Late Presentation for Human Immunodeficiency Virus Care in the United States and Canada


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(See the editorial commentary by Gay, on pages 1521–1523.)

Background. Initiatives to improve early detection and access to human immunodeficiency virus (HIV) services have increased over time. We assessed the immune status of patients at initial presentation for HIV care from 1997 to 2007 in 13 US and Canadian clinical cohorts.

Methods. We analyzed data from 44,491 HIV-infected patients enrolled in the North American–AIDS Cohort Collaboration on Research and Design. We identified first presentation for HIV care as the time of first CD4+ T lymphocyte (CD4) count and excluded patients who prior to this date had HIV RNA measurements, evidence of antiretroviral exposure, or a history of AIDS-defining illness. Trends in mean CD4 count (measured as cells/mm3) and 95% confidence intervals were determined using linear regression adjusted for age, sex, race/ethnicity, HIV transmission risk, and cohort.

Results. Median age at first presentation for HIV care increased over time (range, 40–43 years; P < .01), whereas the percentage of patients with injection drug use HIV transmission risk decreased (from 26% to 14%; P < .01) and heterosexual transmission risk increased (from 16% to 23%; P < .01). Median CD4 count at presentation increased from 256 cells/mm3 (interquartile range, 96–455 cells/mm3) to 317 cells/mm3 (interquartile range, 135–517 cells/mm3) from 1997 to 2007 (P < .01). The percentage of patients with a CD4 count ≥350 cells/mm3 at first presentation also increased from 1997 to 2007 (from 38% to 46%; P < .01). The estimated adjusted mean CD4 count increased at a rate of 6 cells/mm3 per year (95% confidence interval, 5–7 cells/mm3 per year).

Conclusion. CD4 count at first presentation for HIV care has increased annually over the past 11 years but has remained <350 cells/mm3, which suggests the urgent need for earlier HIV diagnosis and treatment.

Approximately 21% of the estimated 1.1 million Americans and 58,000 Canadians living with human immunodeficiency virus (HIV) infection are unaware they are infected [1, 2]. Among the estimated 56,000 new infections occurring each year in the United States [3], over half are estimated to be transmitted by persons who are unaware of their HIV infection [4]. In the United States, from 2000 to 2006, rates for a history of...
ever being tested for HIV infection have remained stable at <40%; among persons with established risk factors for HIV during 2006, only 23% were tested [5]. In Canada in 2003, a general population survey found that 29% of women and 24% of men reported ever being tested for HIV [6]; in 1996, 71% of men who have sex with men (MSM), 62% of injection drug users (IDUs), and 51% of high-risk heterosexuals reported ever being tested, although these higher proportions may be due to testing for research participation [2]. Even among pregnant women in the United States in 2006, only 61% had been tested in the preceding 12 months despite long-standing recommendations for routine opt-out testing and many years of work to integrate universal opt-out testing into pregnancy care [5, 7]. Although data suggest that more women are tested by the time they reached labor and delivery [8, 9], this cross-sectional survey suggests that screening remains incomplete early in pregnancy and that opportunities for antiretroviral treatment of the mother (if needed) and antiretroviral prophylaxis to prevent perinatal HIV transmission to the fetus are missed. Similar guidelines for testing during pregnancy exist in Canada; however, prenatal HIV screening programs vary. Data from 2002 to 2006 show the percentage of pregnant women screened for HIV ranges from 60% in Manitoba to ≥95% in Alberta, Newfoundland and Labrador, and the Northwest Territories [2]. Persons who are unaware of their HIV status are unable to benefit from the advances made in HIV treatment, and late presentation for HIV care is associated with higher mortality, even after receipt of antiretroviral therapy [10, 11], and a diminished recovery of CD4+ T lymphocytes (CD4) [12]. Late presenters also have a prolonged opportunity to transmit HIV while unaware of their HIV infection.

To assess when individuals are entering HIV care, we analyzed the immune status in patients who newly presented for care over the past 11 years in the United States and Canada. Given the improvements that have occurred in HIV therapy, and efforts to improve early diagnosis and treatment of HIV [13–15], our objective was to assess whether patients presented for HIV care earlier in the course of their HIV infection over time and to determine factors associated with a later presentation to HIV care.

**METHODS**

**Study design and population.** All patients were part of the North American Cohort Collaboration on Research and Design (NA-ACCORD), a regional group of the International Epidemiological Databases to Evaluate AIDS project. The NA-ACCORD is a multisite collaboration of 8 interval and 14 clinical cohort studies with sites in the United States and Canada [16]. Each cohort’s participation in NA-ACCORD was approved by the respective local institutional review boards. Contributing cohorts have used standardized methods of data collection and have submitted demographic, treatment, clinical, laboratory, and vital status data on enrolled participants.

**Inclusion criteria and variables of interest.** Only participants from clinical cohorts were included in this study. Because our interest was in the degree of immunosuppression at first presentation for HIV clinical care; the interval research cohorts in the NA-ACCORD do not administer clinical care. All of the 14 clinical cohorts agreed to participate in this study, although 1 was excluded because its study population enrollment criteria required that participants be in the later stages of HIV disease. These 13 clinical cohorts have clinical sites in the following US states and territories and Canadian provinces: Alberta, Alabama, California, Colorado, Florida, Georgia, Illinois, Maryland, Michigan, Missouri, New York, North Carolina, Ohio, Ontario, Oregon, Pennsylvania, Quebec, Tennessee, Texas, Washington, and Washington, DC. Due to the geographic dispersion of these clinical cohorts where individuals are receiving their HIV care, the possibility that an individual is participating in more than one of the clinical cohorts is low.

We analyzed data from HIV-infected adults (≥18 years of age) who first presented for clinical care during the period from January 1997 through December 2007, where first presentation for HIV clinical care was defined as the date (month and year) at which the first CD4 count was reported. The clinical cohorts of the NA-ACCORD are well established and have procedures to determine medical histories at first presentation for care. HIV-related treatments, laboratory results, and diagnoses prior to enrollment are routinely recorded.

Several methods were used to eliminate patients who might have been receiving HIV care prior to their first recorded CD4 count. First, we excluded patients who were taking antiretroviral therapy or had an HIV RNA measurement recorded prior to the date of first measured CD4 count. Second, we also excluded those patients who had an AIDS-defining diagnosis recorded >3 months prior to the first measured CD4 count. A period of 3 months prior to the first measurement was utilized to include those who may have had an AIDS-defining diagnosis at the time of HIV diagnosis and to exclude those who may have been seeking care elsewhere. Third, for each cohort, we excluded all individuals contributing data during the first year that the cohort contributed data to the NA-ACCORD who may have been patients previously in care but who contributed data to a new cohort data capture system. Although these criteria might not completely exclude earlier presentation for HIV care (particularly presentation at clinical sites outside of the participating cohort), we believe that these criteria minimize the possibility that the patients in this study had presented for HIV care at an earlier time.

The first measured CD4 count was our outcome of interest. The month and year in which the CD4 count was measured were recorded. If there was >1 measurement in the first month
Table 1. Characteristics of Patients at First Presentation for Human Immunodeficiency Virus (HIV) Clinical Care, by Year at First Presentation, the North American Cohort Collaboration on Research and Design, 1997–2007

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<td>4657 (96)</td>
<td>5083 (97)</td>
<td>4082 (96)</td>
<td>3837 (95)</td>
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<td>3101 (92)</td>
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<td>203 (5)</td>
<td>200 (4)</td>
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<td>176 (4)</td>
<td>226 (6)</td>
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<td>190 (5)</td>
<td>231 (7)</td>
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<td>3843 (86)</td>
<td>3716 (84)</td>
<td>3886 (80)</td>
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<td>1213 (27)</td>
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<td>911 (17)</td>
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<td>684 (24)</td>
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<td>2032 (46)</td>
<td>2202 (45)</td>
<td>2447 (47)</td>
<td>1805 (42)</td>
<td>1651 (41)</td>
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<td>532 (12)</td>
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<td>595 (14)</td>
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<td>873 (18)</td>
<td>932 (18)</td>
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<td>1090 (25)</td>
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<td>1192 (32)</td>
<td>1140 (33)</td>
<td>1166 (35)</td>
<td>951 (33)</td>
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<tr>
<td>IDUs</td>
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<td>1198 (26)</td>
<td>1121 (23)</td>
<td>1188 (23)</td>
<td>844 (20)</td>
<td>691 (17)</td>
<td>557 (15)</td>
<td>529 (14)</td>
<td>501 (14)</td>
<td>450 (13)</td>
<td>403 (14)</td>
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<td>848 (19)</td>
<td>1120 (23)</td>
<td>1451 (28)</td>
<td>1076 (25)</td>
<td>960 (24)</td>
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<td>967 (26)</td>
<td>813 (23)</td>
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<td>Other/unknown</td>
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<td>1480 (33)</td>
<td>1316 (30)</td>
<td>1283 (26)</td>
<td>1221 (23)</td>
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<td>1120 (30)</td>
<td>1085 (29)</td>
<td>1032 (30)</td>
<td>958 (29)</td>
<td>834 (29)</td>
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<td>CD4+ T lymphocyte count, median (IQR), cells/mm³</td>
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NOTE. Data are no. (%) of patients, unless otherwise indicated. IDUs, injection drug users; IQR, interquartile range; MSM, men who have sex with men.

*P* values calculated using the Cochran-Armitage test for categorical variables or the Cuzick test for continuous variables.
at presentation for HIV care, we calculated the mean CD4 count for the month. Other information obtained at first presentation for care included self-reported date of birth, sex, race/ethnicity, and HIV transmission risk group. Race/ethnicity was categorized as black, white, Latino, and other/unknown. HIV transmission risk group was categorized as MSM, IDU, heterosexual, and other/unknown. Participants with both sexual and IDU transmission risk were categorized as IDU.

Statistical analysis. Statistical comparisons of demographic and clinical characteristics across calendar dates were made using the Cochran-Armitage trend test for categorical variables (eg, country of care, sex, race/ethnicity, and HIV transmission risk group) or using the Cuzick trend test for continuous variables (eg, age and CD4 count). We determined the median absolute CD4 count at first presentation for HIV clinical care annually from 1997 through 2007. Multivariate linear regression models were used to describe the annual trends in estimated mean CD4 count using a linear variable for year and adjusting for cohort demographic and risk characteristics; 95% confidence intervals (CIs) were also estimated using these models. Two-way interactions between calendar year and age, sex, race/ethnicity, and HIV transmission group were considered. Nonlinearity of the relationship between calendar time and CD4 count at first presentation for HIV care was assessed by including a quadratic term for calendar year. Results with a 2-sided P value of <.05 were considered statistically significant. Analyses were conducted using SAS, version 9 (SAS Institute).

RESULTS

A total of 67,961 patients receiving clinical care at one of the participating NA-ACCORD sites during the period from 1997 through 2007 had complete information on date and measurement of CD4 count. Of these, 21,983 (32%) had a prior history of antiretroviral therapy or HIV RNA results, and 1487 (2%) had an AIDS-defining diagnosis recorded 3 months prior to the first recorded CD4 count. Thus, our study population consisted of 44,491 HIV-infected individuals.

The characteristics of individuals who first presented for HIV care each year are shown in Table 1. Over time, the median age at first presentation increased (range, 40–43 years; P<.01). The percentage of white patients decreased over time (from 30% in 1996 to 24% in 2007; P<.01), whereas the percentage of black patients fluctuated but remained higher than the percentage of white and Latino patients (P<.01). The percentage of patients with IDU transmission risk decreased (from 26%
in 1997 to 14% in 2007; $P < .01$) and heterosexual transmission risk increased (from 16% in 1997 to 23% in 2007; $P < .01$). There was a slight increase in the percentage of Canadian patients; however, the percentage remained <10% over time ($P < .01$).

The median CD4 count of the study population increased over time, but the changes were within a range of 61 cells/mm$^3$ over all 11 years (Figure 1). The percentage of patients presenting with a CD4 count $\geq 350$ cells/mm$^3$ increased from 38% in 1997 to 46% in 2007 ($P < .01$) (Figure 1). The overall estimated annual change in mean CD4 count was 6 cells/mm$^3$ (95% CI, 5–7 cells/mm$^3$), adjusting for age, race/ethnicity, transmission risk group, and cohort. The quadratic term for calendar year was not significant ($P = .13$), which suggests that the relationship between calendar year and CD4 count at first presentation for HIV care was not U-shaped. However, there were significant interactions between the change in CD4 count per year and race/ethnicity ($P = .01$) and transmission risk group ($P < .01$), but not sex ($P = .13$).

Table 2 displays the results from the overall and stratified multivariate models. Although women had higher observed mean CD4 counts in 1997, the estimated mean increase in CD4 count per year among women was less than that among men (women: 5 cells/mm$^3$ per year [95% CI, 3–7 cells/mm$^3$ per year]; men: 6 cells/mm$^3$ per year [95% CI, 5–7 cells/mm$^3$ per year]). Latinos had the greatest annual increase in estimated mean CD4 count since 1997 (9 cells/mm$^3$ [95% CI, 7–12 cells/mm$^3$]), and blacks had the smallest increase (5 cells/mm$^3$ [95% CI, 3–7 cells/mm$^3$]). Latinos showed a lower observed mean CD4 count (293 cells/mm$^3$) in 1997, compared with whites (328 cells/mm$^3$) and blacks (305 cells/mm$^3$). The estimated annual change in mean CD4 count at first presentation was 7 cells/mm$^3$ (95% CI, 6–9 cells/mm$^3$) among MSM, 5 cells/mm$^3$ (95% CI, 3–7 cells/mm$^3$) among IDUs, and 2 cells/mm$^3$ (95% CI, 0–4 cells/mm$^3$) among those with heterosexual transmission risk. MSM showed low observed mean CD4 counts in 1997 (303 cells/mm$^3$), whereas IDUs and those with heterosexual transmission risk had a slightly higher observed mean CD4 count in 1997 (334 and 328 cells/mm$^3$, respectively).

Patients who were older had lower CD4 counts at first presentation for HIV care, with an average decrease of 24 cells/mm$^3$ (95% CI, −27 to −21 cells/mm$^3$) at the time of first presentation for care over 11 years, adjusting for sex, race/ethnicity, transmission risk group, and cohort. The interaction of age and calendar time on CD4 count at first presentation for HIV care was borderline statistically significant ($P = .05$).

After stratifying by cohort, 6 cohorts showed a significant increase in estimated mean annual change in CD4 count at presentation (range, 5–8 cells/mm$^3$), and 7 cohorts showed no difference in estimated mean CD4 count over time (Figure 2). Cohort 3 had a borderline significant decrease of 5 cells/mm$^3$ per year. Participants in cohort 3 had the highest mean CD4 count in 1997; 78% were black, and 53% reported heterosexual transmission risk.
Figure 2. Observed mean CD4 count (year) and estimated mean annual change in CD4 count and 95% confidence interval at first presentation for human immunodeficiency virus (HIV) clinical care, by cohort, North American Cohort Collaboration on Research and Design, 1997–2007.

al transmission risk—all factors potentially contributing to this decrease.

**DISCUSSION**

Since the mid-1990s, public health efforts have focused on identifying HIV infection at an early stage, which should imply an increase in patients presenting for HIV care earlier in the course of disease. Our data from multiple clinical sites across the United States and Canada indicate that, although the observed mean CD4 count at presentation has increased since 1997, most patients continue to first present for HIV care with a CD4 count below 350 cells/mm$^3$, the level at which initiation of antiretroviral therapy is currently recommended by multiple major national guideline committees for persons living in developed countries [17–21]. Stratifying out results by cohort demonstrated that our findings were not an artifact of the combined data set. Knowing that within-patient variation in CD4 counts is $\sim 25\%$ with increased variation at lower CD4 counts, our estimated mean annual increase in the CD4 count is likely of little clinical relevance [22].

Several smaller regional studies have also found that patients present late in the course of HIV infection. Among 1209 patients who newly presented for care in an infectious diseases clinic in Alabama, 41% had already progressed to AIDS [23]. In South Carolina from 2001 to 2005, 41% of AIDS cases were diagnosed within 1 year of HIV diagnosis [24]; in North Carolina from 2000 to 2003, 50% had a CD4 count $<200$ cells/mm$^3$ at first presentation for HIV care [25]; in Washington, DC, from 1997 to 2006, 66% of AIDS cases were diagnosed within 1 year of HIV diagnosis [26]; and in Maryland, the CD4 count at first presentation for HIV care declined from 371 to 276 cells/mm$^3$ from 1990 to 2006 [27]. A Centers for Disease Control and Prevention analysis of data collected in 33 US states from 2001 to 2003 found a median CD4 count within 12 months of diagnosis of HIV infection of only $\sim 170$ cells/mm$^3$ [28]. In a population of primarily Canadian aboriginal patients newly diagnosed with HIV from 1998 to 2003, the median CD4 count was 330 cells/mm$^3$; 28% had a CD4 count $<200$ cells/mm$^3$ at diagnosis, and median time to care was 27 days [29]. Another study from Calgary, Canada, found that 39% of patients first presented with a CD4 count $<200$ cells/mm$^3$ and had care costs that were 200% higher than for patients who presented with higher CD4 counts [30]. In addition to age, sex, and race/ethnicity [23, 25, 27, 29], these studies have also
shown associations between CD4 count at first presentation and insurance type [23] and nonmetropolitan residence [29] in multivariate analyses; we were unable to systematically measure these variables in our participating cohorts.

Over time, the demography of the HIV epidemic in the United States and Canada has shifted [2, 31]. Although the greatest percentage of persons diagnosed with HIV/AIDS remain MSM, the percentages of persons diagnosed with HIV/AIDS who are women, who are of minority race/ethnicity, and who have as their principal HIV transmission risk factor IDU or heterosexual contact have increased. US national surveillance data from 2000 to 2003 demonstrated that late testers (persons who had their first positive HIV test within 1 year before diagnosis of AIDS) were significantly more likely to be younger (age range, 18–29 years), black or Latino, and to have been infected through heterosexual contact [32]. In Canada from 1997 to 2004, various studies report younger individuals (age range, 25–34 years) and those who are at higher risk for acquiring HIV infection (ie, MSM, IDUs, and ≥2 partners in the last year among heterosexuals) were more likely to be tested [2]. We did not see this shift to younger patients at time of presentation or the significantly greater percentages among Latino HIV-infected patients. However, black participants had the smallest mean annual increase in CD4 count at first presentation of any racial group. Similarly, the estimated mean annual increase in CD4 count among those with heterosexual transmission risk was dramatically lower than that among other risk groups. National surveillance data coupled with our findings suggest that the number of blacks and high-risk heterosexuals entering into care at a later stage of disease will grow; however, the impact might be diminished with the expansion of routine HIV testing that would likely result in earlier diagnosis and entry into care.

The public health implications for our findings are clear: (1) delayed diagnosis reduces survival, and (2) individuals who entered into HIV care had a lower CD4 count than that mentioned in the guideline for antiretroviral therapy initiation. A study from the Netherlands found that mortality after starting antiretroviral therapy could be reduced by 20% if patients were to present for HIV care with a CD4 count ≥400 cells/mm³ [8]. Current guidelines recommend starting antiretroviral therapy before the CD4 count reaches 350 cells/mm³, and recent data from across the United States and Canada suggest that initiating therapy at even higher CD4 levels improves survival [33]. This underscores the importance of identifying infection and engaging in HIV care at a earlier stage than is occurring currently.

A delay in presentation for treatment not only increases the chance of clinical disease progression for that patient but also increases the risk of ongoing transmission. Early effective antiretroviral treatment can lower circulating HIV RNA levels, thereby decreasing the risk of HIV transmission [34–36]. Patients who learn they are infected with HIV may reduce their HIV RNA level with effective antiretroviral treatment and may reduce their risk-taking behavior, consequently resulting in reduced risk of transmitting HIV to others [37].

Our results found no significant differences in CD4 count trends over time based by sex. Some women were likely tested as part of prenatal screening (pregnant women are not excluded from these clinical care cohorts), and it is possible the CD4 count at which they presented for care was higher than the CD4 count at which nonpregnant women were tested and subsequently entered care. Because the circumstances under which women were tested and subsequently entered care were unknown, we were unable to determine differences in CD4 counts at first presentation for care for these 2 groups of women.

There is clearly a need for earlier HIV diagnosis and intervention. Relying on clinical indicators for HIV infection to prompt testing is inadequate. A study from a large managed care organization in California indicated that only 22% of patients in medical care had at least 1 of 8 clinical indicators suggested in the literature as reasons to test for HIV within 1 year of being diagnosed [38]. A recent study among US veterans suggested that delayed presentation for HIV care is not a result of lack of medical care access for this population [39].

HIV testing is entering a new era as practice guidelines have recently changed to address the need for increased, earlier testing and with linkage to care. In September 2006, the Centers for Disease Control and Prevention released Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings [40]. These recommendations advised routine HIV screening in health-care settings of adults and adolescents aged 13–64 years and of all pregnant women with prior notification and opt-out allowed. Separate informed consent, a barrier to HIV testing [41, 42], is no longer recommended. More recently, the American College of Medicine released recommendations for universal HIV screening [43]. If we are to make any impact on improving the health of HIV-infected persons and reducing the spread of the virus, public health officials, hospital administrators, and clinicians will need to adopt these recommendations into practice and change policies (eg, legal requirements for informed consent for HIV testing and elimination of the need for HIV pretest counseling in most US states and Canadian provinces) to ensure that more persons are screened and referred for early treatment.

In summary, between 1997 and 2007 in the United States and Canada, there was little improvement in the immunologic stage of HIV infection among patients entering HIV care. Patients presented with relatively low CD4 counts, at a stage of disease where the effectiveness of treatment is reduced, providing an extended opportunity to transmit HIV to others. These data provide strong evidence that implementation of
new strategies for earlier HIV testing and effective linkage into care are urgently needed.

NA-ACCORD PARTICIPATING COHORTS (REPRESENTATIVES)

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7. U.S. Public Health Service recommendations for human immunode-