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# Late diagnosis of HIV infection at two academic medical centers: 1994–2004

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## Abstract

Over the last decade, there has been increased attention to the role of earlier HIV testing in the United States. Our objective was to determine if this has translated into changes in the proportion of inpatients with advanced disease at the time of initial HIV diagnosis. We identified inpatients discharged with a new diagnosis of HIV infection or AIDS between 1994 and 2004 at two academic medical centers. We examined trends in initial CD4 count at diagnosis over three time periods: 1994–1996, 1997–2000 and 2001–2004. Between 1994 and 2004, 235 inpatients were newly diagnosed with HIV infection or AIDS in the two centers. For the 217 patients with available CD4 count data, the median initial CD4 count was 41/μl (interquartile range 19–138/μl). Of the 217 patients, 184(85%) had CD4 ≤200/μl and 119/217 (55%) had CD4 ≤50/μl. There were no significant differences in median CD4 count by time period. A large majority of inpatients with newly diagnosed HIV infection at two academic medical centers between 1994 and 2004 had signs of advanced immunodeficiency. Over this recent 11-year period there was no evidence that inpatients with a new HIV diagnosis were identified at earlier stages of disease.

### Keywords

HIV infections/testing; HIV infections/epidemiology; HIV infections/diagnosis

## Introduction

Major strides continue to be made in the treatment of individuals with HIV infection in the United States (Crum et al., 2006; Palella et al., 1998; Walensky et al., 2006). However, achieving the full benefits of therapy depends on timely diagnosis. Many individuals with HIV infection present for care late, often with evidence of severe immunodeficiency and many years after infection (Dybul et al., 2002; Fleming, Wortley, Karon, DeCock, &



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Janssen, 2000; Katz, Bindman, Keane, & Chan, 1992; Liddicoat et al., 2004). Some patients delay seeking care for years even after receiving a new diagnosis of HIV infection (Samet et al., 1998). However, evidence suggests that most of the delay in presentation to care is due to the long interval between acquisition of HIV infection and diagnosis (Samet, Freedberg, Savetsky, Sullivan, & Stein, 2001).

Since 1993, the US Centers for Disease Control and Prevention (CDC) has recommended routine, voluntary HIV testing for inpatients in acute care hospitals in the US in areas with an HIV prevalence of at least 1% (CDC, 1993). In 2003, the CDC recommended that HIV testing be offered to patients in all clinical settings in high prevalence areas (CDC, 2003). More recently, in 2006, the CDC for the first time advocated routine, voluntary HIV testing in all adults and adolescents ages 13–64 in US healthcare settings (Branson et al., 2006). Programs promoting routine, voluntary HIV testing have proven effective in inpatient and urgent care settings (Walensky, Losina et al., 2005; Walensky, Losina, Steger-Craven, & Freedberg, 2002) and recent studies suggest that routine, voluntary HIV testing is also cost-effective (Paltiel et al., 2006; Paltiel et al., 2005; Sanders et al., 2005; Walensky, Weinstein et al., 2005). Despite these changes in guidelines and improved and more acceptable testing diagnostics, programs promoting routine, voluntary HIV testing in hospitals in high-prevalence areas have not been widely implemented (Walensky et al., 2002).

Given the increased public and physician awareness of HIV infection since the late 1980s and the increasingly effective treatments for HIV since the mid 1990s, one might think that patients with HIV infection would be diagnosed earlier in the course of their disease, even in the absence of formal voluntary HIV testing programs (Palella et al., 1998; Walensky et al., 2006). Our objective was to evaluate if there is evidence of earlier HIV diagnosis among inpatients between 1994 and 2004.

## Methods

We identified inpatients newly diagnosed with HIV infection during a hospitalization at two urban academic medical centers in Boston between 1994 and 2004 using the Partners Healthcare System Research Patient Data Registry (RPDR) (Partners Research Computing RPDR Web Page, 2007). The RPDR is a central data warehouse that collects data from several Partners HealthCare System-affiliated inpatient and outpatient electronic systems, including the electronic medical record and physician billing system. It can identify patients for research purposes based on specific diagnoses, demographics or laboratory tests. The study protocol was approved by the Partners Human Research Committee.

Using the RPDR Query Tool, we identified patients who met the following inclusion criteria: age ≥18 years, admitted to Massachusetts General Hospital (MGH) or Brigham and Women's Hospital (BWH) between January 1, 1994 and December 31, 2004, and having an ICD-9-CM diagnosis during that inpatient encounter of HIV or AIDS (042) or HIV infection causing other specified conditions (043). We reviewed the electronic medical record for each patient and excluded the following three groups: (1) patients who were known to have HIV infection or AIDS prior to the index admission; (2) patients who had no medical records available corresponding to the index admission dates; and (3) patients who, upon review of their medical record, had no evidence of HIV infection (i.e. were miscoded).

To examine trends over time, we divided the sample into three time periods: 1994–1996, 1997–2000 and 2001–2004. The main outcomes of interest were initial CD4 count, presence of opportunistic infection or other AIDS-defining illness at the time of diagnosis and number of prior inpatient or outpatient visits within the Partners HealthCare System within one year or five years of HIV diagnosis. Chi-square tests were used to identify differences in

categorical patient demographics and the proportion of patients with signs of advanced immunodeficiency (CD4≤50 cells/μl; CD4≤200 cells/μl; or the presence of at least one opportunistic infection or other AIDS-defining illness) by time period. Mood's Median Test was used to compare median age and median CD4 counts across time periods.

For the analysis, initial CD4 count was defined as the first CD4 count within three months of the admission date. We included the following opportunistic infections: candidiasis (oropharyngeal, vulvovaginal or esophageal), cervical dysplasia, cervical intraepithelial neoplasia, cervical cancer, coccidioidomycosis, cryptococcosis, cryptosporidiosis, cytomegalovirus infection, herpes simplex virus infection, herpes zoster, histoplasmosis, isosporiasis, *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, recurrent bacterial pneumonia, *Pneumocystis jiroveci* pneumonia, progressive multifocal encephalopathy, salmonella and toxoplasmosis (Centers for Disease Control and Prevention, 1992). Other AIDS-defining illnesses included HIV dementia, HIV encephalopathy, HIV wasting syndrome, Kaposi's sarcoma, non-Hodgkins lymphoma, primary central nervous system lymphoma and progressive multifocal leukoencephalopathy (CDC, 1992).

Prior visits within the Partners HealthCare System were defined as any inpatient or outpatient encounters at MGH, BWH or their affiliated outpatient healthcare centers prior to the index admission. In order to limit the analyses to encounters where one could reasonably expect HIV testing to be offered, visits to the following locations and providers were excluded: pharmacy, laboratory, radiology, pathology, electrocardiogram laboratory, nuclear cardiology, endoscopy, dental, podiatry, anticoagulation management service, physical therapy and rehabilitation, speech language pathology, nutrition and social services. Visits occurring on the day of admission were also excluded.

## Results

The initial RPDR query yielded 2,224 patients who met the inclusion criteria. Of these, 1,991 patients were excluded based on review of their medical records: 1,883 had been diagnosed with HIV infection prior to the admission examined, 51 had no discharge summary or other medical records available, 36 had no evidence of HIV infection, 14 did not have sufficient evidence in available medical records to confirm whether or not they were newly diagnosed with HIV infection, four were presumptively diagnosed with HIV infection based on clinical history but declined HIV testing and one patient was less than 18 years old. From the initial query, 235 patients were confirmed to have been newly diagnosed with HIV infection during an inpatient encounter between 1994 and 2004 and they formed the study sample.

The median age of those in the study sample was 39 years (Table 1). Nearly two-thirds were male and 55% were Black or Hispanic. Median age and admission hospital varied significantly by time period ($p$=0.02 and $p$=0.03, respectively). There were no significant differences in patient gender, race/ethnicity, admitting service or hospital transfer status by time period.

The median initial CD4 count for the 217 patients with available CD4 data was 41/μl. The median CD4 count increased from 41/μl to 45/μl from Period 1 to Period 2 and then decreased to 36 cells/μl in Period 3, but these differences were not statistically significant (Table 2). More than half of the patients in each time period had initial CD4 counts≤50/μl, while 28–34% of patients in each time period had CD4 counts between 51 and 200/μl (Table 2). Among newly diagnosed patients, 76% had an opportunistic infection. At the time, 69% of these were potentially preventable with guideline-concordant prophylaxis (USPHS/IDSA Prevention of Opportunistic Infections Working Group, 1997; USPHS/IDSA

Prevention of Opportunistic Infections Working Group, 2000; USPHS/IDSA Prevention of Opportunistic Infections Working Group, 2002; USPHS/IDSA Prevention of Opportunistic Infections Working Group, 1995). At the time of HIV diagnosis, 78% of patients had an opportunistic infection or other AIDS-defining condition. There was no significant change in the proportion of patients with opportunistic infections or other AIDS-defining illnesses at the time of diagnosis by time period.

Of the 235 study patients, 99 (42%) and 114 (49%) had a prior visit in the system within one or five years of admission (Table 3). The proportion of patients with prior visits did not differ significantly by time period. Patients with initial CD4 count ≤200/μl were less likely to have had prior inpatient or outpatient visits within one and five years of admission compared to patients with initial CD4 count> 200/μl; however, this result was statistically significant for prior inpatient visits only.

## Discussion

Both general surveillance and detailed research data suggest that many patients in the US, and throughout the world, present with HIV infection at an advanced stage of disease (Dybul et al., 2002; Katz et al., 1992; Liddicoat et al., 2004; Louis, Ivers, Fawzi, Freedberg, & Castro, 2007; Manfredi, Calza, & Chiodo, 2001; Samet et al., 1998). We found that the majority of inpatients newly diagnosed with HIV at two academic medical centers in Boston had evidence of severe immunodeficiency at the time of diagnosis as manifested by low CD4 counts, opportunistic infections or other AIDS-defining illnesses. Over the 11-year period from 1994–2004, there was no increase in the median CD4 count, no decrease in the proportion of patients with low (≤200/μl) or very low (≤50/μl) CD4 counts and no decrease in the proportion of patients with opportunistic infections or other AIDS-defining illnesses at the time of HIV diagnosis. This pattern held true for both medical centers. These data provide further evidence that despite nearly 15 years of CDC recommendations for routine, voluntary HIV testing of inpatients in high-prevalence settings, new cases of HIV infection in the US are still usually identified at very late stages of illness in the inpatient setting.

While this study spans over a decade of care, the results are consistent with the findings of several earlier studies. Sackoff and Shin (2001) examined trends in the immunologic status of 545 newly diagnosed patients initiating HIV care in several New York City clinics between 1994 and 1999 and found no significant improvement in CD4 count over time. Loupa et al. (2005) examined 806 patients presenting for initiation of HIV care in Cleveland and found no significant change in median CD4 count from 1995 to 2002. While these studies included patients diagnosed in a variety of settings, the current study is the first to examine trends over time among new cases of HIV infection diagnosed in the inpatient setting in the US.

Median age was significantly lower in the first compared to the second or third time periods, which may reflect a shift in the population most affected by HIV/AIDS in the communities served by the study institutions. There was also a statistically significant change in the ratio of patients identified at each hospital from roughly 2:1 in the first and second periods to 1:1 in the third period. We are unaware of any demographic or practice shifts at the two institutions that may have accounted for this change; however, analysis of study outcomes stratified by admitting hospital did not differ significantly from combined analyses (data not shown).

Nearly half of patients with newly diagnosed HIV infection had a prior visit in the same health care system within five years of HIV diagnosis; the vast majority of these visits occurred within one year of diagnosis. As we were unable to identify medical encounters at

institutions outside of the study system, these results offer a minimum estimate of the total number of prior medical encounters. These data are consistent with several prior studies demonstrating that patients with newly diagnosed HIV infection often had repeated medical encounters in the years prior to their HIV diagnosis (Hightow, MacDonald, & Boland, 2005; Klein, Hurley, Merrill, & Quesenberry, 2003; Liddicoat et al., 2004). These previous encounters all represent clear, missed opportunities for HIV testing and diagnosis. Given the advanced level of immunodeficiency at the time of HIV diagnosis in our study population and the high proportion of patients whose only prior visits occurred within one year of diagnosis, it is likely that even if patients had been diagnosed at a prior visit, they would have still been quite immunodeficient. However, some of their clinical complications may have still been preventable. In our study, relatively few patients (12%) had a prior inpatient visit within five years, but nearly half had an outpatient visit. This suggests that programs to promote more effective HIV testing should be targeted to both inpatient and outpatient settings; testing may have the most impact in the outpatient setting among patients in whom providers might think there is a lower pre-test probability of disease.

This study has several limitations. Due to the relatively small sample size, we had limited power to detect small changes in median CD4 count or the proportion of patients with opportunistic infections or other AIDS-defining illnesses at the time of HIV diagnosis. The study population included individuals diagnosed with HIV infection as inpatients at one of two academic tertiary care centers in a single North-east US city. Thus, the results may not be generalizable to outpatient settings, non-urban areas, community hospitals or other regions of the US. The median initial CD4 count of patients in the study (41/μl was much lower than the median CD4 count of patients in studies examining presentation to out-patient centers for initiation of HIV care (median CD4 count 254–280/μl) (Katz et al., 1992; Klein et al., 2003). The lower CD4 counts in the current study may reflect sicker patients (inpatients versus out-patients) as well as referral bias, since 20% of patients were transferred from outside hospitals. The median CD4 count of patients in our study was similar, however, to that of another study of hospitalized inpatients (Lubelchek et al., 2005). In that study based in Chicago in 2003–2004, median CD4 counts ranged from 27–43/μl.

This study was also a retrospective analysis limited to database searching and medical record review and may have been subject to misidentification of cases. Since diagnoses in the database are based on encounter and billing data, patients whose HIV tests were pending at discharge, but later returned positive, may not have been assigned an encounter diagnosis of HIV infection or AIDS for their inpatient encounter. Consequently, these patients would have been missed in the initial screening. We did not have data on the number of newly diagnosed patients who had been previously tested for HIV infection, who had been offered HIV testing in the past but declined, or the reasons why HIV tests were offered. Thus, we cannot definitively state whether the missed opportunities for testing were primarily the result of healthcare providers' failure to offer HIV testing or patients' reluctance to consent to HIV testing.

Finally, for patients who present to medical attention for the first time at advanced stages of HIV infection, it would be helpful to know what factors contribute to their presenting to care so late. While the demographic characteristics available in our data set – race, gender and age – did not explain the late presentation to care, an analysis of patients' more detailed socioeconomic and medical characteristics such as income, education, health literacy, health insurance status, access to primary care, housing or co-morbid medical illnesses would be informative in future studies.

Despite these limitations, we documented consistently low median CD4 counts over an 11-year period at two large hospitals, each with a documented inpatient HIV prevalence of

greater than 1% and each providing HIV care to a sizable proportion of the city's HIV-infected residents. Thus, these results are likely relevant to similar institutions in high HIV prevalence cities. The data contribute to the mounting evidence that HIV infection is commonly diagnosed late in the US. Changes in HIV testing recommendations and diagnostics made little difference in these trends for 1994–2004.

In order to promote earlier detection and treatment of HIV infection, the CDC issued new recommendations for HIV screening in September 2006, which address several barriers to routine HIV testing and aim to make HIV screening a routine part of medical care for 13-to-64-year-olds in the US (Branson et al., 2006). By removing the requirements for HIV prevention counseling and separate written consent and promoting the concept of HIV testing as a routine part of medical care regardless of risk factors, the new guidelines address some of the commonly cited provider and patient level barriers to HIV testing such as time constraints and stigma. These new recommendations have been met with some resistance based on anticipated costs and reimbursement challenges, operational difficulties and ethical concerns (Lifson & Rybicki, 2007). While routine HIV testing efforts must address each of these concerns systematically, the widespread and mounting evidence that HIV infection continues to be diagnosed very late, leading to increased morbidity and mortality among infected patients, even in the current era of heightened HIV awareness and improved care, suggests that these concerns should not get in the way of considerate action.

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**Table 1**

Demographic characteristics of a sample of inpatients with newly diagnosed HIV infection at two academic medical centers: 1994–2004.

| | All | 1994–1996 | 1997–2000 | 2001–2004 | *p*-value* |
|---|---|---|---|---|---|
| *n* | 235 | 75 | 91 | 69 | |
| Age – median years (interquartile range) | 39 (34–45) | 36 (31–42) | 41 (34–51) | 40 (35–45) | 0.01 |
| Gender (%) | | | | | 0.30 |
| Male | 66 | 71 | 60 | 70 | |
| Race/ethnicity (%) | | | | | 0.55 |
| White | 41 | 48 | 35 | 41 | |
| Black | 35 | 29 | 38 | 36 | |
| Hispanic | 20 | 19 | 23 | 19 | |
| Asian | 1 | 0 | 2 | 0 | |
| Other/unknown | 3 | 4 | 2 | 4 | |
| Hospital§ (%) | | | | | 0.03 |
| MGH | 62 | 69 | 66 | 49 | |
| BWH | 38 | 31 | 34 | 51 | |
| Admitting service (%) | | | | | 0.11 |
| Medicine | 66 | 61 | 67 | 70 | |
| Neurology | 11 | 5 | 12 | 17 | |
| Surgery | 3 | 4 | 2 | 3 | |
| Obstetrics/gynecology | 3 | 4 | 2 | 3 | |
| Other/unknown | 17 | 26 | 17 | 7 | |
| Outside hospital transfer¶ (%) | 20 | 10 | 26 | 22 | 0.10 |

* *p*-value is for overall trend.

§ MGH: Massachusetts General Hospital; BWH: Brigham and Women's Hospital

¶ *n*=168. Data on outside hospital transfer status not available for 67 patients.

**Table 2**

Immunologic and clinical characteristics of a sample of inpatients with newly-diagnosed HIV infection at two academic medical centers: 1994–2004.

| | All | 1994–1996 | 1997–2000 | 2001–2004 | *p*-value |
|---|---|---|---|---|---|
| CD4 count (cells/μl) | | | | | |
| Median | 41 | 41 | 45 | 36 | 0.81 |
| 25th–75th percentile | 19–138 | 12–100 | 19–158 | 20–92 | |
| Range | 0–910 | 0–625 | 0–910 | 2–847 | |
| Initial CD4 count distribution[#] | | | | | |
| ≤50 cells/μl (%) | 55 | 58 | 51 | 57 | 0.65 |
| 51–200 cells/μl (%) | 30 | 34 | 29 | 28 | 0.73 |
| >200 cells/μl (%) | 15 | 8 | 20 | 15 | 0.16 |
| Opportunistic infection | | | | | |
| Any[*] (%) | 76 | 80 | 73 | 77 | 0.53 |
| Preventable[§] (%) | 53 | 60 | 51 | 48 | 0.33 |
| Opportunistic infection or other AIDS-defining condition (%) | 78 | 80 | 74 | 83 | 0.36 |

[#]Initial CD4 count distribution excludes patients with missing CD4 count data. CD4 count data missing for 16 patients in Period 1; 1 patient in Period 2; and 1 patient in Period 3.

[*]Opportunistic infections include candidiasis (oropharyngeal, vulvovaginal, or esophageal), cervical dysplasia, cervical intraepithelial neoplasia, cervical cancer, coccidioidomycosis, cryptococcosis, cryptosporidiosis, cytomegalovirus infection, herpes simplex virus infection, herpes zoster, histoplasmosis, isosporiasis, *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, recurrent bacterial pneumonia, *Pneumocystis jiroveci* pneumonia, progressive multifocal encephalopathy, salmonella and toxoplasmosis.

[§]Preventable opportunistic infections include *Pneumocystis jiroveci* pneumonia, toxoplasmosis, *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, and cytomegalovirus infection.

[¶]Other AIDS-defining conditions include HIV dementia, HIV encephalopathy, HIV wasting syndrome, Kaposi's sarcoma, non-Hodgkins lymphoma, primary central nervous system lymphoma and progressive multifocal leukoencephalopathy.

## Table 3

Prior visits stratified by CD4 count in a sample of inpatients with newly diagnosed HIV infection at two academic medical centers: 1994–2004.

| CD4 Count (cells/μl) | Total (*n*=235) | ≤200/μl* (*n*=184) | >200/μl* (*n*=33) | *p*-value§ |
|---|---|---|---|---|
| Any prior visit (%) | | | | |
| 1 year | 42 | 43 | 48 | 0.55 |
| 5 years | 49 | 48 | 61 | 0.17 |
| Prior inpatient visit (%) | | | | |
| 1 year | 9 | 7 | 18 | 0.04 |
| 5 years | 12 | 10 | 24 | 0.03 |
| Prior outpatient visit (%) | | | | |
| 1 year | 42 | 42 | 48 | 0.51 |
| 5 years | 48 | 47 | 61 | 0.14 |

*CD4 count data is missing for 18 patients.

§*p*-value is for comparison of patients with initial CD4 count ≤ 200/μl versus>200/μl.