury as potential methods in reducing liver-related complications including hospitalizations.

Surgery as the cause of hospitalization occurred at an increasing rate, and by the last period was the primary reason for 29% of admissions. The most common surgeries were orthopedic in nature and were usually the result of degenerative disease or injury. The rising rate of surgery likely is a reflection of the aging of the HIV population and the military population served who may experience work-related injuries [20]. It may also reflect the increased willingness to perform surgical procedures as HIV patients are less often succumbing to opportunistic diseases [30,31].

We evaluated factors associated with hospitalizations and found that higher nadir and proximal CD4 counts were associated with a reduced rate of hospitalizations. A CD4 count of >350 cells/mm^3 was significantly related to a lower rate of admissions. Other studies have also noted the relationship between lower CD4 counts and hospitalizations [2,5,6,13,32]. These data emphasize the need for early diagnosis and treatment to maintain robust CD4 counts to further reduce hospitalization events.

Previous studies suggest that reductions in hospitalizations during the HAART era may be reaching its threshold [13]. In a study examining trends between 1996 and 2000 in 12 States, hospitalization rates substantially dropped after the introduction of HAART (by 25% between 1996–1998), but the subsequent decline was less robust (6% between 1998–2000) [32]. Similarly, a recent study showed that although rates continued to decline, they did so only modestly during the most recent period [6]. Most of the decrease in these hospitalization rates, especially during the early HAART era, was attributed to a reduction in AIDS-defining conditions. More recently, however, there has been an increase in hospitalizations due to non-AIDS-related diagnoses (e.g., liver disease) [32] suggesting that hospitalization rates could stabilize or increase over time. Our study showed stable admission rates over the late HAART era, perhaps due to the more recent time period examined (1999–2007), the early-diagnosed and treated cohort evaluated who had few AIDS-defining events, and aging of our population during the study period.

Although it is known that HAART has played a critical role in decreasing opportunistic events [14,33], its role on the impact of other causes of hospitalization is less defined. Since most admissions in our study were due to non-AIDS related causes, we were able to assess the relationship between HAART and non-AIDS hospitalizations. We found that HAART use was associated with approximately a 30% reduction in both all-cause and non-AIDS-defining hospitalization rates among those with CD4 counts <350 cells/mm^3. Although the risk of all-cause hospitalizations was lower among those on HAART at CD4 counts 350–500 cells/mm^3, this did not reach statistical significance. These data demonstrate that

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HAART use is beneficial in reducing hospitalizations when utilized at a threshold consistent with the current treatment guidelines [16]. Additionally, there may be potential benefits of HAART at higher CD4 counts (>350 cells/mm^3) for reducing specific types (e.g., infection-related) hospitalizations; further studies to confirm this finding are needed.

Increasing age was also associated with trends for increased hospital admissions, especially for non-AIDS causes and surgical procedures. These data suggests that the aging of the HIV population may be contributing to hospitalization rates in this population and may continue to impact these rates in the upcoming years. We noted that females during some time periods had a higher rate of hospitalization similar to other studies [6,13,32,34]; the exact nature of this finding is uncertain.

Like all studies, ours had potential limitations. Our cohort was comprised of mainly male patients; although this is similar to the male predominant HIV population in the U.S., we could not assess the factors specifically associated with hospitalizations among women or the impact of obstetric diagnoses. Our study did not ascertain if the cause of hospitalization was related to ARV toxicities; another study showed that 7% of admissions were related to ARV toxicities [35]. Although ARV toxicities probably accounted for some hospitalizations, it is likely that HAART is more apt to prevent, than cause, hospital admissions. Another potential limitation is that the diagnosis listed on discharge paperwork may not always accurately reflect the cause of admission; however, we reviewed the cases when the diagnosis was in question and verified the cause for these admissions. To maintain statistical power, we calculated rates based on broad categories of causes of hospitalization; however, we also performed a review of all hospitalization diagnoses and created other clinically relevant diagnosis categories. Regarding our findings of the protective benefit of HAART on hospitalizations, we acknowledge that HAART may also be a surrogate for better follow-up and healthier behaviors; however, only those who attended study and clinical care visits were included in our analyses. We also acknowledge the effect of HAART is difficult to assess in an observational study due the fact that discontinuation of HAART may be related to illness or other factors related to hospitalization. Finally, we did not have an HIV-negative comparator group for our study population.

Our study had several strengths including the availability of detailed and time-updated information on HIV specific factors. We also had access to detailed information on the cause of hospitalization with ability to verify the diagnoses, a unique characteristic in comparison to several prior studies. Our population consisted of HIV patients who had equal access to care, stable socioeconomic status, little illicit drug use, and universal healthcare coverage – characteristics which are known to affect hospitalizations [6,9,36,37], but were uniform in our population allowing for us to focus on the effect of HIV-specific factors on hospitalization rates. Our study cohort also was not affected by changing insurance policies which can impact hospitalizations over time; to our knowledge, there were consistent decisions and policies regarding hospitalizations at our medical facilities during the study period.

In summary, HIV-infected persons continue to experience high rates of hospitalizations in the late HAART era. Non-AIDS-related comorbidities are currently the most common cause of hospitalizations, with increasing rates of hospitalizations due to skin and soft infections, MRSA, and liver disease. Maintaining CD4 counts >350 cells/mm^3 and the use HAART among persons with a CD4 count <350 cells/mm^3 are associated with reduced hospitalization rates. These data emphasize the importance of early diagnosis and entry into care in further reducing hospitalizations among HIV-infected persons.

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Appendix

Specific diagnoses in each category and number of total hospitalizations for each cause:

Cancer

lymphoma – non-Hodgkins (28), lymphoma- Hodgkins (6), anal (12), melanoma (4), lung (3), prostate (3), Kaposi's sarcoma (2), breast (1), and other (9).

Cardiovascular

coronary artery disease/myocardial infarction (47), cerebrovascular disease/stroke (14), severe hypertension (13), deep vein thrombosis (10), peripheral artery disease (10), arrhythmia (7), pericarditis (3), congestive heart failure (2), myocarditis (2), cardiomyopathy (1), pericardial effusion (1), and other (45).

Gastrointestinal

Pancreatitis (45), cholelithiasis/cholecystitis (21), cirrhosis (20), peptic ulcer disease/reflux (9), chronic diarrhea (6), oral ulcer (1), esophagitis (1), other (204). The other category represents diagnoses without a specific code in our dataset; on individual review these were appendicitis (37), hernia repair (30), gastrointestinal bleeding (22), nausea/vomiting/ dehydration (17), gastroenteritis (16), small bowel obstruction (13), acute diarrhea (11), diverticular disease (9), and other (49).

Genitourinary

Nephrolithiasis (29), acute renal failure (19), and other (17).

Musculoskeletal

inflammatory arthropathy (7), avascular necrosis (6), degenerative arthropathy (3), myopathy (1), and other (118). The other categories contained most commonly an orthopedic surgical procedure (84) including back, knee, hip or shoulder surgeries and a variety of other diagnoses (34).

Neurological

meningitis – non-bacterial (23), seizures (18), neuropathy (7), encephalitis (4), AIDS-dementia complex (2), myelopathy (1), and other (39).

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Psychological

Major depression (74), bipolar disorder (9), schizophrenia (10), suicide attempt (10), sleep disorder (9), anxiety disorder (8), post-traumatic stress (1).

Respiratory

pneumonia (108), sinusitis (19), asthma exacerbation (11), pulmonary embolism (7), pneumothorax (6), chronic obstructive lung disease (2), lymphocytic interstitial pneumonia (1), and other (51).

Bacterial

Cutaneous abscess (34), cellulitis (30), perirectal abscess (26), syphilis (25), bacteremia (19), urinary tract infection/pyelonephritis (16), MRSA (10), C. difficile colitis (7), gonorrhea (5), Shigella (5), Salmonella (4), epididymitis (3), proctitis (2), MSSA (2), bacterial meningitis (1), endocarditis (1), and other (41).

Viral

human papillomavirus (24), herpes zoster (16), herpes simplex (9), hepatitis B (8), hepatitis C (5), cytomegalovirus (3), progressive multifocal leukoencephalopathy (3), mononucleosis (1), hepatitis A (1), varicella (1), and other (15).

Fungal

Pneumocystis (jiroveci) carinii (40), candidiasis (16), cryptococcus (4), coccidioidomycosis (1), and histoplasmosis (1).

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Table 1

Characteristics[1] of Study Population, 1999–2007

Characteristic[2]	All periods	1999–2001	2002–2004	2005–2007
Age, years	36.8 (9.7)	36.4 (8.9)	38.1 (9.4)	39.8 (10.1)
Female	213 (8.8%)	171 (9.6%)	172 (9.4%)	142 (8.0%)
Race				
Caucasian	1007 (41.5%)	725 (40.6%)	757 (41.3%)	743 (42.0%)
African American	1106 (45.5%)	849 (47.6%)	858 (46.8%)	796 (44.9%)
Hispanic	212 (8.7%)	143 (8.0%)	144 (7.9%)	154 (8.7%)
Other	104 (4.3%)	68 (3.8%)	75 (4.1%)	78 (4.4%)
Chronic hepatitis B	104 (4.3%)	95 (5.3%)	94 (5.1%)	81 (4.6%)
Chronic hepatitis C	150 (6.2%)	96 (5.4%)	120 (6.5%)	127 (7.2%)
HIV Duration, years	6.6 (5.4)	6.4 (4.7)	7.8 (5.6)	9.1 (6.5)
Currently on HAART, yes	1516 (62.4%)	1194 (66.9%)	1174 (64.0%)	1229 (69.4%)
HAART duration, years	3.8 (2.2)	2.5 (1.2)	4.6 (2.2)	6.5 (3.2)
Nadir CD4 count, cells/mm^3	327 (200)	316 (199)	315 (193)	306 (189)
Proximal CD4 count, cells/mm^3	554 (286)	534 (290)	571 (295)	563 (278)
HIV RNA, $\log_{10}$ copies/ml	2.9 (1.3)	2.8 (1.2)	2.9 (1.3)	2.6 (1.3)
HIV RNA <400 copies/ml	1155 (51.5%)	809 (54.6%)	866 (50.6%)	982 (58.4%)
Number of Patients followed	2429	1785	1834	1771

[1] Characteristics were at the midpoint of the interval

[2] Values are mean (standard deviation) or number (percentage)

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Table 2

Hospitalization Rate by Year[1]

Year	Patients follow-up during period	Patients hospitalized during period	Total Hospitalizations	Person-years of follow-up	Rate (95% CI) of Hospitalization[2]
1999–2007	2429	822	1770	12923	137 (131–143)
1999	1531	136	179	1412	127 (110–147)
2000	1545	165	215	1438	149 (131–171)
2001	1580	152	193	1450	133 (116–153)
2002	1621	162	212	1491	142 (124–163)
2003	1649	167	234	1518	154 (136–175)
2004	1609	151	222	1511	147 (129–168)
2005	1544	151	202	1443	140 (122–161)
2006	1515	140	181	1371	132 (114–153)
2007	1466	108	132	1290	102 (86–121)

[1] Unadjusted relative rate (95% CI) over time is 1.00 (0.98–1.02) and age adjusted rate is 0.98 (0.96–1.01) from Poisson Models

[2] Rates per 1,000 person-years

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Table 3

Hospitalization Rate[1] by Primary Organ and Disease System Category during Study Period, 1999–2007

Cause of Hospitalization	All periods	1999–2001	2002–2004	2005–2007	Relative Rate[2] (95% CI)	p-value[3]
Cancer						
Patients hospitalized	33	9	14	13		
Total hospitalizations	68	11	30	27	1.50 (0.98–2.29)	0.06
Rate	5.3 (4.1–6.7)	2.6 (1.4–4.6)	6.6 (4.5–9.5)	6.6 (4.5–9.6)		
AIDS-Defining Cancers						
Patients hospitalized	12	2	8	3		
Total hospitalizations	30	3	19	8	1.10 (0.92–1.32)	0.31
Rate	2.3 (1.6–3.3)	0.7 (0.2–2.2)	4.2 (2.7–6.6)	1.9 (1.0–3.9)		
Non-AIDS Defining Cancers						
Patients hospitalized	23	7	7	10		
Total hospitalizations	38	8	11	19	1.18 (0.96–1.44)	0.24
Rate	2.9 (2.1–4.0)	1.9 (0.9–3.7)	2.4 (1.3–4.4)	4.6 (2.9–7.2)		
Cardiovascular						
Patients hospitalized	103	31	43	44		
Total hospitalizations	155	36	66	53	1.24 (0.99–1.55)	0.06
Rate	12.0 (10.2–14.0)	8.4 (6.0–11.6)	14.6 (11.5–18.6)	12.9 (9.8–16.9)		
Gastrointestinal						
Patients hospitalized	201	68	87	74		
Total hospitalizations	307	82	129	96	1.14 (0.97–1.33)	0.11
Rate	23.8 (21.3–26.6)	19.0 (15.3–23.6)	28.7 (24.2–34.1)	23.3 (19.1–28.5)		
Genitourinary						
Patients hospitalized	56	22	21	17		
Total hospitalizations	65	23	25	17	0.89 (0.66–1.20)	0.45
Rate	5.0 (3.9–6.4)	5.3 (3.5–8.0)	5.5 (3.7–8.2)	4.1 (2.6–6.7)		
Musculoskeletal						

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Cause of Hospitalization	All periods	1999–2001	2002–2004	2005–2007	Relative Rate[2] (95% CI)	p-value[3]
Patients hospitalized	113	35	42	44		
Total hospitalizations	135	39	44	52	1.19 (0.94–1.50)	0.15
Rate	10.3 (8.7–12.3)	9.1 (6.6–12.4)	9.5 (7.0–12.8)	12.6 (9.6–16.6)		
Neurological						
Patients hospitalized	78	32	30	19		
Total hospitalizations	94	40	33	21	0.75 (0.57–1.01)	0.05
Rate	7.3 (5.9–8.9)	9.3 (6.8–12.7)	7.3 (5.2–10.3)	5.1 (3.3–7.8)		
Psychological						
Patients hospitalized	89	45	31	19		
Total hospitalizations	121	62	38	21	0.60 (0.46–0.77)	<0.01
Rate	9.3 (7.8–11.2)	14.4 (11.2–18.5)	8.4 (6.1–11.5)	5.1 (3.3–7.8)		
Respiratory						
Patients hospitalized	158	65	63	46		
Total hospitalizations	205	76	77	52	0.88 (0.73,1.05)	0.16
Rate	15.8 (13.8–18.2)	17.6 (14.1–22.1)	17.0 (13.6–21.3)	12.6 (9.6–16.6)		
Bacterial						
Patients hospitalized	165	49	70	62		
Total hospitalizations	231	63	89	79	1.17 (0.96–1.42)	0.13
Rate	17.8 (15.7–20.3)	14.6 (11.4–18.7)	19.7 (16.0–24.2)	19.2 (15.4–24.0)		
Viral						
Patients hospitalized	66	36	21	17		
Total hospitalizations	86	40	29	17	0.67 (0.50–0.90)	<0.01
Rate	6.6 (5.4–8.2)	9.3 (6.8–12.7)	6.4 (4.5–9.2)	4.1 (2.6–6.7)		
Fungal						
Patients hospitalized	42	21	12	12		
Total hospitalizations	62	30	17	15	0.73 (0.48–1.10)	0.13
Rate	4.8 (3.7–6.1)	7.0 (4.9–10.0)	3.8 (2.3–6.0)	3.6 (2.2–6.1)		

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Cause of Hospitalization	All periods	1999–2001	2002–2004	2005–2007	Relative Rate[2] (95% CI)	p-value[3]
Other						
Patients hospitalized	185	71	72	56		
Total hospitalizations	241	85	91	65	0.91 (0.78–1.07)	0.27
Rate	18.6 (16.4–21.1)	19.7 (16.0–24.4)	20.1 (16.4–24.7)	15.8 (12.4–20.2)		
Any Reason						
Patients hospitalized	822	376	383	337		
Total hospitalizations	1770	587	668	515	0.99 (0.92–1.07)	0.88
Rate	136.7 (130.5–143.2)	136.3 (125.7–147.8)	147.5 (136.8–159.2)	125.2 (114.9–136.5)		

[1] Rates presented are unadjusted and are per 1,000 person-years

[2] RR are estimated changes from one time interval to the next

[3] P-values from test for trends using 1 degree of freedom

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Table 4

Hospitalization Rate by Primary Specific Cause[1] during Study Period, 1999–2007

Cause of Hospitalization	All periods	1999–2001	2002–2004	2005–2007	Relative Rate[2] (95% CI)	p-value
AIDS Defining Condition						
Patients hospitalized	78	33	29	24		
Total hospitalizations	133	47	49	37	0.95 (0.71–1.27)	0.72
Rate	10.3 (8.7–12.2)	10.9 (8.2–14.5)	10.8 (8.2–14.3)	9.0 (6.5–12.4)		
Infection						
Patients hospitalized	401	171	166	139		
Total hospitalizations	637	230	226	181	0.94 (0.84–1.05)	0.27
Rate	49.2 (45.5–53.2)	53.4 (46.9–60.8)	49.9 (43.8–56.9)	44.0 (38.1–50.9)		
MRSA [3]						
Patients hospitalized	13	1	2	10		
Total hospitalizations	21	2	4	15	3.19 (1.10–9.20)	0.03
Rate	1.6 (1.1–2.5)	0.5 (0.1–1.9)	0.9 (0.3–2.4)	3.6 (2.2–6.1)		
Skin/Soft Tissue Infection						
Patients hospitalized	71	17	26	31		
Total hospitalizations	94	21	30	43	1.50 (1.07–2.09)	0.02
Rate	7.3 (5.9–8.9)	4.9 (3.2–7.5)	6.6 (4.6–9.5)	10.5 (7.8–14.1)		
Pneumonia						
Patients hospitalized	84	37	32	26		
Total hospitalizations	108	42	36	30	0.91 (0.70–1.18)	0.47
Rate	8.3 (6.9–10.1)	9.8 (7.2–13.2)	8.0 (5.7–17.0)	7.3 (5.1–10.4)		
Liver Disease [4]						
Patients hospitalized	21	4	14	7		
Total hospitalizations	34	5	17	12	1.71 (1.03–2.83)	0.04
Rate	2.6 (1.9–3.7)	1.2 (0.5–2.8)	3.8 (2.3–6.0)	2.9 (1.7–5.1)		

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Cause of Hospitalization	All periods	1999–2001	2002–2004	2005–2007	Relative Rate[2] (95% CI)	p-value
Chronic End-Organ Disease [5]						
Patients hospitalized	107	41	47	33		
Total hospitalizations	161	48	68	45	1.02 (0.94–1.10)	0.62
Rate	12.4 (10.7–14.5)	11.1 (8.4–14.8)	15.0 (11.8–19.0)	10.9 (8.2–14.7)		
Surgery, Primary Reason						
Patients hospitalized	218	70	85	91		
Total hospitalizations	283	75	107	101	1.17 (1.01–1.35)	0.04
Rate	21.9 (19.5–24.6)	17.4 (13.9–21.8)	23.6 (19.6–28.6)	24.6 (20.2–29.2)		
Surgery, Any [6]						
Patients hospitalized	310	104	131	126		
Total hospitalizations	424	115	162	147	1.14 (1.01–1.29)	0.03
Rate	32.7 (29.8–36.0)	26.7 (22.2–32.1)	35.8 (30.7–41.7)	35.8 (30.4–42.0)		
Drug-Related [7]						
Patients hospitalized	34	16	10	12		
Total hospitalizations	47	20	12	15	0.89 (0.59–1.35)	0.59
Rate	3.6 (2.7–4.8)	4.6 (3.0–7.2)	2.7 (1.5–4.7)	3.6 (2.2–6.1)		
Suicide Attempt						
Patients hospitalized	19	7	7	6		
Total hospitalizations	20	7	7	6	0.96 (0.56–1.64)	0.87
Rate	1.5 (1.0–2.4)	1.6 (0.8–3.4)	1.5 (0.7–3.2)	1.5 (0.7–3.2)		
Trauma/Injury-Related						
Patients hospitalized	37	19	13	6		
Total hospitalizations	41	22	13	6	0.54 (0.35–0.83)	<0.01
Rate	3.2 (2.3–4.3)	5.1 (3.4–7.8)	2.9 (1.7–4.9)	1.5 (0.7–3.2)		

[1] Rates per 1,000 person-years. Rates are unadjusted and based on clinically relevant diagnoses which were not mutually exclusive from the organ and disease categories presented in Table 3.

[2] RR are estimated changes from one time interval to the next

[3] MRSA was based on positive culture confirmation

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[4]Liver disease defined as an admission due to cirrhosis, hepatitis B, C, or other any other form of hepatitis

[5]Chronic end-organ diseases included chronic obstructive lung disease, asthma, congestive heart failure, cardiomyopathy, arrhythmia, coronary artery disease, cerebrovascular disease, hypertension, pancreatitis, chronic liver disease, and chronic renal disease

[6]Surgery performed during hospitalization regardless if it was the primary reason for admission

[7]Drug-related defined as alcohol or illicit drug use or an overdose as the cause of admission

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Table 5

Characteristics[1] of HIV-Infected Persons Hospitalized during the Study Period

Characteristics[2]	All periods	1999–2001	2002–2004	2005–2007	p-value[3]
Age, years	40.7 (10.2)	39.4 (10.3)	40.5 (10.2)	42.6 (9.7)	<0.001
Female	204 (11.5%)	96 (16.4%)	69 (10.3%)	39 (7.6%)	0.11
Race/ethnicity					0.99
Caucasian	775 (43.8%)	258 (44.0%)	295 (44.2%)	222 (43.1%)	
African American	769 (43.4%)	257 (43.8%)	283 (42.4%)	229 (44.5%)	
Hispanic	173 (9.8%)	55 (9.4%)	68 (10.2%)	50 (9.7%)	
Other	53 (3.0%)	17 (2.9%)	22 (3.3%)	14 (2.7%)	
Chronic hepatitis B	132 (7.5%)	44 (7.5%)	56 (8.4%)	32 (6.2%)	0.29
Chronic hepatitis C	213 (12%)	47 (8.0%)	93 (13.9%)	73 (14.2%)	<0.01
HIV Duration, years	9.7 (5.6)	8.2 (4.5)	9.8 (5.5)	11.2 (6.3)	<0.001
Nadir CD4 count, cells/mm^3	223 (181)	212 (183)	218 (184)	242 (173)	<0.01
Proximal CD4 Cell Count, cells/mm^3	437 (313)	409 (304)	437 (327)	466 (302)	0.18
Viral Load, $\log_{10}$ copies/ml	3.1 (1.5)	3.3 (1.5)	3.2 (1.4)	2.8 (1.4)	<0.001
Undetectable Viral Load <400 copies/ml	751 (46.8%)	238 (46.6%)	265 (43.4%)	248 (51.5%)	0.15
Currently receiving HAART, yes	1238 (69.9%)	396 (67.5%)	478 (71.6%)	364 (70.7%)	0.14
Duration of HAART Use, years	5.0 (2.8)	3.1 (1.3)	5.2 (2.2)	7.0 (3.2)	<0.001

[1] Characteristics were at the visit before hospitalization

[2] Values are mean (standard deviation) or number (percentage)

[3] P-values examine changes over the three time periods

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Table 6

Multivariate Analyses of Factors Associated with Hospitalization

	All Hospitalizations		Non-AIDS-Defining		Infectious Cause		Primary Surgical	
Factor	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**
Age, per 10 years	1.08 (0.98–1.19)	0.12	1.11 (1.00–1.21)	0.05	0.96 (0.83–1.11)	0.60	1.25 (1.06–1.48)	<0.01
Gender, female vs. male	1.34 (0.99–1.80)	0.05	1.38 (1.04–1.83)	0.02	0.71 (0.40–1.24)	0.22	1.49 (0.95–2.35)	0.08
Race/ethnicity								
African American vs. Caucasian	0.88 (0.73–1.06)	0.18	0.85 (0.71–1.02)	0.09	1.09 (0.86–1.39)	0.48	0.58 (0.41–0.81)	<0.01
Other vs. Caucasian	1.01 (0.76–1.32)	0.99	0.97 (0.74–1.27)	0.84	0.95 (0.59–1.51)	0.82	0.82 (0.50–1.34)	0.42
Chronic hepatitis B	1.19 (0.82–1.71)	0.36	1.23 (0.86–1.76)	0.26	1.21 (0.80–1.81)	0.37	1.31 (0.79–2.17)	0.30
Chronic hepatitis C	1.46 (1.05–2.03)	0.02	1.57 (1.13–2.20)	<0.01	0.97 (0.66–1.43)	0.87	1.59 (0.99–2.55)	0.06
Nadir[1] CD4 count, per 50 cells/mm^3	0.92 (0.89–0.95)	<0.01	0.94 (0.91–0.97)	<0.01	0.86 (0.82–0.91)	<0.01	1.03 (0.98–1.09)	0.28
Proximal CD4 count								
350–499 vs. <350	0.71 (0.59–0.86)	<0.01	0.75 (0.62–0.91)	<0.01	0.67 (0.51–0.89)	<0.01	0.92 (0.60–1.41)	0.69
≥500 vs. <350	0.67 (0.56–0.81)	<0.01	0.70 (0.58–0.84)	<0.01	0.56 (0.44–0.72)	<0.01	0.82 (0.54–1.25)	0.36
Receipt of HAART [2]								
At CD4 <350	0.72 (0.55–0.94)	0.02	0.73 (0.54–0.97)	0.03	0.62 (0.45–0.84)	<0.01	1.71 (0.69–4.22)	0.25
At CD4 350–499	0.81 (0.53–1.24)	0.33	0.81 (0.52–1.26)	0.35	0.58 (0.34–0.99)	0.05	1.09 (0.50–2.37)	0.83
At CD4 ≥500	1.06 (0.79–1.41)	0.71	1.01 (0.76–1.32)	0.97	1.34 (0.85–2.10)	0.21	0.79 (0.48–1.31)	0.35
HAART × CD4 level interaction		0.13		0.30		0.07		0.13

[1] Nadir represents the lowest CD4 count from HIV diagnosis through the prior year to hospitalization

[2] Results from separate analyses for proximal CD4 levels < 350, 350–499, and 500+ including same covariates. RR, relative rate