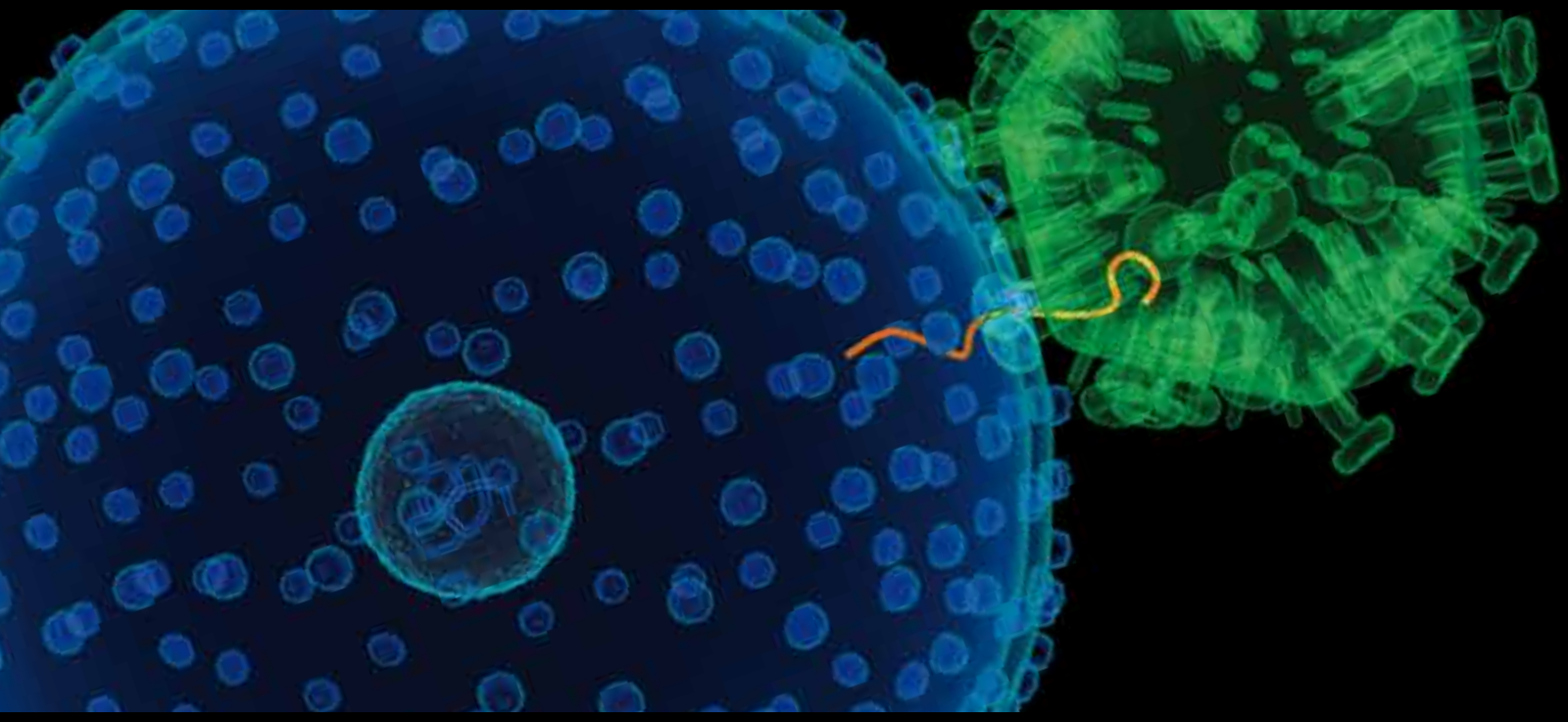
AIDS Research and Treatment

HIV-Infected Late Presenter Patients

Guest Editors: Antonella d'Arminio Monforte, Andrea Antinori, Enrico Girardi, Francesca Ceccherini-Silberstein, Giulia Marchetti, Caroline Anne Sabin, and Julio S. Montaner



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Editorial Board

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 902679, 2 pages
doi:10.1155/2012/902679

Editorial

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Received 13 September 2011; Accepted 13 September 2011

The idea of dedicating a special issue of the journal to explore the challenges posed by late presentation of HIV infection is based upon several considerations. In 2010, after three decades since the beginning of the AIDS epidemics, still 15–38% of patients with HIV infection continue to be diagnosed late. As expected, late presenters demonstrate a less favourable clinical course, with reduced or incomplete treatment response, more rapid clinical progression, and higher risk of mortality. In addition, they generate a considerable and avoidable resource burden to the healthcare system. Furthermore, undiagnosed HIV-infected individuals contribute disproportionatelly to the spread of HIV disease. The latter has become even more important now that antiretroviral therapy has been conclusively shown to decrease HIV transmision by greater than 90%. As a result, expanding and even normalizing HIV testing is increassingly recognized by international guidelines to be a key public health priority, in order to improve access to care, to allow an earlier antiretroviral treatment initiation, and ultimately to decrease HIV-related morbidity and mortality as well as HIV transmission.

This issue contains five key papers. L. Saganic and colleagues report a persistent unacceptably high proportion of late diagnoses of HIV in Washington state between 2000 and 2009, despite the implementation of CDC recommendations for HIV testing in the last five years. The conclusion is that HIV screening procedures, largely dependent on an individual's perception of his/her HIV risk, have failed; in fact, people who are more likely to be diagnosed late with HIV usually do not consider themselves as "risk categories" and have poor access to HIV testing. Consistent with several other publications, also in this study, heterosexuals, women, elderly people, foreign-born individuals, and people residing in a rural area showed higher risk of late HIV diagnosis. Interestingly, two different measures of late presentation are compared: the lab-based measure (CD4+ T-cell count at presentation <350 cells/mmc) and the time-based one (AIDS event within 12 months of initial HIV diagnosis). Both measures underline the same risk factors for late HIV testing. The laboratory-based definition, however, appears to be the more clinically relevant one due to the fact that it reflects the importance of the CD4+ T-cell count for determining the optimal time to initiated antiretroviral therapy; although the application of this definition may be limited in some settings, this should improve as the quality of laboratory systems improves in the future. Nevertheless, the contemporary use

of both measures may offer a consistent assessment of the problem of late presentation.

Also in the study conducted by K. Buchacz and colleagues, the proportion of HIV-positive patients who first present a CD4+ T-cell count <350 cells/mmc at first presentation to care was extremely high (58%) consistent with the previous paper. K. Buchacz analyzed data from participants in the HIV Outpatient Study (HOPS) from eight USA cities, including Washington, over the same time period considered by L. Saganic (2000–2009). Again, similar risk factors for Late Presentation were identified (heterosexual transmission, older age, and nonwhite ethnicity). Interestingly, the median CD4+ T-cell count at HIV diagnosis remained stable over time, with only a trend towards higher CD4+ T-cell counts in those infected via heterosexual sex and people attending public facilities. Taken together, these studies provide a strong rationale for the normalization of HIV testing.

One of the limitations of many analyses of late presentation is that definitions do not generally incorporate information on duration of infection prior to diagnosis (which is often unknown). The CD4+ T-cell count at diagnosis is therefore used as a surrogate for this. To get around this problem, P. Sobrino-Vegas et al. used a multiple imputation method to estimate the probable date of HIV seroconversion for all patients in their Spanish cohort (some of whom were known seroconverters); late diagnosis was then defined as an interval of greater than 4.19 years between the time of seroconversion and the time of first testing. This group, which comprised 34% of the cohort, were more often male, older, and of non-Spanish origin. Using this definition, 39% of newly diagnosed subjects had presented late; these individuals were more commonly intravenous drug users. Use of this different approach to the estimation of late diagnosis underlines the importance of further strengthening HIV screening procedures.

From an immunological perspective, F. Bai et al. reported that late presenters tend to be characterized by CD127 down-regulation on CD4+ T-cells and immune activation; as these patients are in an advanced stage of infection and are at higher risk of disease progression and of poor immune reconstitution, when they start antiretroviral therapy, peripheral T lymphocytes immune phenotypes could be proposed as adjunctive markers to complement CD4+ count when attempting to identify and monitor late presenters. The distinctive immunological patterns seen in late presenters were similar regardless of the definition of late HIV diagnosis that was used: CD4+ T-cell count <350 cell/mmc (late presentation), CD4+ T-cell count <200 cells/mmc (Advanced HIV disease), or AIDS defining condition at presentation regardless of the patient's CD4+ T-cell counts (AIDS presentation).

Finally, H. B. Krentz and M. J. Gill report a similarly high proportion of new patients who present late (59%) and describe the significantly higher costs incurred by this group, most notably when considering inpatient costs and any costs incurred during the first year after entry to care. In particular, the economic burden associated with late presentation remained elevated after the first year, at twice that of patients presenting with a CD4+ T-cell count >350 cells/mm^3.

As underlined by these works, late presentation for HIV remains a key unresolved challenge in HIV/AIDS with serious adverse consequences at the individual and societal levels. The tools are available to fully address this problem. Implementation science and operations research initiatives are urgently needed to better define the best strategies to eliminate late presentation. This will be an essential step to control HIV morbidity, mortality, and transmission.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 182672, 8 pages
doi:10.1155/2012/182672

Research Article

Comparing Measures of Late HIV Diagnosis in Washington State

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Received 14 May 2011; Accepted 26 August 2011

Academic Editor: Enrico Girardi

As more US HIV surveillance programs routinely use late HIV diagnosis to monitor and characterize HIV testing patterns, there is an increasing need to standardize how late HIV diagnosis is measured. In this study, we compared two measures of late HIV diagnosis, one based on time between HIV and AIDS, the other based on initial $CD4^+$ results. Using data from Washington's HIV/AIDS Reporting System, we used multivariate logistic regression to identify predictors of late HIV diagnosis. We also conducted tests for trend to determine whether the proportion of cases diagnosed late has changed over time. Both measures lead us to similar conclusions about late HIV diagnosis, suggesting that being male, older, foreign-born, or heterosexual increase the likelihood of late HIV diagnosis. Our findings reaffirm the validity of a time-based definition of late HIV diagnosis, while at the same time demonstrating the potential value of a lab-based measure.

1. Background

Approximately one in five people living with HIV in the United States is unaware of their HIV status [1]. Research suggests that many of these individuals—at least a quarter of a million people—regularly receive health care services, yet they are not tested for HIV [2]. These missed opportunities are costly, preventing early detection of HIV infection and prolonging the HIV epidemic within our nation [3]. The National HIV/AIDS Strategy includes a goal to reduce HIV infections by increasing the proportion of infected individuals who know their status, from an estimated 79% to 90% by 2015 [4]. Accomplishing this goal will require a substantial increase in HIV testing. Moreover, prevention programs will need better ways to identify and characterize people who are at risk for HIV but who are not routinely tested for HIV.

Routine HIV screening, which leads to early diagnosis, is an efficacious and cost-effective strategy for HIV prevention [5–7]. Early diagnosis of HIV infection can reduce the costs of HIV treatment, improve health outcomes, and prevent others from becoming exposed to the virus [8–11]. Since 2006, the U.S. Centers for Disease Control and Prevention (CDC) have recommended that all adult and adolescent patients in health care settings be regularly screened for HIV, regardless of known risk behaviors [2]. Similar recommendations have been issued by the World Health Organization and by the American College of Physicians [12]. Patients and health care providers are encouraged to consider routine HIV screening as a standard medical practice, similar to screenings performed for other chronic health conditions, such as cancer and cardiovascular disease.

A growing number of US HIV surveillance programs are routinely monitoring late HIV diagnosis, or the proportion of new HIV cases that are diagnosed late in the course of their HIV illness. Late HIV diagnosis is a measure of program performance within the Washington State Department of Health's HIV Prevention Program and is currently one of three HIV-related metrics which are being used by CDC's Winnable Battles effort to monitor and support state-specific progress towards curbing the HIV epidemic [13]. Surveillance data describing late HIV diagnosis provide a measure of HIV testing frequency and help characterize HIV-infected people who are unaware of their HIV status. Yet, there is currently a lack of consensus regarding how late diagnosis should be measured. More than 20 different measures of late

diagnosis have been cited in various publications [14]. In 2009, the European Late Presenter Consensus working group established a harmonized definition of late HIV diagnosis [15]. However, in the US, a standard definition has yet to be adopted. Most surveillance programs use a time-based approach in which newly diagnosed HIV cases defined as late are individuals diagnosed with AIDS within a short-time period after initial diagnosis of HIV infection, for example one month [16], three months [17], twelve months [18–20], or even 3 years [21]. However, this approach can require a lengthy follow-up period and hinges on our somewhat limited ability to determine when a diagnosis first occurred. Also, the chosen time interval between diagnosis of HIV and AIDS often varies across jurisdictions. The inconsistencies in defining late HIV diagnosis make examination of factors associated with late diagnosis difficult [17].

Outside the United States, surveillance programs commonly use initial $CD4^+$ T-cell count to determine a patient's stage of HIV illness at the time of diagnosis [22]. This approach is not dependent on long-term follow-up and could provide a more reliable and comparable definition for late diagnosis of HIV infection. Yet, while the completeness of laboratory data has improved over time, many US jurisdictions remain wary of potential bias associated with the incomplete reporting of laboratory results [17]. This is also a concern in Washington state, where comprehensive HIV laboratory reporting has only been in place since 2006.

We designed this study with three objectives in mind. First, we wish to inform state and local HIV prevention efforts by characterizing people with HIV who are diagnosed late in the course of their HIV illness. Second, we wish to determine whether the proportion of new HIV cases diagnosed late has changed over the past decade. Third, we compare two alternative measures of late HIV diagnosis, evaluating whether these measures lead us to similar or different conclusions about late HIV diagnosis in our state, and whether stated concerns about bias associated with either measure are justified.

2. Methods

We used surveillance data from Washington state's core HIV/AIDS reporting system (eHARS). This data system contains information about all individuals who have received a confidential diagnosis of HIV or AIDS while residing in Washington. The state also maintains a comprehensive laboratory reporting system which can be linked to eHARS and which contains all reported $CD4^+$ T-cell test results associated with each HIV/AIDS case.

We analyzed adult cases, ages 18 years and older, who were diagnosed with HIV infection while residing in Washington state between 2000 and 2009. The time-based measure defines a case as late if the individual is diagnosed with AIDS within 12 months of initial HIV diagnosis. In our analysis of the time-based measure, we excluded cases with incomplete or missing dates of HIV or AIDS diagnosis (missing either month or year). When calculating the time-based measure, we also excluded cases diagnosed with HIV in 2009, since reporting delays would prevent us from being able to identify all cases that received an AIDS diagnosis within the 12-month follow-up period. The lab-based measure defines cases as late if the initial $CD4^+$ T-cell count is <350 cells/mL, based on current WHO recommendations for HIV treatment initiation. We excluded cases from our analysis if the initial lab result was based on a specimen collected ≥90 days after HIV diagnosis.

We used SAS software (version 9.2) to generate descriptive statistics and conduct logistic regression, with relative likelihood for late HIV diagnosis described using adjusted odds ratios. Covariates in the multivariate regression model included gender, age at HIV diagnosis, race and Hispanic ethnicity, mode of HIV exposure, county of residence (at diagnosis), and foreign-born status.

To test for trends over time, we used a JoinPoint regression program (version 3.0) developed by the National Cancer Institute. Slope was calculated based on the model $\ln(y) = xb$. Standard error of the dependent variable was based on the assumption that the underlying data fit a Poisson distribution. Annual percent change (APC) was used to describe change in the proportion of cases diagnosed late over time. APC assumes that rate of change occurs as a constant percentage over a defined time period.

3. Results

Among the 5,639 new HIV cases in Washington state between 2000 and 2009, 91% had adequate data to calculate a time-based measure of late HIV diagnosis (Table 1). All but one of the cases with incomplete data were diagnosed in 2009, which was too recent to determine whether an AIDS diagnosis took place during the 12-month follow-up period. Over the same time period, 71% of new cases had documentation of a valid $CD4^+$ T-cell test result within 90 days of HIV diagnosis. While the proportion of cases without a $CD4^+$ T-cell laboratory result was relatively high (29%), it appeared to decrease over time, from 35% in 2000 to only 17% in 2009. Regardless of measure, cases with complete data generally resembled those with missing or incomplete data. There were no statistical differences by gender or race/ethnicity. However, we did observe small but statistically significant differences with respect to age at HIV diagnosis, mode of HIV exposure, and county of residence (lab-based measure only).

Overall, a lower proportion of new HIV cases was diagnosed late using the time-based measure (37%) compared with the lab-based measure (56%; Table 2). However, within demographic and risk strata, the adjusted odds of being a late HIV diagnosis were similar regardless of measure. Men in our sample had 1.9–2.5 times the odds of being diagnosed late compared to women. We also found strong evidence for a positive association between late diagnosis and increasing age at HIV diagnosis. For example, older adults (ages 45 and older) had 1.8–2.2 times greater odds of being diagnosed late than did adults in their late twenties and early thirties. New HIV cases reporting heterosexual exposure had more than twice the odds of late diagnosis compared to those

Table 1: Comparing cases meeting two definitions of late HIV diagnosis, 2000–2009.

Lab-based measure of late diagnosis	Time-based measure of late diagnosis			
	Late	Not late	Missing	Total
	No. (% of total)	No. (% of total)	No. (% of total)	No. (% of total)
Late	1575 (28)	432 (8)	236 (4)	2243 (40)
Not late	113 (2)	1450 (26)	209 (4)	1772 (31)
Missing	216 (4)	1317 (23)	91 (2)	1624 (29)
Total	1904 (34)	3199 (57)	536 (10)	5639 (100)

Table 2: Characteristics of late HIV diagnoses, including adjusted* odds ratios, Washington state, 2000–2009.

	Time-based late measure 2000–2008 (Late = AIDS within 12 months)			Lab-based late measure 2000–2009 (Late = CD4$^+$ T-cell < 350 cells/mL)		
	No.	% Late	Odds ratio (95% CI)*	No.	% Late	Odds ratio (95% CI)*
Total late HIV diagnoses	1904	37%	n/a n/a	2243	56%	n/a n/a
Gender						
Male	1622	38%	**1.88 (1.53–2.31)**	1905	56%	**2.54 (1.98–3.25)**
Female	282	36%	Reference	338	54%	Reference
Race/ethnicity						
White, NH	1077	34%	Reference	1273	51%	Reference
Black, NH	382	42%	**1.20 (1.01–1.43)**	423	61%	1.21 (0.98–1.48)
Hispanic	273	43%	**1.33 (1.07–1.65)**	348	66%	**1.61 (1.26–2.05)**
Asian	80	44%	1.35 (0.95–1.90)	102	65%	1.34 (0.92–1.95)
NHOPI**	11	46%	1.68 (0.71–3.95)	11	55%	1.08 (0.43–2.71)
AI/AN	45	48%	**1.68 (1.09–2.60)**	44	67%	**1.94 (1.13–3.34)**
Multiple/unknown	36	39%	1.45 (0.93–2.28)	42	61%	**1.72 (1.03–2.87)**
Age at HIV diagnosis						
18–25 yrs	91	16%	**0.42 (0.33–0.54)**	150	38%	**0.57 (0.45–0.72)**
25–34 yrs	479	30%	Reference	601	51%	Reference
35–44 yrs	753	41%	**1.59 (1.38–1.83)**	847	59%	**1.38 (1.18–1.62)**
45 yrs and over	581	50%	**2.18 (1.85–2.57)**	645	65%	**1.82 (1.51–2.18)**
Mode of HIV exposure						
MSM	971	33%	Reference	1202	52%	Reference
IDU	179	42%	**1.44 (1.15–1.81)**	160	57%	**1.41 (1.07–1.87)**
MSM/IDU	97	25%	**0.72 (0.56–0.92)**	119	41%	**0.67 (0.52–0.86)**
Heterosexual	284	44%	**1.92 (1.53–2.41)**	318	57%	**2.51 (1.90–3.32)**
Blood/pediatric	7	50%	2.23 (0.75–6.58)	7	64%	1.85 (0.56–6.12)
NIR	366	51%	**2.04 (1.67–2.48)**	437	71%	**2.62 (2.06–3.34)**
Residence at HIV diagnosis						
Inside King county	1049	34%	Reference	1298	53%	Reference
Outside King county	855	42%	**1.36 (1.20–1.53)**	945	61%	**1.37 (1.19–1.58)**
Country of origin						
US-born	1352	35%	Reference	1567	52%	Reference
Foreign-born	552	46%	**1.26 (1.06–1.51)**	676	67%	**1.34 (1.09–1.64)**

* Adjusting for gender, race/ethnicity, risk category, age at HIV diagnosis, residence in King County, and foreign-born status.
** Native Hawaiian or other Pacific Islander.

categorized as men who have sex with men (MSM). Non-MSM male cases, including those with no identified risk category, actually had among the highest proportions of late diagnoses: 54% and 75% according to the time-based and lab-based measures, respectively. Cases residing outside King County at the time of HIV diagnosis had odds of late diagnosis that were nearly 1.4 times larger than cases residing inside King County.

Foreign-born status was strongly associated with late HIV diagnosis. Overall, the odds of late diagnosis were

Table 3: Late HIV diagnoses by race/ethnicity and foreign-born status, Washington State, 2000–2009.

	Time-based late measure 2000–2008 (Late = AIDS within 12 months of HIV)			Lab-based late measure 2000–2009 (Late = initial CD4 < 350)		
	No.	% Late	Odds ratio (95% CI)*	No.	% Late	Odds ratio (95% CI)*
US-born						
White, NH	1011	34%	Reference	1190	51%	Reference
Black, NH	196	37%	1.07 (0.87–1.31)	203	55%	1.09 (0.86–1.38)
Hispanic	58	30%	0.98 (0.70–1.37)	83	57%	**1.51 (1.06–2.16)**
Asian	12	39%	1.59 (0.75–3.39)	15	54%	1.34 (0.62–2.88)
NHOPI**	3	30%	1.10 (0.27–4.42)	3	38%	0.69 (0.16–2.98)
AI/AN	43	49%	**1.67 (1.06–2.61)**	40	65%	1.68 (0.96–2.93)
Multiple/unknown	29	37%	1.35 (0.82–2.21)	33	58%	1.65 (0.95–2.86)
Foreign-born						
White, NH	66	31%	Reference	83	53%	Reference
Black, NH	186	49%	**2.16 (1.42–3.30)**	220	69%	**1.76 (1.08–2.88)**
Hispanic	215	48%	**2.33 (1.61–3.37)**	265	70%	**2.16 (1.43–3.27)**
Asian	68	46%	**2.03 (1.28–3.22)**	87	67%	**1.72 (1.03–2.88)**
NHOPI	8	43%	**3.41 (1.08–10.8)**	8	67%	2.11 (0.58–7.65)
AI/AN	2	33%	1.68 (0.29–9.85)	4	100%	n/a
Multiple/unknown	7	54%	3.13 (0.96–10.2)	9	75%	2.48 (0.61–10.1)

* Adjusting for gender, risk category, age at HIV diagnosis, and residence in King County.
** Native Hawaiian or other Pacific Islander.

about 1.3 times greater among cases born outside the United States versus those born within. However, foreign-born status seemed to confound the association between race/ethnicity and late HIV diagnosis (Table 3). Among cases born in the US, there was generally little evidence to suggest an association between race/ethnicity and late HIV diagnosis. The odds of late diagnosis among US-born American Indians and Alaska Natives (AI/AN) were about 1.7 times larger than those among US-born whites. Using the lab-based measure, US-born Hispanics had 1.5 times greater odds of late diagnosis compared to their white counterparts. However, the time-based measure provided no evidence for such an association. Among cases born outside the US, differences in the odds of late diagnosis were much greater between racial/ethnic groups. Among foreign-born cases, nonwhite cases had 1.7–3.4 times greater odds of late diagnosis compared to white cases.

Statewide, there is some evidence to suggest that the occurrence of late HIV diagnosis has decreased over the past decade (Figure 1). JoinPoint regression of both measures showed an average decrease of about 2 percent per year. However, only the slope associated with the lab-based measure (APC = −2.00) was statistically significant at the $P = 0.05$ level. Most of the change appears to be explained by significant decreases in late diagnosis among US-born cases (APC = −2.53), which comprise roughly 75% of all new HIV cases in Washington (Figure 2). The proportion of new HIV cases that are foreign-born has steadily risen over the past decade.

4. Discussion

As our state's HIV epidemic nears the end of its third decade, the proportion of new HIV cases which are diagnosed late remains unacceptably high. Although CDC recommendations for the expansion of HIV testing have been in place for more than five years, a substantial proportion of new cases is still being detected late in the course of their HIV illness, after the point at which treatment should have been initiated. Statewide, declines in late HIV diagnosis over the past ten years appear to be minimal. Indeed, our findings support the notion that targeted HIV testing efforts, which depend heavily on patient and provider perceptions of HIV risk, cannot by themselves reduce the number of HIV-infected people who are infected but unaware of their status [3, 23]. Many of the characteristics we observed to be associated with late HIV diagnosis, such as being heterosexual, or residing in a rural area, are not traditionally considered strong indicators of HIV risk. Therefore, HIV testing efforts need to be broadened to include people who are at elevated risk for HIV but who are, for a variety of reasons, not getting tested.

Men in our sample were more likely to be diagnosed late than women. This finding is consistent with several published studies [24–26]. However, other attempts to characterize the association between gender and late diagnosis have proven inconclusive [18, 27]. Using either measure of late diagnosis, the difference in the proportions of male and female cases that were diagnosed late was relatively small (<2%), suggesting the direction of the gender association

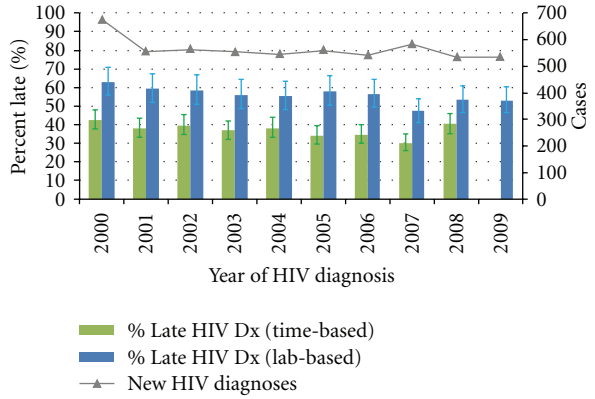

Figure 1: New HIV diagnoses and proportions that were diagnosed late, by year of HIV diagnosis, Washington State, 2000–2009.

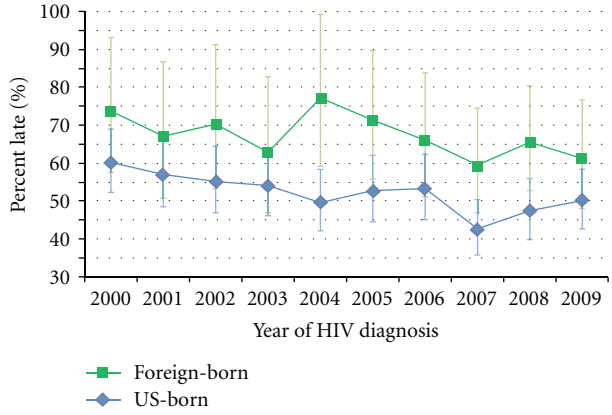

Figure 2: Trends in late HIV diagnosis (lab-based) and foreign-born status, Washington State, 2000–2009.

could be sensitive to relatively minor differences in testing patterns. As reported elsewhere, we observed men with mode of transmission categorized as MSM or MSM/IDU to be among the least likely to be a late HIV diagnosis [28]. These cases comprise the majority of HIV cases in Washington state. However, since these risk categories do not by definition contain female cases, they were effectively ignored by our multivariate regression model, with gender comparisons and resulting odds ratios limited mainly to cases falling into three risk categories: heterosexuals, injection drug users, and cases with no identified risk factors.

Although women are generally less likely to perceive themselves as being at risk for HIV, which would seem to favor late diagnosis, they typically demonstrate higher utilization of health services compared to men, and HIV testing is more widely accessible to women as result of both prenatal HIV screening as well as cervical cancer screening [29, 30]. On the other hand, the association between gender and late diagnosis could also be influenced by lower levels of HIV testing within certain male subgroups, some of whom may actually be MSM but have not been reported as such. For example, research suggests that male Latinos at risk for HIV tend to get tested for HIV less frequently, and often do not identify as being gay or bisexual despite engaging in MSM behaviors [31–35].

We expected a positive correlation between increasing age and late diagnosis. The very act of delaying testing requires the passage of time, and as time passes, people get older. Also, as the body ages, $CD4^+$ T-cell counts tend to naturally decrease [36]. This results in a less-effective specific immune response, leading to greater viremia and less time to AIDS among individuals who seroconvert [37, 38]. Finally, some research indicates that older MSM test less often than younger MSM [39].

Overall, we expected a stronger relationship between race/ethnicity and late diagnosis than we observed, given the widely documented lower testing rates among racial/ethnic minorities [16, 21]. While crude associations were apparent, racial/ethnic differences in late diagnosis were substantially smaller once we controlled for foreign-born status. The increased risk for late diagnosis among Native Americans is consistent with other evidence showing higher levels of poverty and limited access to health services within this population [40]. Likewise, late diagnosis among Hispanics could be due to barriers to HIV testing, particularly stigma-induced fear of testing positive and difficulty communicating with providers among individuals who do not speak English [41, 42].

Our finding that foreign-born status confounds the associations between race/ethnicity and late HIV diagnosis is consistent with other published findings [2, 18, 43]. While foreign-born cases are more likely than US-born cases to be diagnosed late, it is difficult to determine how much of this increased likelihood is due to lower HIV testing versus other reasons. As result of strict HIV surveillance reporting requirements in the US, some foreign-born cases could be diagnosed outside the US but lack required documentation to demonstrate that a previous diagnosis took place. This could result in misclassification bias, causing some foreign-born cases to appear as late diagnoses when they really are not. Needs assessments data have suggested that as many as one quarter of foreign-born HIV cases diagnosed in our state were actually diagnosed at least one year earlier than the reported date of HIV diagnosis [32, 44]. Yet, differences in testing behaviors could also be explained by other factors associated with recent immigration to the US, such as poor access to HIV testing services, language barriers, social isolation, financial instability, or lack of knowledge about HIV [16, 27, 45].

4.1. Data Completeness and Limitations. Differences between cases with and without supporting data were relatively small and similar between late measures. The similarity in findings suggests that both measures would be prone to the same kinds of minimal bias.

The completeness of data supporting the time-based measure is higher than that of the lab-based measure in our study. However, this is heavily dependent on the duration of the chosen observation period. Had we evaluated late HIV diagnosis over a five-year time period, completeness would have been lower for the time-based definition.

Although we tend to assume that people with AIDS have serious health conditions that compel them to seek treatment, not all cases who develop AIDS seek care in a timely manner. Thus we may have misclassified some cases categorized as "not late" because although they have progressed to AIDS, they have not yet been linked to care or reported to our surveillance system. The time-based measure is also a subject to reporting delays associated with the diagnosis of HIV and AIDS, as well as our ability to monitor diagnoses that take place either out-of-state or outside the country.

Completeness of the data for the lab-based measure is strongly dependent on whether a given jurisdiction has implemented comprehensive lab reporting. Nevertheless, we are aware that a growing proportion of providers in our state are using out-of-state labs to process HIV-related specimens. Laws governing the reporting of laboratory results vary by state [46]. Although Washington has laws intended to ensure the comprehensive reporting of all HIV and AIDS test results, these laws do not apply to laboratories located outside state borders. Hence, many $CD4^+$ T-cell results likely remain unreported each year, especially if they do not correspond to an HIV or AIDS case definition, such as $CD4^+$ T-cell counts over 200.

The logistic regression models were based on cross-sectional comparisons and do not indicate whether testing patterns have changed over time. Cases with complete data necessary to calculate either measure of lateness might not be representative of all new HIV cases, resulting in selection bias. Moderate case counts resulted in lower stratified cell sizes and wider confidence intervals that prevented our ability to detect trends in late diagnosis within stratified subgroups.

The adjusted odds ratios generated by our logistic regression model provide an indication of which variables are associated with late HIV diagnosis in our state, as well as some idea as to relative strength of those associations. However, since late HIV diagnosis is a common event within our sample, the odds ratios likely represent a substantial overestimation of corresponding relative risks.

Among new HIV cases categorized as foreign-born in our analysis, approximately 20% are missing information about country of birth. Although some of these cases might actually have been born in the US, we do not consider this to be a large limitation. By misclassifying some native-born cases as foreign-born, we would essentially dilute the latter group, making them appear more like native-born cases than they actually are. Accurate classification of these cases would likely result in better separation between native and foreign-born cases, which would likely improve our ability to measure an association and strengthen our findings.

4.2. Strengths and Future Implications. To our knowledge, this is the first study which uses HIV surveillance data to compare two measures of late HIV diagnosis. Our results indicate that both measures point to the same risk factors for late HIV diagnosis. The relative strength and direction of these associations were also very similar.

The lab-based measure is more clinically relevant because it is based on the current recommendations for treatment initiation and can be easily modified as the standard of care evolves. In addition, it allows the inclusion of at least one additional year of data (the most recent). As our laboratory reporting system matures, and with the expected introduction of health information exchanges, the quality and completeness of laboratory data should continue to improve over time [47]. Among the 536 cases with missing data needed to calculate the time-based measure, nearly half were identified as late using the lab-based measure. On the other hand, using both measures together could provide a broader and potentially more informative understanding of late diagnosis, offering additional information about cases that lack adequate data to support either one measure or the other.

Strengths of our study include the use of nine years of statewide surveillance data as well as an evaluation of two different ways of measuring late HIV diagnosis. Also, our use of multiple logistic regression allowed us to control for numerous potential confounders. Our results reaffirm the validity of a time-based definition of late HIV diagnosis, while at the same time demonstrating the potential value of a lab-based measure. Moreover, because it is a subject to fewer potential limitations, the lab-based measure might be a better alternative in jurisdictions with comprehensive laboratory reporting.

Acknowledgment

The authors would like to thank Eric Ossiander, Ph.D. of the Center for Health Statistics at the Washington State Department of Health for help with the statistical issues.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 869841, 7 pages
doi:10.1155/2012/869841

Research Article

CD4 Cell Counts at HIV Diagnosis among HIV Outpatient Study Participants, 2000–2009

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Received 13 May 2011; Revised 27 June 2011; Accepted 28 June 2011

Academic Editor: Giulia Marchetti

Background. It is unclear if CD4 cell counts at HIV diagnosis have improved over a 10-year period of expanded HIV testing in the USA. *Methods*. We studied HOPS participants diagnosed with HIV infection ≤6 months prior to entry into care during 2000–2009. We assessed the correlates of CD4 count <200 cells/mm^3 at HIV diagnosis (late HIV diagnosis) by logistic regression. *Results*. Of 1,203 eligible patients, 936 (78%) had a CD4 count within 3 months after HIV diagnosis. Median CD4 count at HIV diagnosis was 299 cells/mm^3 and did not significantly improve over time ($P = 0.13$). Comparing periods 2000-2001 versus 2008-2009, respectively, 39% and 35% of patients had a late HIV diagnosis ($P = 0.34$). Independent correlates of late HIV diagnosis were having an HIV risk other than being MSM, age ≥35 years at diagnosis, and being of nonwhite race/ethnicity. *Conclusions*. There is need for routine universal HIV testing to reduce the frequency of late HIV diagnosis and increase opportunity for patient- and potentially population-level benefits associated with early antiretroviral treatment.

1. Introduction

Recent HIV surveillance data suggest that approximately 33% of HIV-infected persons in the United States present for HIV testing late and have AIDS (CD4+ cell count <200 cells/mL or an AIDS-defining illness) within one year after HIV diagnosis [1, 2]. Patients are less likely to experience the full benefits of highly active combination antiretroviral (cART) therapy if they enter HIV care and initiate treatment at a CD4 count <350 cells/mm^3 [3, 4]; the clinical cost is even more profound when the CD4 count is <200 cells/mm^3 or the patient has already developed clinical AIDS [5–8]. In addition, persons who remain unaware of their HIV-positive status (estimated 21% to 25% of infected persons in the USA in recent years) [9, 10] may not only miss the benefits of earlier cART treatment, but are also more likely to remain chronically viremic and are thereby more likely to transmit HIV to their sexual and needle-sharing partners [9].

The CDC has been promoting strategies to encourage more widespread HIV screening to diagnose infected persons earlier in the course of their illness, including by releasing in 2006 the guidelines for implementing routine universal opt-out testing in healthcare settings [11]. Yet, the latest HIV surveillance data [1, 2] and epidemiologic studies in multiple US populations indicate that the proportion of persons who are diagnosed late in the course of HIV infection [2, 12, 13] or present late for HIV care [14, 15] remains unacceptably high. Stable or worsening trends in the proportion of patients HIV diagnosed with low CD4 counts have also been observed internationally [16–18]. However, encouraging trends have been seen in select US jurisdictions which have dramatically expanded their HIV testing programs [19, 20]. With the recent shift in antiretroviral treatment guidelines toward earlier therapy initiation to benefit patients' health [21] and the growing interest in HIV "test and treat" and "test and link to care-plus" strategies to limit the spread of the US epidemic [22], it is important to understand the burden of late HIV

diagnosis among contemporary US patients as it affects the likelihood of success of these interventions.

We studied participants in the HIV Outpatient Study (HOPS) who were recently diagnosed with HIV infection to examine the trends in median CD4 count at diagnosis and the proportion of patients diagnosed with CD4 count <200 cells/mm^3 (also termed "late HIV diagnosis") during 2000–2009.

2. Methods

2.1. The HIV Outpatient Study (HOPS). The HOPS is an ongoing, open prospective observational cohort study that has continuously recruited and followed HIV-infected patients since 1993. Since the HOPS' inception, the study sites have included 10 clinics (6 university, 2 public, 2 private) in eight US cities and provided care for about 3,000 HIV-infected patients per year. Over 9,600 HOPS patients have been seen during more than 390,000 clinical encounters. The study protocol is approved and renewed annually by each participating institution's ethical review board. All study participants provide written, informed consent.

HOPS clinicians have extensive experience treating HIV-infected patients. Information is abstracted from outpatient charts at each visit, entered electronically by trained staff, compiled centrally, and reviewed and edited before being analyzed. Abstracted information includes demographic characteristics and risk factors for HIV infection; diagnoses; symptoms; prescribed medications, including dose and duration; laboratory values, including CD4 counts and plasma HIV viral loads; causes of mortality and hospitalizations.

2.2. Study Population. We analyzed data from HOPS participants using the dataset updated as of March 30, 2011. The 10 clinics included in the analyses were located in Tampa, FL (2 sites); Washington, DC; Denver, CO (2 sites); Chicago, IL (2 sites); Stony Brook, NY; Oakland, CA; Walnut Creek, CA, and Philadelphia, PA. We limited analyses to patients who had been HIV-diagnosed during 2000–2009, within ≤6 months before entry into care at a HOPS site (i.e., had a recent HIV diagnosis), had complete records of antiretroviral use (if any), and had a CD4 count measured at the time of HIV diagnosis (up to 3 months after HIV diagnosis date) and before having received any antiretroviral treatment. Thus we focused on subset of patients who entered HOPS care after a recent (i.e., within the past 6 months) diagnosis of HIV infection, for whom we had more complete data on CD4 count at HIV diagnosis.

We defined medical coverage/insurance (insurance) as private for the following payer categories: health maintenance organization, preferred provider organization, point of service plans, "self-pay/fee-for-service," and "other private insurance." We defined the following payer categories as public insurance: Medicaid, Medicare, Ryan White/AIDS Drug Assistance Program, and "public, state funded." We defined the categories other, unknown, and "clinical study" as other or unknown insurance.

We classified the following HOPS sites, which serve diverse patient populations, including indigent patients, as public facilities: State University of New York (SUNY), Stony Brook, NY; Temple University School of Medicine, Philadelphia, PA; University of Illinois at Chicago, Chicago, IL. The remaining institutions listed in the Acknowledgments were classified as private facilities.

2.3. Analysis Methods. We used chi-square or Fisher's Exact test to analyze categorical variables and the Wilcoxon rank sum test to compare distributions of continuous variables. We examined median CD4 counts and the proportion of patients having a CD4 count <200 cells/mm^3 at HIV diagnosis during the entire period 2000–2009 and by five two-year periods within this time frame: 2000-2001, 2002-2003, 2004-2005, 2006-2007, and 2008-2009. We assessed temporal trends in the distribution of CD4 counts at HIV diagnosis using the Jonckheere-Terpstra nonparametric test and assessed trends in the proportion of persons diagnosed with CD4 count <200 cells/mm^3 by calendar period using the Cochran-Armitage test. Factors associated with having a CD4 count <200 cells/mm^3 at HIV diagnosis (also termed "late HIV diagnosis" henceforth) were examined using multiple logistic regression. Factors considered in the logistic models included patient's age, gender, race/ethnicity, HIV risk, and patient's insurance (private versus public or none). We chose to evaluate patient's insurance rather than the type of HOPS site (private versus public facility) in the primary multivariable model because these two variables were correlated and because we hypothesized that patient's insurance would be more closely tied to behaviors and circumstances associated with late HIV testing; we evaluated type of HOPS facility, in place of patient's insurance, in an alternate multivariable model.

We also performed additional analyses of trends in CD4 count at diagnosis after transforming data on the square-root scale. The data describing the location of initial HIV diagnosis were collected systematically since mid-2005 and were analyzed only for patients diagnosed in 2006–2009.

Finally, we evaluated the percentage of persons who developed AIDS (defined as CD4 count of <200 cells/mm^3 or CD4+ T-lymphocyte percentage of total lymphocytes of <14 or documentation of an AIDS-defining condition) within 12 months of HIV diagnosis [1].

3. Results

Of 3,670 new HOPS participants seen at 10 HIV clinics during 2000–2009, 1,223 (33%) had a recent HIV diagnosis (≤6 months before entry into care at a HOPS site). Compared with the 2,447 patients who were diagnosed with HIV infection >6 months prior to entry into care at a HOPS site (and may have been in care elsewhere), recently diagnosed patients were significantly ($P < 0.05$) more likely to be ARV naïve (86% versus 16%), younger (median age of 38 versus 40 years), to have heterosexual activity as their sole risk for HIV infection (37% versus 25%), to be privately insured (61% versus 51%), less likely to be male (75% versus 80%), less

Table 1: Characteristics of patients diagnosed with HIV infection within 6 months before study entry with available CD4 count data* by study period during which HIV diagnosis occurred, the HIV Outpatient Study, 2000–2009.

	2000-2001 ($n = 213$)	2002-2003 ($n = 224$)	2004-2005 ($n = 207$)	2006-2007 ($n = 145$)	2008-2009 ($n = 147$)	P value for trend†	All years ($n = 936$)
Males, %	75	71	81	81	76	0.21	77
Age, median years (IQR)	37 (30–45)	38 (30–45)	39 (31–46)	36 (28–46)	36 (28–46)	0.50	38 (30–46)
Race/ethnicity, %							
Non-Hispanic white	44	39	47	48	36	0.67	43
Non-Hispanic black	37	44	36	34	44	0.83	39
Hispanic	15	13	14	14	18	0.59	15
Other or unknown	4	3	3	4	3	0.65	3
HIV infection risk group, %							
Men who have sex with men (MSM)	50	48	57	69	49	0.08	54
High-risk heterosexual	39	41	32	21	44	0.26	36
Injection drug use (IDU, including MSM IDU)	6	6	6	3	1	0.02	5
Other or unknown	5	6	5	6	7	0.54	6
Medical insurer, %							
Privately insured	57	67	67	70	58	0.51	64
Publically insured	34	29	29	24	33	0.37	30
Other or unknown	9	4	3	6	10	0.70	6
Type of facility, %							
Public	28	46	42	28	49	0.03	39
Private	72	54	58	72	51	0.03	61

* For inclusion in this analysis, patients must have had a CD4 cell count measured within 1 month prior to or up to 3 months after the date of HIV diagnosis while remaining antiretroviral-naïve.
† By Cochran-Armitage test for proportions (%), and by Jonckheere-Terpstra nonparametric test for continuous variables.

likely to be of white race (40% versus 47%), and less likely to have injection drug use (IDU) activity as their sole risk for HIV infection (6% versus 11%).

Of the 1,223 patients with recent diagnoses, 936 (77%) had a CD4 count documented within 3 months following HIV diagnosis while still antiretroviral naïve (a median of 15 days, IQR: 4–34 days after diagnosis). Of these 936 patients (median age = 38, range: 17–77 years), 77% were male, 43% were white, 39% were black, 54% were men who had sex with men (MSM), 36% had heterosexual HIV risk, and 5% were injection drug users (Table 1). The 23% of patients whom we excluded because they did not have a CD4 count documented in the relevant timeframe were significantly more likely to have had a history of IDU (9% versus 5%), to have public insurance (41% versus 29%), and to have been antiretroviral-experienced (23% versus 7%) at entry into care at a HOPS site.

3.1. Trends in CD4 Counts at HIV Diagnosis. The overall median CD4 count at HIV diagnosis was 299 cells/mm^3 (mean = 339, IQR 100–498); among patients diagnosed in 2000-2001 and 2008-2009 the median CD4 counts were 284 cells/mm^3 and 314 cells/mm^3, respectively, (P value for trend across the five two-year time periods = 0.13) (Table 2). We also found no linear trend in CD4 counts at diagnosis by calendar period after data were transformed on the square-root scale to normalize the distributions and were analyzed by generalized linear models (data not shown). Although not statistically significant, there was a trend toward improvement in CD4 cell counts among patients who had heterosexual contact as a risk factor for HIV infection and those seen in public HOPS clinics (Table 2).

3.2. Low CD4 Counts at HIV Diagnosis. Among the 936 recently diagnosed patients who had CD4 cell count data available, 337 (36%) were diagnosed with a CD4 count <200 cells/mm^3 (i.e., had a late HIV diagnosis), 39% of patients diagnosed in 2000-2001 and 35% of patients diagnosed in 2008-2009 (Cochran-Armitage test for trend across the five two-year periods, $P = 0.21$) (Figure 1). During 2000–2009, late HIV diagnoses were significantly ($P < 0.05$) more common among black (42%) and Hispanic (46%) patients compared with white patients (28%), among patients with public (42%) versus private insurance (34%), and among patients entering care at public versus private HOPS clinics (45% versus 30%, resp.). The frequency of late HIV diagnoses was significantly lower among MSM (27%) compared with all other risk groups (47%).

Table 2: Median CD4 cell count (cells/mm^3) at HIV diagnosis* by demographic characteristics and study period during which HIV diagnosis occurred, the HIV Outpatient Study, 2000–2009. Table presents only strata including at least 100 patients in the study.

	2000-2001 ($n = 213$)	2002-2003 ($n = 224$)	2004-2005 ($n = 207$)	2006-2007 ($n = 145$)	2008-2009 ($n = 147$)	P value for trend†	All years ($n = 936$)
Overall, median (interquartile range)	284 (99–438)	298 (71–523)	288 (110–501)	320 (139–517)	314 (90–502)	0.13	299 (100–498)
Overall, mean (95% confidence interval)	312 (277–347)	346 (306–386)	341 (302–380)	354 (312–396)	353 (303–402)	—	339 (321–358)
By gender							
Male ($n = 716$)	272	320	293	355	305	0.34	304
Female ($n = 220$)	287	258	283	222	374	0.22	286
By race/ethnicity							
Non-Hispanic white ($n = 400$)	362	333	316	383	352	0.69	348
Non-Hispanic black ($n = 365$)	243	272	282	264	276	0.60	271
By HIV infection risk group							
MSM ($n = 505$)	351	375	308	386	336	0.80	351
Heterosexual ($n = 372$)	209	247	229	288	293	0.09	247
By medical insurer							
Privately insured ($n = 596$)	284	336	301	343	328	0.38	310
Publicly insured ($n = 283$)	230	267	234	213	294	0.27	260
By type of facility							
Public ($n = 361$)	208	225	277	212	276	0.10	247
Private ($n = 575$)	331	337	310	343	352	0.32	330

* For inclusion in this analysis, patients must have had a CD4 cell count measured within 1 month prior to or up to 3 months after the date of HIV diagnosis while remaining antiretroviral-naïve.
† By Jonckheere-Terpstra nonparametric test for continuous variables.
‡ Differences in CD4 counts by race/ethnicity, HIV infection risk group, insurance, and type of facility were all statistically significant (nonparametric Wilcoxon rank sum test $P < 0.05$).

Five hundred forty-one (58%) patients were HIV-diagnosed with a CD4 count <350 cells/mm^3, 61% of patients diagnosed in 2000-2001 and 56% of patients diagnosed in 2008-2009 (Cochran-Armitage test for trend across the five two-year time periods, $P = 0.29$). The percentages of HIV diagnoses made among persons with a CD4 count <350 cells/mm^3 were also significantly higher for blacks (63%) and Hispanics (65%) compared with whites (50%), for patients with public (63%) versus private (55%) insurance, and for patients entering care at public versus private HOPS clinics (66% versus 53%, resp.). The frequency of HIV diagnoses made with an initial CD4 count <350 cells/mm^3 was lower among MSM (50%) compared with all other risk groups (67%). Only about 25% of patients were HIV-diagnosed with CD4 cell counts ≥500 cells/mm^3, and could potentially benefit from early antiretroviral treatment initiation per the latest US guidelines [21].

Univariate analyses of factors associated with an HIV diagnosis at a CD4 count <200 cells/mm^3 did not reveal substantive differences in associated predictors across the five two-year analysis periods(data not shown). In univariate logistic regression analyses for all patients ($n = 936$), factors associated with late HIV diagnosis included white race/ethnicity (odds ratio OR = 0.53, 95% confidence interval CI: 0.40–0.70); age <35 years old (OR = 0.45, 95% CI: 0.32–0.64 versus age 35–42 years old); having as a risk for HIV infection not being MSM, or in other words, having high-risk heterosexual, IDU, or another risk (e.g., hemophilia, blood transfusion or occupational exposure) (OR = 2.49, 95% CI: 1.90–3.28 versus MSM), and having public insurance at entry into care at a HOPS site (OR = 1.43, 95% CI: 1.07–1.93 versus private insurance).

In multivariable logistic regression analyses, independent correlates of HIV diagnosis with CD4 count <200 cells/mm^3 were having as a risk for HIV infection not being MSM (OR = 1.99, 95% CI 1.45–2.72), age ≥35 years at diagnosis (OR = 2.14, 95% CI 1.59–2.87), and being of nonwhite race (OR = 1.45, 95% CI 1.05-2.01). The association between late HIV diagnosis and having public insurance that was observed in the univariate analyses did not persist in the adjusted analyses. In an alternate multivariable model, which included type of HOPS site (public versus private facility)

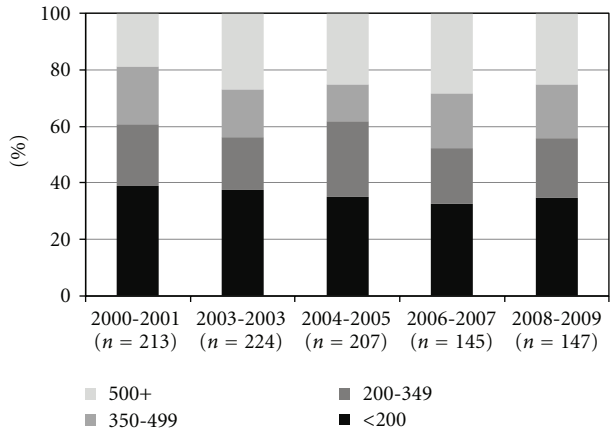

Figure 1: CD4 cell count (cells/mm^3) by period of HIV diagnosis, the HIV Outpatient Study 2000–2009 ($N = 936$).

instead of patient's insurance, the type of HOPS site was also not associated with late HIV diagnosis after controlling for patient's age, race/ethnicity, and HIV risk group.

3.3. AIDS within 1 Year of HIV Diagnosis. Because documentation of AIDS opportunistic illnesses may be incomplete at the time of initial HIV diagnosis, we evaluated the percentage of persons who developed AIDS (by immunologic or clinical criteria) ≤12 months of HIV diagnosis. Across the five two-year periods, respectively, that percentage ranged from 50.2% for patients diagnosed in 2000-2001 to 50.3% for patients diagnosed in 2008-2009 (test for trend $P = 0.66$).

3.4. Circumstances of the Initial HIV Diagnosis. Data on the venue of initial HIV diagnosis were available for 246 of 292 patients diagnosed in 2006–2009. The predominant situations in which HIV diagnoses were made included screening at a routine provider visit ($n = 75$, 30%), testing during inpatient hospitalization ($n = 43$, 17%), testing at a symptom-driven visit ($n = 29$, 12%), and testing at a sexually transmitted disease clinic ($n = 25$, 10%); the circumstances surrounding initial HIV diagnosis were recorded as "unknown" for 29 (12%) of participants.

4. Discussion

Among HOPS patients recently diagnosed with HIV infection, we found no statistically significant improvement in the median CD4 count at diagnosis during 2000–2009. Overall, 36% of patients were diagnosed with a CD4 count <200 cells/mm^3 and 58% with a CD4 count <350 cells/mm^3. Persons whose risk for HIV infection was other than being MSM, persons aged ≥35 years, and persons of nonwhite race/ethnicity were more likely to be diagnosed with a CD4 count <200 cells/mm^3 and thus more likely to have missed an opportunity for timely access to HIV care and initiation of ARV therapy; the correlates of HIV diagnosis with CD4 <350 cells/mm^3 were largely similar. Our finding that MSM were less likely to be diagnosed with advanced HIV infection than some other risk groups (e.g., IDUs) is consistent with the findings from US HIV surveillance [1, 2] and data from other HIV cohorts reporting on late HIV diagnosis [23] and presentation for care [15]. The association of younger age (<35 years) with a lower likelihood of late HIV diagnosis may be partially explained by the fact that younger persons *de facto* have had less lifetime opportunity, if they became HIV-infected, to progress to CD4 <200 cells/mm^3; older age has been associated with late HIV diagnosis previously [2, 15].

In a recent study by Althoff and colleagues of 44,491 HIV-infected patients enrolled in the North American-AIDS Cohort Collaboration on Research and Design (NA-ACCORD), the median CD4 count at first presentation to HIV care increased from 256 cells/mm^3 (interquartile range, 96–455 cells/mm^3) to 317 cells/mm^3 (interquartile range, 135–517 cells/mm^3) from 1997 to 2007 ($P < 0.01$). The median CD4 count at HIV diagnosis for HOPS patients whom we studied (who all entered care within 6 months of diagnosis, per inclusion criteria) was remarkably similar to median CD4 count at first presentation to HIV care among NA-ACCORD participants. Our findings of a high (approximately 34%) prevalence of late HIV diagnosis during the period 2004–2007 correspond well with the estimate from national HIV surveillance (34%) for 2005–2007, and the national surveillance system also detected no marked increases in CD4 counts at diagnosis over time [1]. The reason why the median CD4 counts in the HOPS and NA-ACCORD population were higher as compared with those in HIV surveillance may be related to several factors. First, compared with the nationwide HIV epidemic, the HOPS is enriched in whites and MSM, populations who tend to be diagnosed at higher CD4 cell counts. Second, HIV testing capacity and therefore the opportunity for timely diagnosis vary by jurisdiction. HOPS clinics are located in major urban centers with large HIV epidemics where testing opportunities might be greater leading to a greater likelihood of indentifying infected persons earlier in the course of their disease. Third, the CD4 count findings from national HIV surveillance are derived from 37 states, some of only report CD4 counts <200 cells/mm^3 for HIV-infected persons, a practice that would tend to bias the median CD4 cell count downwards [2].

Our results should be interpreted in light of some additional important caveats. First, we restricted our analyses to patients diagnosed with HIV within 6 months prior to entry into care at a HOPS site. We used this criterion because HOPS patients who initiated HIV care earlier elsewhere often lack documentation of their initial CD4 count value. The timeframe of ≤6 months between HIV diagnosis and entry into care at a HOPS site, however, appeared to capture well the patients who newly entered care (only 7% of these patients had any previous ARV exposure). Although we have thus excluded a subset of patients who delay entry into HIV care (who may also be more likely to be diagnosed late in HIV infection) a recent meta-analysis suggests that approximately 72% of patients enter care within 4 months of HIV diagnosis [24]. Second, we studied a self-selected group of recently diagnosed patients who, by definition, entered HIV care and were also willing to consent to enrollment in the HOPS; these patients could potentially differ from

patients not entering care [25, 26]. Available resources constrain some HOPS sites from enrolling the entire clinic population, and although attempts are made to balance the representativeness of the enrollees there is some opportunity for convenience sampling bias. Additionally, the HOPS does not enroll patients who present to a HOPS clinic for care but die prior to the opportunity to consent for the study. Both of these effects are greater at public facilities compared with private facilities. Consequently, there might be a tendency for the HOPS to enroll healthier patients, and, therefore, our findings would not represent the entire clinic population served by HOPS sites or be generalizable to all patients in cities where HOPS sites are located. Third, the 23% of patients with recent HIV diagnoses who were excluded due to missing CD4 count data were more likely to be IDU and publically-insured, subgroups that tended to have lower CD4 counts at diagnosis. Therefore our finding that approximately one-third of patients were diagnosed with HIV infection at a CD4 count <200 cells/mm^3 might be an underestimate due to this information bias. Finally, because of small sample sizes in some sociodemographic subgroups (e.g., Hispanics, high-risk heterosexuals, persons with a history of IDU) we could not accurately estimate median CD4 counts and proportions of patients with CD4 counts <200 at diagnosis by calendar period for these subgroups; furthermore, estimates for some groups (e.g., women) could be subject to considerable random variability over time.

The CDC recommendations for universal opt-out HIV testing were published in September 2006; in light of inherent reporting delays with HIV surveillance data and data incompleteness, the evidence as to whether these guidelines have led to earlier HIV diagnosis (i.e., at higher CD4 counts) nationwide is not likely to be apparent for some time. Nonetheless, encouraging trends have been seen in jurisdictions that have dramatically expanded HIV testing [19, 20]. In our study, we did not detect a statistically significant trend to higher CD4 cell counts at HIV diagnosis overall, although the pattern of change was in the direction of increasing CD4 cell counts, particularly for patients with heterosexual exposure as a risk factor for HIV infection and those presenting to public facilities.

In conclusion we have found that even among HOPS participants who successfully entered care, over one-third were diagnosed with CD4 counts <200 cells/mm^3 and over one-half were diagnosed with CD4 count <350 cells/mm^3, the threshold at which initiating cART is unequivocally recommended (up to CD4 count of 500 cells/mm^3, above which level it is to be considered) [21]. These findings should raise concern. Prompt HIV diagnosis, entry into care, and timely initiation of cART are critical for reducing the risk of both opportunistic and nonopportunistic disease, prolonging survival, and reducing onward HIV transmission. Our findings also suggest that expanding testing and reducing late HIV diagnosis need to be a priority, if the programs related to improving linkage to care and earlier antiretroviral treatment initiation [22] are to reach patients and potentially alter the trajectory of the US HIV epidemic [27]. An estimated 21 to 25% of HIV-infected persons in the USA remain undiagnosed [9, 10], with the prevalence of unrecognized HIV infection approaching 50% among some urban MSM [28]. Many untested persons either perceive themselves to be at low risk of HIV infection or are fearful of learning their HIV status [28]. Such persons are more likely to have a late stage or illness-triggered diagnosis. Our findings reinforce the need to establish universal routine HIV testing as standard of care for all adolescents and adults seen in private and public care settings, regardless of patient-reported HIV risk [11]. It is only under such circumstances that late-stage or illness-triggered HIV diagnoses will be reduced and that sociodemographic disparities in stage of HIV disease at diagnosis be eliminated.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conflict of Interests

None of the authors have conflict of interests.

Acknowledgments

This paper is founded by Centers for Disease Control and Prevention (Contract nos. 200-2001-00133 and 200-2006-18797). The HIV Outpatient Study (HOPS) Investigators (2011) include the following investigators and sites: John T. Brooks, Kate Buchacz, Marcus Durham, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention (NCHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, GA; Kathleen C. Wood, Rose K. Baker, James T. Richardson, Darlene Hankerson, and Carl Armon, Cerner Corporation, Vienna, VA; Frank J. Palella, Joan S. Chmiel, Carolyn Studney, and Onyinye Enyia, Feinberg School of Medicine, Northwestern University, Chicago, IL; Kenneth A. Lichtenstein and Cheryl Stewart, National Jewish Medical and Research Center Denver, CO; John Hammer, Benjamin Young, Kenneth S. Greenberg, Barbara Widick, and Joslyn D. Axinn, Rose Medical Center, Denver, CO; Bienvenido G. Yangco and Kalliope Halkias, Infectious Disease Research Institute, Tampa, FL; Douglas J. Ward and Jay Miller, Dupont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, and Jane Esteves, State University of New York (SUNY), Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, Faye Ruley and Dania Beadle, Temple University School of Medicine, Philadelphia, PA; Richard M. Novak and Andrea Wendrow, University of Illinois at Chicago, Chicago, IL.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 725412, 9 pages
doi:10.1155/2012/725412

Research Article

Imputation of the Date of HIV Seroconversion in a Cohort of Seroprevalent Subjects: Implications for Analysis of Late HIV Diagnosis

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Received 11 May 2011; Revised 27 July 2011; Accepted 4 August 2011

Academic Editor: Caroline Anne Sabin

Objectives. Since subjects may have been diagnosed before cohort entry, analysis of late HIV diagnosis (LD) is usually restricted to the newly diagnosed. We estimate the magnitude and risk factors of LD in a cohort of seroprevalent individuals by imputing seroconversion dates. *Methods*. Multicenter cohort of HIV-positive subjects who were treatment naive at entry, in Spain, 2004–2008. Multiple-imputation techniques were used. Subjects with times to HIV diagnosis longer than 4.19 years were considered LD. *Results*. Median time to HIV diagnosis was 2.8 years in the whole cohort of 3,667 subjects. Factors significantly associated with LD were: male sex; Sub-Saharan African, Latin-American origin compared to Spaniards; and older age. In 2,928 newly diagnosed subjects, median time to diagnosis was 3.3 years, and LD was more common in injecting drug users. *Conclusions*. Estimates of the magnitude and risk factors of LD for the whole cohort differ from those obtained for new HIV diagnoses.

1. Introduction

The majority of clinical cohorts of HIV-infected people are made up of seroprevalent subjects whose dates of seroconversion are unknown [1–3]. Seroprevalent subjects have been used to quantify the magnitude and risk factors of late diagnosis of HIV infection, an important public health problem which, by definition, cannot be studied in seroconverter cohorts [4, 5]. Although there are multiple definitions of late diagnosis based on different biological markers [4, 6–8], most of them are based on the patient's CD4 lymphocyte count close to the date of HIV diagnosis. For some persons, HIV may have been diagnosed before their inclusion in a clinical cohort; therefore, no CD4 counts close to HIV diagnosis are usually available. Consequently, these people are ignored, and estimates are obtained only from those with available CD4 counts—largely the new HIV diagnoses—rather than from the whole cohort. Most clinical cohorts include newly diagnosed people as well as people who have been diagnosed in the past, but the latter group is rendered

invisible. The use of multiple imputation techniques to estimate the time between HIV seroconversion and HIV diagnosis could overcome the aforementioned problem. These techniques, which so far have not been applied to study late HIV diagnosis, are based on the correlation between certain biological markers like CD4 lymphocytes and the duration of infection [9–11].

The magnitude of late HIV diagnoses in the subgroup of new HIV diagnoses in cohorts from industrialized countries ranges from 18% to 39% [4, 5, 12–14]. For these cohorts, the proportion of subjects who are new HIV diagnoses—and therefore can be analyzed—ranges from 4% to 73% [4, 5, 12–15]. In Spain, considering late diagnosis as subjects with a CD4 lymphocyte count of <200 cells/mm^3 or an AIDS-defining disease in the first year after HIV diagnosis, we reported 37% of late diagnosis in 2004–06 in the 68% of subjects who could be evaluated because they were newly diagnosed at inclusion in the cohort [16]. Risk of late diagnosis increased with age, was higher in men than in women, and, contrary to previous publications [12, 17, 18], was higher in heterosexuals and injection drug users (IDUs) compared to men who have sex with men (MSM). We hypothesized that this unexpected finding may reflect that the new diagnoses represent a different population than the old ones, which could not be evaluated for late diagnosis analyses [16]. To test this hypothesis, we estimated the magnitude and risk factors of late HIV diagnosis, in all cohort members and separately in those newly diagnosed, in a multicenter cohort of seroprevalent subjects in Spain for whom we have imputed their HIV seroconversion dates.

2. Methods

CoRIS is an open, multicenter, and prospective cohort of adult patients with confirmed HIV infection who are naive to antiretroviral treatment (ART) at the first visit to any of the CoRIS centers and who agree to participate in the study by signing an informed consent form. A complete description has been published elsewhere [19]. Briefly, CoRIS collects a minimum dataset which is subject to internal and external quality controls. Between January 2004 and October 2008, 4,057 subjects were recruited from 27 participating centers where the percentage of CD4 lymphocytes (hereinafter referred to as "CD4%") was measured. A total of 231 subjects were excluded because they had recently been recruited, and no CD4% results were available, and 159 were excluded because their first CD4% values were recorded after ART initiation. Accordingly, 3,667 patients were available for analysis.

Subjects were classified as late diagnosis (LD) when the diagnosis of HIV infection was made more than 4.19 years after seroconversion. This cut-off point was chosen because, in a previous publication [20], it was estimated that this was the time elapsed from seroconversion to reaching a CD4 threshold of <350. In turn, this CD4 lymphocyte threshold is used in the new definition of late presentation recommended by the European Late Presenter Consensus Working Group [6].

A multiple imputation technique was used to estimate the date of seroconversion of all CoRIS subjects, based on the model for progression of infection described by Muñoz et al. [10], which has been used in Spain [11]. These authors use parametric survival models based on the Weibull distribution to estimate the time elapsed between the date of HIV seroconversion and the date of first CD4% in the absence of ART, on the basis of that first CD4%. Their paper describes the model's parameter for each of the five thresholds in which CD4% is categorized.

This model and its coefficients allow us to know the probability that the date of seroconversion falls before a given date, conditioned by the fact that it must be between the date when the subject started being at risk for HIV infection and the date of HIV diagnosis. From this model equation, we can estimate (impute) the timespan between the date of seroconversion and the date of HIV diagnosis when the following information is made available for each subject: (a) date when the subject started being at risk for HIV infection, (b) date of HIV diagnosis, and (c) the value of CD4% and the date it was measured.

We used the following imputation process: (1) for each individual, a random number was drawn from a Weibull distribution with the parameters corresponding to his/her CD4% threshold, which was considered a random estimate of the timespan between the date of seroconversion and the date of first CD4% (t). This made it possible to calculate the timespan between the date of seroconversion and the date of HIV diagnosis ("time to HIV diagnosis", t_1), and the date of seroconversion as the difference between the date of first CD4% minus time t. Subjects whose time t_1 was longer than 4.19 years were considered late diagnoses. (2) The preceding process was replicated 20 times. Twenty different databases were generated with the information obtained in each replication. (3) The subsequent analyses were made by combining the results obtained when analyzing these 20 databases separately.

We also present the results obtained using the definition that classified subjects as delayed diagnosis (DD) when they had a CD4 lymphocyte count of <350 cells/mm^3 in the first year after HIV diagnosis or an AIDS-defining disease in the first three months after HIV diagnosis. Thus, this definition only permitted the evaluation of subjects for whom that information was available, that is, the new HIV diagnoses.

We assumed that the date when a subject started being at risk for HIV infection was the beginning of the epidemic in Spain, 1 January 1980, except in (a) patients infected by the sexual route or by injecting drug use who were born after 1 January 1965; for these subjects, we used the date of their 15th birthday, and (b) patients in the remaining transmission categories who were born after 1 January 1980, for whom we used their date of birth.

We present a descriptive analysis of the characteristics of subjects included in the analysis, as well as their time to HIV diagnosis. We used an analysis of variance for the comparison of means, to compare the time to HIV diagnosis according to patient characteristics.

To evaluate the factors independently associated with late diagnosis, we used a multivariate logistic regression model. In this model, robust methods were used to estimate the confidence intervals, assuming correlation among subjects

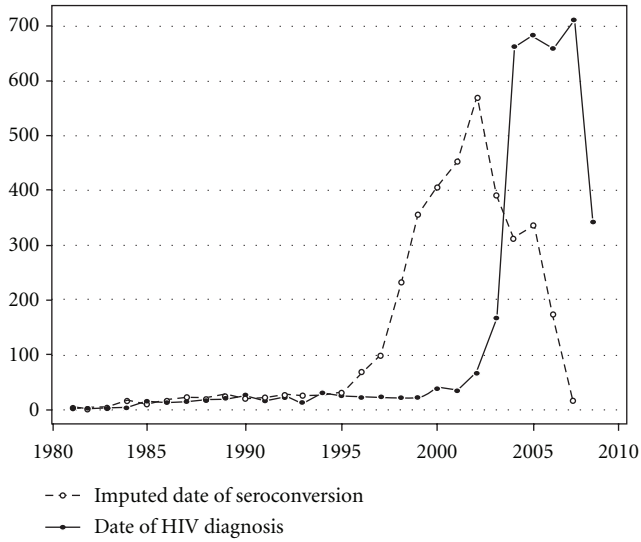

Figure 1: Distribution of date of seroconversion and date of HIV diagnosis.

recruited in each center and independence between subjects in different centers [21].

The analyses were performed using R version 2.13 [22] and Stata 11.

3. Results

Of the 3,667 patients included in this analysis, most were men (77.8%), were infected by sexual transmission (43.1% MSM and 37.5% heterosexual), and were Spanish nationals (68.5%); 15.8% had been infected through injecting drug use. The mean age at HIV diagnosis was 34.8 years (SD = 10.2) and the median follow-up time was 1.38 years. At cohort entry, 442 patients (12%) had been diagnosed with AIDS, another 191 (5.2%) developed AIDS, and 86 persons (2.3%) died during followup.

3.1. Description of Time from Imputed Seroconversion to HIV Diagnosis

3.1.1. Results for All Subjects Included in the Cohort (n = 3667). The distribution of the dates of HIV diagnosis and the mean imputed seroconversion date per individual can be seen in Figure 1. The shape of the figure is similar in both cases, but with a shift over time. The median date of HIV diagnosis was October 2005 (IQR: June 2004–February 2007) while the median date of seroconversion was February 2002 (IQR: May 1999–May 2004).

Table 1 shows the distribution of years elapsed between the mean imputed date of seroconversion and the date of HIV diagnosis. Overall, the median time to HIV diagnosis was 2.8 years (IQR: 1.2–5.2).

Time to HIV diagnosis was longer in men, in persons with heterosexual or "other" routes of transmission (vertical, transfusions, tattoos, ...), and, in those from countries other than Spain, it also increased with age at HIV diagnosis and was longer in patients who developed AIDS and in those who died.

Table 2 shows the distribution of late diagnosis according to the sociodemographic characteristics of the subjects and the odds ratio based on the multivariate analysis. Factors independently associated with late diagnosis in the multivariate analysis were male gender, place of origin Sub-Saharan Africa or Latin America, and older age at HIV diagnosis. Subjects with heterosexual transmission had a higher frequency of late diagnoses than MSM although that higher frequency did not attain statistical significance.

3.1.2. Results in the Subgroup of New HIV Diagnoses (n = 2928). In this subgroup of new HIV diagnoses ($n = 2,928$), the median time to HIV diagnosis was 3.3 years (IQR: 1.6–5.7) (Table 3), longer than the median of 2.8 years estimated for the whole cohort.

These differences can partly be explained by the fact that the 739 subjects excluded from the analyses were significantly different ($P < 0.05$) from the 2,928 who were included; in the following ways, they were younger at diagnosis (mean age 30 versus 36 years) and at seroconversion (mean age 28 versus 32 years); they were more frequently IDUs (38.2% versus 10.1%); they were more often of Spanish origin (75.0% versus 66.9%).

Table 2 shows the distribution of late diagnosis and the results of the multivariate analysis in this subcohort. Unlike what was seen in the whole cohort of 3,667 subjects, IDUs had a higher frequency of late diagnoses compared with MSM. Subjects with heterosexual transmission also had a significantly higher frequency of late diagnoses than MSM.

With regard to sex, age of diagnosis, and country of origin, the results were similar to those for the whole cohort.

Table 3 shows the estimated time to HIV diagnosis in this group and the percentage of delayed diagnoses according to the definition DD. For each of the sociodemographic characteristics studied in the subgroup of 2,928 new HIV diagnoses, we observed high consistency, except in women, between time from imputed seroconversion date to HIV diagnosis and frequency of delayed diagnoses (DD).

4. Discussion

This study illustrates the application of a multiple imputation method to estimate the date of HIV seroconversion in a cohort of seroprevalent patients who are not all newly diagnosed with HIV at entry. We defined as late diagnosis the subjects with times to HIV diagnosis longer than 4.19 years. The advantage of this definition is that it allows estimation of late diagnosis in the whole cohort and not just in patients with CD4 markers close to the time of HIV diagnosis.

Half of the cohort members were not diagnosed with HIV until 2.8 years after becoming infected, and one fourth were not diagnosed until 5.2 years after infection. Based on the multivariate analysis, the time between the imputed date of HIV seroconversion and HIV diagnosis was longer in men, increased with age, and was longer in persons from Sub-Saharan Africa and Latin America compared to Spaniards. In contrast, half of the new HIV diagnoses at entry into the cohort were not diagnosed until 3.3 years after their imputed

Table 1: Years between imputed date of seroconversion and date of HIV diagnosis in the whole cohort ($n = 3667$).

	Years between imputed date of seroconversion and date of HIV diagnosis			
	N	Median (P_{25}–P_{75})	Mean	*P*
Sex				<0.001
Men	2854	2.90 (1.24–5.40)	3.66	
Women	813	2.32 (0.98–4.60)	3.15	
Age at HIV diagnosis				<0.001
Up to 20	158	1.31 (0.49–2.55)	1.66	
21–30	1239	2.11 (0.86–4.36)	2.93	
31–40	1361	2.99 (1.32–5.56)	3.78	
41–50	599	3.67 (1.70–6.05)	4.25	
51–60	219	4.16 (2.18–6.44)	4.59	
Over 60	74	4.27 (2.22–6.42)	4.57	
Not available	17	3.66 (2.04–5.57)	4.11	—
Transmission category				<0.001
Injection drug user	578	1.82 (0.59–4.40)	2.87	
Men who have sex with men	1581	2.73 (1.25–5.17)	3.57	
Heterosexual risk exposure	1376	3.08 (1.38–5.53)	3.76	
Other (vertical, transfusions, tattoos, etc.)	58	3.03 (1.33–5.48)	3.63	
Don't know/No answer	74	3.81 (1.83–6.10)	4.28	
Educational level				0.790
No education or less than primary	257	2.88 (1.07–5.20)	3.46	
Primary	1214	2.68 (1.09–5.20)	3.49	
Secondary completed	1011	2.79 (1.22–5.25)	3.57	
University completed	524	2.84 (1.29–5.33)	3.66	
Not available	661	2.75 (1.19–5.20)	3.54	—
Country of origin				0.011
Spain	2512	2.57 (1.07–5.06)	3.42	
Western Europe	114	2.96 (1.23–5.40)	3.74	
Eastern Europe and Russia	72	2.97 (1.46–5.16)	3.58	
Sub-Saharan Africa	246	3.54 (1.68–5.88)	4.04	
North Africa	58	3.89 (1.77–6.35)	4.51	
Latin America	631	3.04 (1.36–5.45)	3.71	
Other/not available	34	2.84 (1.46–5.25)	3.77	
AIDS				<0.001
Yes	633	4.13 (2.01–6.19)	4.32	
No	3034	2.49 (1.09–4.90)	3.38	
Death				0.081
Yes	86	4.08 (1.84–6.12)	4.25	
No	3581	2.73 (1.16–5.21)	3.53	
Total	3667	2.76 (1.17–5.24)	3.54	

HIV seroconversion date, and diagnostic delay was more common in IDUs.

By imputing the date of seroconversion, we have shown that the magnitude of late diagnosis in the whole cohort was smaller than in the subgroup of new diagnoses (34% versus 39%). In addition, we found differences not only in the magnitude of late diagnosis but also in the associated risk factors. These differences reflect the important changes in HIV epidemiology, and probably in HIV testing practices as well, that have taken place in Spain in the last decade: a major reduction in the number of IDUs who were exposed to frequent HIV testing opportunities, together with an increase in sexually acquired infections which continues to require more active HIV testing approaches. As CoRIS is not population based, these conclusions cannot be extrapolated to the whole HIV-positive population in Spain.

Our group had already evaluated late diagnosis in the cohort, but limited to those patients with an HIV diagnosis close to the time of their inclusion in the cohort [16]. We had observed a very high prevalence of late diagnoses in IDUs,

Table 2: Factors associated with late diagnosis (time to HIV diagnosis over 4.19 years).

	Whole cohort ($N = 3667$)				New HIV diagnoses ($N = 2928$)			
	LD*/Total	%	Adjusted OR (95% CI)	P	LD*/Total	%	Adjusted OR (95% CI)	P
Sex								
Men	1018/2854	36	1.67 (1.27–2.21)	<0.001	936/2287	41	1.77 (1.30–2.40)	<0.001
Women	233/813	29	1		211/641	33	1	
Age at HIV diagnosis				<0.001				<0.001
Up to 30	337/1397	24	1		296/964	31	1	
31–40	498/1361	37	1.79 (1.46–2.19)	<0.001	459/1133	41	1.49 (1.19–1.87)	<0.001
Over 41	408/892	46	2.64 (2.10–3.30)	<0.001	392/830	47	1.95 (1.56–2.45)	<0.001
Not available	7/17	42	1.99 (0.61–6.54)	0.256	1/1	—	—	0.808
Transmission category				0.055				0.043
Injection drug user	154/578	27	0.83 (0.62–1.09)	0.176	136/296	46	1.60 (1.10–2.32)	0.014
Men who have sex with men	526/1581	33	1		479/1339	36	1	
Heterosexual risk exposure	516/1376	37	1.26 (0.98–1.62)	0.069	483/1187	41	1.39 (1.06–1.82)	0.016
Other (vertical, transfusions, tattoos, etc.)	21/58	37	1.08 (0.56–2.09)	0.820	20/46	44	1.36 (0.68–2.72)	0.385
Don't know/No answer	34/74	45	1.47 (0.77–2.79)	0.241	30/60	50	1.70 (0.89–3.21)	0.105
Country of origin				0.004				0.065
Spain	812/2512	32	1		743/1958	38	1	
Western Europe	41/114	36	1.14 (0.68–1.93)	0.615	34/82	41	1.11 (0.59–2.09)	0.744
Eastern Europe and Russia	25/72	35	1.48 (0.77–2.86)	0.243	23/64	37	1.13 (0.56–2.29)	0.731
Sub-Saharan Africa	104/246	42	1.75 (1.20–2.56)	0.004	95/215	44	1.54 (1.04–2.29)	0.032
North Africa	27/58	47	1.75 (0.85–3.59)	0.129	27/56	49	1.49 (0.70–3.14)	0.297
Latin America	231/631	37	1.38 (1.09–1.74)	0.008	214/522	41	1.38 (1.08–1.75)	0.009
Other/not available	11/34	34	0.96 (0.39–2.34)	0.925	11/31	36	0.92 (0.39–2.18)	0.846
Total	1251/3667	34			1147/2928	39		

* LD.: Late diagnosis (patients with time to HIV diagnosis over 4.19 years).

a result that differed from other studies carried out in Spain which described very high HIV testing uptake in IDUs [12, 17, 18]. Here, by imputing the date of seroconversion, which allows study of the whole cohort, we no longer see a higher frequency of late diagnoses in IDUs although this pattern continues to be seen in the subgroup of new diagnoses. What this reflects is that IDUs diagnosed with HIV before cohort entry—in drug attention centers—were excluded from the analyses. Together with a marked decline in the number of IDUs among new HIV diagnoses in Spain, the analyses of late HIV diagnosis within the surveillance system have also identified a higher frequency of late diagnosis among IDUs [23]. Consistent with previous publications from Spain and other countries [12, 13, 16, 17, 23], late diagnosis is higher in men, in migrants from non-Western countries, and increases with age.

The results of this study are also important for comparison purposes as the proportion of new HIV diagnoses in a cohort may vary between cohorts and within the same cohort over time. For example, cohorts may increase the number of recruiting sites, or HIV incidence may change in a given group. In this work, we highlight the fact that new HIV diagnoses do not represent the whole cohort and that their relative contribution needs to be taken into account when comparing different cohorts or when interpreting trends over time.

Our results are based on imputing the date of seroconversion by using the first available CD4 percentage from each patient while off treatment. Other authors have observed that this estimate can be improved by using the evolution of various CD4 measurements [24, 25]. We also performed this imputation process for each measurement of CD4 percentage and estimated the date of seroconversion as the median date of seroconversion estimated by the imputation for each value of CD4. No differences were found with this analysis; the median date of seroconversion was 1 July 2002. This may be because the median number of CD4 measurements in persons off treatment was only two, since most people start treatment soon after entry.

We also conducted several sensitivity analyses using different assumptions about the date of initial risk, and the results were similar.

To evaluate the influence of the distribution model initially selected to impute the date of seroconversion [10], we analyzed the data based on Weibull models with different parameters which, in some cases, permitted a subject to have

Table 3: Years between the imputed date of seroconversion and the date of HIV diagnosis. Results in the subcohort of new diagnoses ($n = 2928$).

	Years between imputed date of seroconversion and date of HIV diagnosis				
	N	% DD*	Median (P_{25}–P_{75})	Mean	*P*
Sex					<0.001
Men	2287	51.8	3.42 (1.65–5.83)	4.07	
Women	641	50.2	2.77 (1.32–5.04)	3.51	
Age at HIV diagnosis					<0.001
Up to 20	93	33.3	1.94 (1.08–3.05)	2.15	
21–30	871	39.6	2.76 (1.33–5.01)	3.46	
31–40	1133	52.0	3.36 (1.62–5.89)	4.09	
41–50	549	61.9	3.83 (1.87–6.18)	4.38	
51–60	209	69.9	4.22 (2.25–6.42)	4.60	
Over 60	72	75.0	4.37 (2.29–6.47)	4.63	
Not available	1	100.0	5.25 (5.25–5.25)	5.25	—
Transmission category					0.111
Injection drug user	296	66.6	3.86 (1.93–6.11)	4.34	
Men who have sex with men	1339	41.3	2.97 (1.42–5.43)	3.77	
Heterosexual risk exposure	1187	58.0	3.39 (1.62–5.79)	4.00	
Other (vertical, transfusions, tattoos, etc.)	46	63.0	3.71 (2.02–5.94)	4.18	
Don't know/No answer	60	63.3	4.18 (2.12–6.44)	4.57	
Educational level					0.640
No education or less than primary	187	63.1	3.62 (1.77–5.85)	4.06	
Primary	928	57.0	3.40 (1.62–5.82)	4.05	
Secondary completed	853	46.0	3.13 (1.48–5.57)	3.85	
University completed	443	41.3	3.07 (1.48–5.55)	3.85	
Not available	517	54.9	3.30 (1.61–5.61)	3.96	—
Country of origin					0.410
Spain	1958	49.4	3.14 (1.49–5.58)	3.87	
Western Europe	82	50.0	3.47 (1.77–5.80)	4.19	
Eastern Europe and Russia	64	51.6	3.15 (1.59–5.33)	3.74	
Sub-Saharan Africa	215	61.9	3.73 (1.82–6.05)	4.21	
North Africa	56	60.7	4.09 (1.88–6.49)	4.62	
Latin America	522	54.8	3.43 (1.70–5.81)	4.04	
Other/not available	31	38.7	3.09 (1.52–5.73)	3.97	
All	2928	51.4	3.26 (1.56–5.68)	3.94	

* DD: Delayed diagnosis (patients with CD4 count <350 cells/mm^3 in the first year after HIV diagnosis or with AIDS-defining disease in the the first three months after HIV diagnosis).

been infected for 30 years at the time of CD4 measurement. The results obtained did not differ substantially from those presented.

Time to HIV diagnosis and delayed diagnosis (DD) was not highly consistent in women. Some studies have shown that, after seroconversion, women take longer than men to reach the same CD4 level [20, 26]. Lodi et al. estimate these differences at between 6 and 12 months [20]. We conducted an analysis considering for women a Weibull distribution with the same shape parameter, but with a median of 9 months longer than for men. In this simulation, differences between men and women in time to diagnosis and in the percentage of late diagnosis disappear.

In conclusion, estimates of the magnitude and risk factors of late HIV diagnoses for an entire cohort may differ from those obtained for new HIV diagnoses, a finding that highlights the need to both improve and expand HIV testing practices in our setting.

Appendix

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Funding

The RIS cohort (CoRIS) is funded by the *Instituto de Salud Carlos III* through the *Red Temática de Investigación Cooperativa en Sida* (ISCIII-RETIC RD06/006).

Conflict of Interests

The authors declared that there is no conflict of interests.

Acknowledgments

The authors acknowledge that this study would not have been possible without the collaboration of all the patients, physicians, nurses, and data managers who have taken part in the project. They want to thank Dr. P. Alcamí for his help in immunological interpretation. CoRIS members belong to Cohorte de la Red de Investigación en Sida, Spain.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 314849, 10 pages
doi:10.1155/2012/314849

Research Article

Reduced Central Memory CD4+ T Cells and Increased T-Cell Activation Characterise Treatment-Naive Patients Newly Diagnosed at Late Stage of HIV Infection

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Received 23 May 2011; Revised 5 August 2011; Accepted 23 August 2011

Academic Editor: Francesca Ceccherini-Silberstein

Objectives. We investigated immune phenotypes of HIV+ patients who present late, considering late presenters (LPs, CD4+ < 350/μL and/or AIDS), advanced HIV disease (AHD, CD4+ < 200/μL and/or AIDS), and AIDS presenters (AIDS-defining condition at presentation, independently from CD4+). *Methods*. Patients newly diagnosed with HIV at our clinic between 2007–2011 were enrolled. Mann-Whitney/Chi-squared tests and logistic regression were used for statistics. *Results*. 275 patients were newly diagnosed with HIV between January/2007–March/2011. 130 (47%) were LPs, 79 (29%) showed AHD, and 49 (18%) were AIDS presenters. LP, AHD, and AIDS presenters were older and more frequently heterosexuals. Higher CD8+%, lower CD127+CD4+%, higher CD95+CD8+%, CD38+CD8+%, and CD45R0+CD38+CD8+% characterized LP/AHD/AIDS presentation. In multivariate analysis, older age, heterosexuality, higher CD8+%, and lower CD127+CD4+% were confirmed associated with LP/AHD. Lower CD4+ and higher CD38+CD8+% resulted independently associated with AIDS presentation. *Conclusions*. CD127 downregulation and immune activation characterize HIV+ patients presenting late and would be studied as additional markers of late presentation.

1. Introduction

Despite reduced morbidity and mortality achieved by highly active antiretroviral therapy (HAART) and extensive work encouraging earlier HIV testing, late presentation of HIV remains a relevant clinical problem. Up to 15%–38% of HIV positive patients present late for testing with a low CD4+ T-cell count, high viral load, and severe alterations of their immune system [1]. Focusing on the Italian scenario, 39% of new HIV diagnosis occur late [2]. Compared to patients diagnosed with HIV early in the course of infection, late presenters are at higher probability of clinical progression and treatment-related adverse events and introduce HAART later than recommended by current antiretroviral therapy guidelines [3, 4]. Furthermore, late presentation deeply impacts on healthcare system and community in terms of resource use and higher risk of HIV transmission to sexual partners [5]. Recently, two different classifications of late presentation have been established by the European AIDS Clinical Society [6]: all patients who present with a CD4+ T-cell count less than 350 cells/μL and/or an AIDS-defining condition at, or within a month after, HIV diagnosis are identified as "late presenters." This definition allows for the identification of patients that should be considered for treatment in accordance with current guidelines. Secondly, focusing on the established risk cutoff for developing opportunistic infections, all patients who present with a CD4+ T-cell count less than 200 cells/μL and/or an AIDS event should be considered to have "advanced HIV disease" [7, 8].

Previous studies identified the demographic parameters associated with a high risk of late presentation. Older age, heterosexual transmission of infection, and foreign birth (non-White and in particular Black African ethnicity) may influence the risk of late diagnosis [1–13]. On the contrary,

a clear association between gender and late HIV testing has not been recognized [9–14].

As expected, low CD4+ T-cell count at presentation associates with increased risk of AIDS defining illnesses. The most commonly diagnosed AIDS conditions are *Pneumocystis jiroveci* pneumonia and tuberculosis, followed by Cytomegalovirus infections, toxoplasmosis, and wasting syndrome. Patients with AIDS at presentation represent a real medical challenge because of their advanced clinical status and higher risk of clinical progression and mortality. At least two clinical challenges relate to these patients and include the timing of HAART introduction based on the concomitant opportunistic infections and the elevated risk of failing a satisfactory CD4+ recovery, even after long-term virological suppression by HAART [15, 16].

A broad immunological characterization of patients with a late diagnosis of HIV infection and/or an AIDS disease at presentation is still lacking. Detailing the alterations of immune system homeostasis associated to late presentation would allow for the identification of an early immunological marker to complement CD4+ T-cell count in the clinical outcome of late presenter patients; this could be crucial in order to tailor antiretroviral therapy to individual circumstances of late presenters.

In this context, the aim of this study is to analyze the peripheral T lymphocyte phenotypes in patients who were newly diagnosed with HIV and to determine demographic and immunological factors associated with late HIV positive testing, defined in accordance with the two most recent classifications (late presentation and advanced HIV disease).

2. Materials and Methods

2.1. Study Design and Population. We identified all patients aged >18 years who were newly diagnosed with HIV at the Clinic of Infectious Diseases of "S. Paolo" Hospital in Milan, Italy, between January 2007 and March 2011. Analyses were restricted to subjects with a new HIV antibody-positive test and at least one CD4+ T-cell count within 30 days of HIV diagnosis. Persons with a previous positive HIV test were excluded from the analysis.

Information on demographic parameters (sex, date of birth, country of birth) and HIV-related data (HIV exposure category, calendar period of HIV diagnosis, AIDS event, CD4+ T-cell count, HIV-RNA, and HCV coinfection) at presentation were retrospectively collected.

We defined "migrants" patients who were born outside the European Community (including people from Eastern Europe, Africa, Asia, and Latin America).

2.2. Definitions of Late Presentation. We used two different definitions of late presentation, in line with the recent indications by UK Collaborative HIV Cohort (CHIC) study and HIV in Europe group [6, 7]. Definitions were not mutually exclusive.

According to the first classification, all patients whose CD4+ T-cell count at the time of diagnosis was <350 cells/μL were defined "late presenters" (LPs). Secondly, all patients who present with a CD4+ T lymphocyte count <200 cells/μL were considered to have "advanced HIV disease" (AHD). In all definitions, patients presenting with an AIDS defining condition were considered as LP and AHD subjects regardless CD4+ T-cell count. Patients with an AIDS diagnosis at presentation (defined according to the 1993 Centers for Disease Control and Prevention criteria) [17] from 30 days prior to 30 days after their first positive HIV test were considered as AIDS presenters.

2.3. T-Cells Immune Phenotypes. Peripheral T lymphocyte immune phenotypes were recorded for all patients. Lymphocyte surface phenotypes were evaluated by flow cytometry on fresh peripheral blood (Coulter ESP; Beckman Coulter, Hialeah, Fla) using the following fluorochrome-labelled antibodies: CD4-Pcy7, CD8-Pcy5, CD38-FITC, CD45-ECD, CD45R0-PE, CD95-FITC, and CD127-PE. Percentages of each T-cell subpopulations were calculated on whole lymphocyte population. We evaluated activation (expression of CD45R0 and CD38 on CD8+), sensitivity to Fas-mediated cells death (expression of CD95 on CD4+ and CD8+), and IL-7 receptor (CD127) expression on CD8+ and CD4+ T cells. The following combinations were used: CD8/CD38, CD8/CD38/CD45R0, CD8/CD4/CD95, and CD8/CD4/CD127.

2.4. Statistical Analysis. Continuous variables were expressed as median and interquartile range (IQR), categorical variables as absolute numbers and percentages. Baseline differences between LPs, and nonlate presenters (N-LPs, patients with CD4+ T-cell count $\geq$350 cells/μL and without an AIDS diagnosis at presentation), between AHD subjects and patients who did not display advanced HIV disease (N-AHD, CD4+ T-cell count $\geq$200 cells/μL and without an AIDS event at presentation), and finally between AIDS presenters and patients asymptomatic for AIDS diseases at presentation (N-AIDS presenters) were assessed using the Mann-Whitney nonparametric U-test and the Chi-squared test for continuous and categorical variables, respectively.

In addition, we performed further analyses using N-LP as unique comparison group.

Multivariate logistic regression models were used to identify baseline peripheral immune phenotypes that were independently associated with LP, AHD, or AIDS presentation. T lymphocyte phenotypes with a P value $\leq$0.05 in the univariate analyses entered the final multivariate models. Each final model was adjusted for potential confounders: the models were adjusted for the demographic parameters that resulted significantly associated with the outcome in the univariate analysis.

Analyses were performed using SPSS software (version 18.01). A P value $\leq$0.05 was considered to denote statistical significance.

3. Results

3.1. Baseline Characteristics of the Study Population. During the study period (January 2007–March 2011), 275 patients

Table 1: (a) Demographic and immunovirological characteristics of study population. (b) Peripheral T lymphocyte immune phenotypes of study population.

(a)

Characteristics	Patients ($N = 275$)
Age, years*	37 (31–46)
Gender, male°	225 (82)
Risk group°	
Homosexual	152 (55)
Heterosexual	111 (40)
IDUs	10 (4)
Other	2 (1)
Migrants°	73 (26)
HCV coinfection°	16 (6)
Calendar year of presentation°	
2007	85 (31)
2008	61 (22)
2009	61 (22)
2010	61 (22)
January–March 2011	7 (3)
AIDS presenters°	49 (18)
HIV-RNA $\log_{10}$ cp/mL*	4.37 (2.78–5.16)
CD4+ T cells/μL*	396 (234–555)

(b)

T-cells immunophenotypes	Patients ($N = 275$)
CD4 T cells %*	22 (14–30)
CD8 T cells %*	51 (42–60)
CD4+CD127+ cells %*	12 (7–20)
CD8+CD127+ cells %*	11 (8–17)
CD4+CD95+ cells %*	2 (1–4)
CD8+CD95+ cells %*	2 (1–4)
CD8+CD38+ cells %*	6 (3–12)
CD8+CD38+CD45R0+ cells %*	12 (7–20)

Data are presented as *median, (interquartile range, IQR) and °absolute number, (%). IDUs: injection drug users; migrants: people who were born outside the European community (including people from Eastern Europe, Africa, Asia, and Latin America); HCV: hepatitis C virus.

were diagnosed for the first time with HIV infection at our clinic. Characteristics of the 275 subjects at presentation are summarized in Table 1.

Overall, the majority of patients were male (225/275, 82%) with a median age of 37 (IQR 31–46) years and acquired HIV infection mostly through sexual contacts (homosexual transmission 152/275, 55%—heterosexual transmission 111/275, 40%) (Table 1(a)).

A total of 16 (6%) patients displayed HCV coinfection. Most subjects were of white ethnicity, while 73 (26%) HIV-positive patients were born outside the European community.

The proportion of new HIV diagnosis remained stable over time (31% in 2007, 22% in 2008-2009-2010).

3.2. Immunovirological Parameters of the Study Population. Median CD4+ count at first presentation for HIV care was 396 cells/μL (IQR 234–555), and median viral load was 4.37 $\log_{10}$ cp/mL (IQR 2.78–5.16). The other percentages (median, IQR) of peripheral T lymphocytes immune phenotypes were reported in Table 1(b).

3.3. Characteristics of Late Presenters. 130 (47%) patients showed CD4+ T-cell counts <350 cells/μL and/or an AIDS defining event at presentation and were classified as late presenters (LPs) (Table 2). Compared to N-LPs, LPs were older (median age: LP 41, IQR 34–50—N-LP 36, IQR 30–43 years; $P = 0.0001$), contracted HIV infection more frequently through heterosexual contacts (heterosexual transmission: LP 64, 49%—N-LP 47, 32%; homosexual transmission: LP 59, 45%—N-LP 93, 64%; intravenous drug users: LP 6, 5%—N-LP 4, 3%; $P = 0.020$), and resulted more commonly migrants (LP 43, 33%—N-LP 30, 21%; $P = 0.020$). No differences were observed between the two groups of patients regarding gender, coinfections, and calendar year of presentation (Table 2(a)).

Interestingly, analyzing the immune phenotypes of peripheral T lymphocytes, we found that LP were characterized by a significantly different immunological pattern in comparison to N-LP. In particular, LP displayed higher CD8+ T-cells percentages (LP 57, IQR 51–63—N-LP 45, IQR 38–54; $P = 0.0001$), lower IL-7 receptor (CD127) expression on CD4+ T cells (median CD127+CD4+%: LP 7, IQR 4–12—N-LP 19, IQR 12–24; $P = 0.0001$), and higher expression of CD95 receptor (median CD95+CD8+%: LP 3, IQR 2–5—N-LP 2, IQR 1–3; $P = 0.0001$), activated CD38+ (median CD38+CD8+%: LP 9, IQR 3–18—N-LP 5, IQR 2–9; $P = 0.0001$) and terminal-differentiated CD45R0+CD38+ (median CD45R0+CD38+CD8+%: LP 15, IQR 10–25—N-LP 9, IQR 5–16; $P = 0.0001$) on CD8+ T cells. The other immune phenotypes did not result significantly different between LP and N-LP (Table 2(b)).

3.4. Characteristics of Patients Presenting Advanced HIV Disease. Using the second criteria to identify patients with a new diagnosis of HIV infection in a late stage of disease, 79 (29%) subjects presented advanced HIV disease (AHD) (Table 3). Similarly to the first definition, AHD patients resulted older (median age: AHD 42, IQR 34–52—N-AHD 36, IQR 31–44; $P = 0.0001$) and more frequently heterosexual (heterosexual transmission: AHD 41, 52%—N-AHD 70, 36%; homosexual transmission: AHD 34, 43%—N-AHD 118, 60%; intravenous drug users: AHD 4, 5%—N-AHD 6, 3%; $P = 0.044$). The proportion of HIV/HCV coinfection and migrants were comparable between the two groups of patients; in parallel, from 2007 to the first months of 2011, we did not register a substantial decrease of late diagnosis (Table 3(a)).

Diverse immune phenotype patterns were detected in AHD and N-AHD patients: AHD presented higher CD8+

Table 2: (a) Analysis of the association of demographic and HIV-related characteristics with late presentation. (b) Analysis of the association of T-cells subpopulations with late presentation.

(a)

Parameters	Late presenters (CD4 T cell < 350 and/or AIDS defining event)		P
	No (145, 53%)	Yes (130, 47%)	
Age, years*	36 (30–43)	41 (34–50)	0.0001
Gender, male°	120 (83)	105 (81)	0.669
Risk group°			0.020
Homosexual	93 (64)	59 (45)	
Heterosexual	47 (32)	64 (49)	
IDUs	4 (3)	6 (5)	
Other	1 (1)	1 (1)	
Migrants°	30 (21)	43 (33)	0.020
HCV coinfection°	7 (5)	9 (7)	0.382
Calendar year of presentation°			0.385
2007	52 (36)	33 (25)	
2008	32 (22)	29 (22)	
2009	30 (21)	31 (24)	
2010	28 (19)	33 (25)	
January–March 2011	3 (2)		
HIV-RNA $\log_{10}$ cp/mL*	4.33 (3.24–4.96)	4.54 (1.77–5.26)	0.884
CD4+ T cells/μL*	538 (441–698)	218 (100–290)	0.0001

(b)

T-cells immunophenotypes	Late Presenters (CD4 T cell < 350 and/or AIDS defining event)		P
	No (145, 53%)	Yes (130, 47%)	
CD4+ T cells %*	28 (23–35)	14 (10–21)	0.0001
CD8+ T cells %*	45 (38–54)	57 (51–63)	0.0001
CD4+CD127+ cells %*	19 (12–24)	7 (4–12)	0.0001
CD8+CD127+ cells %*	10 (8–15)	11 (7–19)	0.346
CD4+CD95+ cells %*	2 (1–4)	2 (1–3)	0.898
CD8+CD95+ cells %*	2 (1–3)	3 (2–5)	0.0001
CD8+CD38+ cells %*	5 (2–9)	9 (3–18)	0.0001
CD8+CD38+CD45R0+ cells %*	9 (5–16)	15 (10–25)	0.0001

Data are presented as *median, (interquartile range, IQR) and °absolute number, (%). IDUs: injection drug users; migrants: people who were born outside the European community (including people from Eastern Europe, Africa, Asia, and Latin America); HCV: hepatitis C virus.
Comparison between categorical variables was assessed by Pearson's Chi square and between continuous variables by nonparametric Mann-Whitney U-test. $P < 0.05$ was considered to denote statistical significance.

(AHD: 59, IQR 51–66—N-AHD 48, IQR 41–57; $P = 0.0001$), lower CD127+CD4+ (median CD127+CD4+%: AHD 6, IQR 3–11—N-AHD 15, IQR 10–22; $P = 0.0001$), higher CD95+CD8+ (median CD95+CD8+%: AHD 3, IQR 2–6—N-AHD 2, IQR 1–3; $P = 0.0001$), CD38+CD8+ (median CD38+CD8+%: AHD 11, IQR 3–25—N-AHD 5, IQR 2–10; $P = 0.0001$), and CD45R0+CD38+CD8+ (median CD45R0+CD38+CD8+%: AHD 14, IQR 10–25—N-AHD 11, IQR 7–19; $P = 0.008$) percentages in comparison to N-AHD (Table 3(b)).

3.5. AIDS Presenters. An AIDS defining condition was reported for 49/275 (18%) subjects with a new HIV diagnosis during the study period. The most common diseases were Kaposi's Sarcoma (12/49, 24%), *Pneumocystis jiroveci* pneumonia (8/49, 16%), and tuberculosis (7/49, 14%). Other AIDS-related illnesses were CMV infection (sepsis, chorioretinitis, and colitis, 4/49, 8%), neurological diseases (HIV-associated dementia, "HAD," progressive multifocal leukoencephalitis, "PML," and neurotoxoplasmosis, 7/49, 14%), lymphomas (4/49, 8%), esophageal candidiasis (3/49, 7%), Wasting syndrome (3/49, 7%), and cervical cancer (1/49, 2%).

AIDS presenters were more frequently older (median age: AIDS presenters: 42, IQR 35–52—N-AIDS presenters 37, IQR 31–44; $P = 0.0001$), male (AIDS presenters: male 45, 92%—female 4, 8%; N-AIDS presenters: male 180, 80%—female 46, 20%; $P = 0.045$), and heterosexuals (heterosexual transmission: AIDS presenters 29, 59%—N-AIDS presenters 82, 36%; homosexual transmission: AIDS presenters

Table 3: (a) Analysis of the association of demographic and HIV-related characteristics with advanced HIV disease at presentation. (b) Analysis of the association of T-cells subpopulations with advanced HIV disease at presentation.

(a)

Parameters	Advanced HIV disease at presentation (CD4 T cell < 200 and/or AIDS defining event)		P
	No (196, 71%)	Yes (79, 29%)	
Age, years*	36 (31–44)	42 (34–52)	0.0001
Gender, male°	158 (81)	67 (85)	0.414
Risk group°			0.044
Homosexual	118 (60)	34 (43)	
Heterosexual	70 (36)	41 (52)	
IDUs	6 (3)	4 (5)	
Other	2 (1)	0	
Migrants°	50 (26)	23 (29)	0.540
HCV coinfection°	10 (5)	6 (11)	0.304
Calendar year of presentation°			0.136
2007	63 (32)	22 (28)	
2008	40 (20)	21 (26)	
2009	50 (25)	11 (14)	
2010	39 (20)	22 (28)	
January–March 2011	4 (3)	3 (4)	
HIV-RNA $\log_{10}$ cp/mL*	4.31 (3.17–4.99)	4.68 (1.77–5.37)	0.437
CD4+ T cells/μL*	460 (340–614)	110 (56–192)	0.0001

(b)

T-cells immune phenotypes	Advanced HIV disease at presentation (CD4 T cell < 200 and/or AIDS defining event)		P
	No (196, 71%)	Yes (79, 29%)	
CD4+ T cells %*	26 (20–32)	10 (7–17)	0.0001
CD8+ T cells %*	48 (41–57)	59 (51–66)	0.0001
CD4+CD127+ cells %*	15 (10–22)	6 (3–11)	0.0001
CD8+CD127+ cells %*	10 (8–15)	12 (8–22)	0.05
CD4+CD95+ cells %*	2 (1–4)	2 (1–3)	0.713
CD8+CD95+ cells %*	2 (1–3)	3 (2–6)	0.0001
CD8+CD38+ cells %*	5 (2–10)	11 (3–25)	0.0001
CD8+CD38+CD45R0+ cells %*	11 (7–19)	14 (10–25)	0.008

Data are presented as *median, (Interquartile Range, IQR) and °absolute number, (%). IDUs: injection drug users; migrants: people who were born outside the European community (including people from Eastern Europe, Africa, Asia, and Latin America); HCV: hepatitis C virus.
Comparison between categorical variables was assessed by Pearson's Chi square and between continuous variables by nonparametric Mann-Whitney U test. $P < 0.05$ was considered to denote statistical significance.

17, 35%—N-AIDS presenters 135, 60%; intravenous drug users: AIDS presenters 3, 6%—N-AIDS presenters 7, 3%; $P = 0.044$), compared to N-AIDS presenters (226 subjects).

Comparing immune phenotypes between AIDS presenters and N-AIDS presenters, we observed that AIDS presenters were associated with lower CD4+ T-cell count (median CD4+ cells/μL: AIDS presenters 132, IQR 60–286—N-AIDS presenters 438, IQR 286–583; $P = 0.0001$), and higher CD8+ T cells (median CD8+%: AIDS presenters 59, IQR 50–66—N-AIDS presenters 49, IQR 42–59; $P = 0.0001$). AIDS presenters featured lower CD127+CD4+% (median CD127+CD4+%: AIDS presenters 6, IQR 4–11—N-AIDS presenters 14, IQR 8–21; $P = 0.0001$), higher CD95+CD8+% (median CD95+CD8+%: AIDS presenters 3, IQR 2–6—N-AIDS presenters 1, IQR 2–4; $P = 0.003$), CD38+CD8+% (median CD38+CD8+%: AIDS presenters 12, IQR 5–23—N-AIDS presenters 6, IQR 2–11; $P = 0.0001$), and CD45R0+CD38+CD8+% (median CD45R0+CD38+CD8+%: AIDS presenters 16, IQR 10–25—N-AIDS presenters 11, IQR 7–19; $P = 0.02$).

3.6. Factors Independently Associated with Late Presentation. Given that LPs were distinguished by a peculiar peripheral immune phenotype, we investigated the association between T lymphocyte patterns and late presentation, controlling for potentially confounding factors. We performed

a logistic regression model (Table 4) including the peripheral immune phenotypes that resulted significantly associated with LP in the univariate analysis (CD8+%, CD4+CD127+%, CD8+CD95+%, CD8+CD38+%, and CD8+CD38+CD45R0+%) (Table 2(b)), mutually adjusting for demographic factors (age, exposure category for HIV, ethnicity). Higher CD8+ T-cell percentages (AOR 1.051 for each unit more, 95%CI 1.022–1.080, $P = 0.0001$) and lower CD127+ expression on CD4+ cells (AOR 0.887 for each unite more, 95%CI 0.857–0.919, $P = 0.0001$) resulted significantly associated with late presentation, independently of demographic factors.

As expected, also demographic factors were significantly and independently associated with late presentation; in fact, older age (AOR 1.052 for each year more, 95%CI 1.020–1.086, $P = 0.001$), heterosexual acquisition of infection (AOR 2.435 versus other risk groups, 95%CI 1.251–4.741, $P = 0.009$), and non-White race (AOR 2.543 versus white ethnicity, 95%CI 1.178–5.486, $P = 0.017$) were associated with higher risk of delayed HIV testing.

3.7. Factors Independently Associated with Advanced HIV Disease. To identify possible factors associated with AHD, significant T-cells immune phenotypes in the univariate analysis (CD8+%, CD4+CD127+%, CD8+CD95+%, CD8+CD38+%, and CD8+CD38+CD45R0+%) (Table 3(b)) were entered in a logistic regression model, mutually adjusted for age and risk group (Table 5).

The immune phenotypes independently associated with AHD, after controlling for age and risk groups, were higher CD8+% (AOR 1.051 for each unit more, 95%CI 1.022–1.081, $P = 0.001$), lower CD127+CD4+% (AOR 0.909 for each unit more, 95%CI 0.878–0.942, $P = 0.0001$), and, in this case, also higher-activated CD38+CD8+% (AOR 1.065 for each unit more, 95%CI 1.020–1.112, $P = 0.004$) and lower terminal-differentiated CD45R0+CD38+CD8+% (AOR 0.955 for each unit more, 95%CI 0.916–0.996, $P = 0.032$). AHD patients were confirmed again significantly characterized by older age than N-AHD subjects (AOR 1.040 for each year more, 95%CI 1.010–1.071, $P = 0.008$).

3.8. Factors Independently Associated with AIDS Presentation. To explore eventual immune phenotypes specifically characterizing patients with an AIDS-defining pathology at new diagnosis of HIV, we also conducted a multivariate logistic regression analysis considering AIDS presentation (Table 6). Also, in this case, the parameters with a P value ≤ 0.05 in the univariate analysis entered the logistic regression model: the covariates were CD4+%, CD8+%, CD4+CD127+%, CD8+CD95+%, CD8+CD38+%, and CD8+CD38+CD45R0+%, and the model was adjusted for age, gender, and risk group.

The immunological patterns associated with AIDS presentation independently of demographic factors were of course lower CD4+% T cells (AOR 0.996 for each unit more, 95%CI 0.993–0.998, $P = 0.008$) but also higher CD38+CD8+% (AOR 1.049 for each unit more, 95%CI 1.004–1.096, $P = 0.033$). In addition, AIDS presenters were confirmed significantly associated with heterosexual risk group (AOR 4.555 versus other risk categories, 95%CI 1.937–10.711, $P = 0.001$) and male gender (AOR 9.369 versus female, 95%CI 2.401–36.551, $P = 0.001$).

3.9. Comparison between AHD Subjects/AIDS Presenters and N-LP. We further compared the 79 AHD subjects and 49 AIDS presenters each with the 145 N-LP (comparison group).

AHD patients and AIDS presenters resulted older (median age: N-LP 36, IQR 30–43 versus AHD 42, IQR 34–52, $P = 0.0001$; versus AIDS presenters 42, IQR 35–52, $P = 0.0001$) and more frequently heterosexually infected (heterosexuals: N-LP 47, 32% versus AHD 41, 52%, $P = 0.016$; versus AIDS presenters 29, 59%, $P = 0.003$) in comparison to N-LP (see Supplementary Material Table 1 available online at doi: 10.1155/2012/314849).

As concern peripheral T lymphocyte immune phenotypes, compared to N-LP, AHD patients and AIDS presenters were characterized by higher CD8+% (NLP: 45, 38–45 versus AHD: 59, 51–66, $P = 0.0001$; versus AIDS presenters: 59, 50–66, $P = 0.0001$), lower CD127+CD4+% (NLP: 19, 12–24 versus AHD: 6, 3–11, $P = 0.0001$; versus AIDS presenters: 6, 4–11, $P = 0.0001$), higher CD95+CD8+% (NLP: 2, 1–3 versus AHD: 3, 2–6, $P = 0.0001$; versus AIDS presenters: 3, 2–6, $P = 0.0001$), CD38+CD8+% (NLP: 5, 2–9 versus AHD: 11, 3–25, $P = 0.0001$; versus AIDS presenters: 12, 5–23, $P = 0.0001$), and CD45R0+CD38+CD8+% (NLP: 9, 5–16 versus AHD: 14, 10–25, $P = 0.0001$; versus AIDS presenters: 16, 10–25, $P = 0.0001$) (Supplementary Table 1).

Finally, we performed two different logistic regression models to assess eventual independent markers of AHD and AIDS presentation, respectively, always using N-LP as the unique comparison group.

Interestingly, CD8+% (AOR 1.061 for each unit more, 95%CI 1.031–1.093, $P = 0.0001$), CD8+CD38+% (AOR 1.066 for each unit more, 95%CI 1.009–1.126, $P = 0.022$), CD8+CD38+CD45R0+% (AOR 0.955 for each unit more, 95%CI 0.993–0.997, $P = 0.0001$), and CD4+CD127+% (AOR 0.837 for each unit more, 95%CI 0.792–0.884, $P = 0.0001$) were significantly associated with AHD, also after controlling for age and risk groups for HIV infection (Supplementary Table 2).

Indeed, AHD subjects were confirmed older than N-LP (AOR 1.051 for each year more, 95%CI 1.012–0.976, $P = 0.010$) also in the multivariate analysis (Supplementary Table 2).

Similarly, we observed an independent association between AIDS presentation and CD8+CD38+% (AOR 1.078 for each unit more, 95%CI 1.015–1.146, $P = 0.015$), CD8+CD38+CD45R0+% (AOR 0.996 for each unit more, 95%CI 0.994–0.999, $P = 0.004$), and CD4+CD127+% (AOR 0.827 for each unit more, 95%CI 0.759–0.902, $P = 0.0001$). Also, this model was adjusted for age and exposure category for HIV transmission, and, as expected, for each year more of age (AOR 1.065 for each year more, 95%CI 1.019–1.113, $P = 0.005$) and for heterosexual transmission (AOR 3.176 versus other risk categories, 95%CI 1.182–8.531, $P = 0.022$),

Table 4: Multivariate logistic regression analysis of the association of demographic and HIV-related characteristics with late presentation.

	Late presenters (CD4 T cell < 350 and/or AIDS-defining event)		P
	AOR	95% CI	
(a) Patients' factors			
Age, years	1.052	1.020–1.086	0.001
Risk group°			
Heterosexual	2.435	1.251–4.741	0.009
Other	reference		
Ethnicity			0.017
Migrants	2.543	1.178–5.486	
Non-migrants	reference		
(b) T-cells immune phenotypes			
CD8+ T cells/μL % (each unit more)	1.051	1.022–1.080	0.0001
CD4+CD127+ cells/μL % (each unit more)	0.887	0.857–0.919	0.0001
CD8+CD95+ cells/μL % (each unit more)	0.993	0.874–1.129	0.919
CD8+CD38+ cells/μL % (each unit more)	1.038	0.989–1.089	0.132
CD8+CD38+CD45R0+ cells/μL % (each unit more)	1.003	0.962–1.045	0.893

AOR: adjusted odds ratio; 95% CI, 95% confidence interval. $P < 0.05$ was considered to denote statistical significance.
Other: homosexual, intravenous drug users, and other risks groups.

Table 5: Multivariate logistic regression analysis of the association of demographic and HIV-related characteristic with advanced HIV disease at presentation.

	Advanced HIV disease at presentation (CD4 T cell < 200 and/or AIDS-defining event)		P
	AOR	95% CI	
(a) Patient factors			
Age, years	1.040	1.010–1.071	0.008
Risk group°			
Heterosexual	1.788	0.901–3.546	0.096
Other	reference		
(b) T-cells immune phenotypes			
CD8+ T cells/μL % (each unit more)	1.051	1.022–1.081	0.001
CD4+CD127+ cells/μL % (each unit more)	0.909	0.878–0.942	0.0001
CD8+CD95+ cells/μL % (each unit more)	1.063	0.841–1.200	0.327
CD8+CD38+ cells/μL % (each unit more)	1.065	1.020–1.112	0.004
CD8+CD38+CD45R0+ cells/μL % (each unit more)	0.955	0.916–0.996	0.032

AOR: adjusted odds ratio; 95% CI, 95% confidence interval. $P < 0.05$ was considered to denote statistical significance.
Other: homosexual, intravenous drug users, and other risks groups.

we reported a significant increase of risk of AIDS presentation.

4. Discussion

In our clinic, we observed 275 new HIV diagnosis in the period 2007–2011 with no significant differences over time. Still nowadays, the greatest percentages of persons diagnosed with HIV/AIDS are men, of minority ethnicity, and have as principal HIV transmission risk factor sexual contacts. Globally, in our experience, patients who present a new HIV-positive test display a median CD4+ T cells at presentation of 396 cells/μL and, therefore, near the minimum CD4+ count threshold for initiation of HAART, as suggested by the most recent international guidelines [6, 18–20]. In fact, different studies have demonstrated that initiating therapy at CD4+ levels higher than 350 cells/μL improves survival [21]. Furthermore, patients with a CD4+ count between 350 and 500 cells/μL and a HIV-RNA >100.000 copies/mL should be considered for treatment [6]. For this reason, encouraging an earlier recourse to HIV testing and access to care becomes crucial.

Across Europe, many patients still present late in the course of infection [2]. A universal standard definition of late presentation has not still found, even if a common classification could facilitate cross-country comparisons, identification of risk factors for late testing in different

Table 6: Multivariate logistic regression analysis of the association of demographic and HIV-related characteristic with AIDS presentation.

	AIDS presentation (AIDS-defining condition at, or within one month after, HIV diagnosis)		P
	AOR	95% CI	
(a) Patient factors			
Age, years	1.015	0.982–1.050	0.374
Gender°			0.001
Male	9.369	2.401–36.551	
Female	reference		
Risk group°			
Heterosexual	4.555	1.937–10.711	0.001
Other	reference		
(b) T-cells immune phenotypes			
CD4+ T cells/μL % (each unit more)	0.996	0.993–0.998	0.002
CD8+ T cells/μL % (each unit more)	0.977	0.931–1.026	0.356
CD4+CD127+ cells/μL % (each unit more)	0.963	0.891–1.042	0.349
CD8+CD95+ cells/μL % (each unit more)	0.994	0.874–1.130	0.922
CD8+CD38+ cells/μL % (each unit more)	1.049	1.004–1.096	0.033
CD8+CD38+CD45R0+ cells/μL % (each unit more)	1.002	0.956–1.052	0.923

AOR: adjusted odds ratio; 95% CI, 95% confidence interval. $P < 0.05$ was considered to denote statistical significance.
Other: homosexual, intravenous drug users, and other risks groups.

settings and trends in the rate of late presentation over time. A recent work by UK Collaborative Cohort (UK CHIC) has proposed two definitions: "late presentation" (LP), presentation when CD4+ cell count is below the limit of antiretroviral therapy introduction (current CD4+ < 350 cells/μL and/or a clinical AIDS event at HIV diagnosis); "advanced HIV disease" (AHD), presentation associated with a substantial increase in clinical progression/death risk (current CD4+ < 200 cells/μL and/or AIDS event) [7].

In our study, we reported a prevalence of 47% of LP and 29% of AHD, in line with recent Italian surveys [22, 23]. Regarding demographic parameters associated with LP and AHD, we confirm that older age and foreign birth outside European community are risk factors for late HIV testing, as already widely demonstrated in previous studies [13]. Indeed, LP and AHD were more frequently heterosexuals, even if absolute numbers of homosexual people presenting late remain high because of the high prevalence of homosexuals among those HIV infected [22–25]. We observed few cases of LP/AHD among intravenous drug users (IDUs): this scenario is confirmed by other Italian studies that did not find an association between late presentation, and IDUs [11]. On the contrary, in other European works, the proportion of IDUs who were diagnosed for HIV infection late reached 38.7%, but this difference could reflect dissimilar screening policies among IDUs [26].

We did not observe differences in gender between LP/AHD and N-LP/N-AHD: in literature, there are some works that found an association between males and late HIV testing, while others described an increased risk of late presentation in women, particularly migrants [11, 14, 15].

We also recorded a high but stable proportion of LP/AHD in the study period (2007–2011); previous literature reports described the same temporal trends [27], but other studies conducted on larger population observed a decline in the numbers of patients presenting with advanced disease in 2000–2010 [28].

We then focused our attention on the immunological phenotype of T lymphocytes in peripheral blood associated with late presentation. As expected, we found that LP and AHD were characterized by higher percentages of CD8+ T cells, also in the multivariate analysis. It is known that during HIV infection, persistent viral replication determines immune perturbation with high levels of CD8+ T-cells activation/turnover [29]. Interestingly, LP/AHD also displayed significantly lower percentages of CD127 on the CD4+ pool. The expression of interleukin- (IL-) 7 receptor (CD127, IL-7R) and the activity of IL-7/CD127 system are central for the generation, survival, and differentiation of naïve and central memory T cells; in fact, perturbations in this system are linked to faster disease progression in acute and chronic HIV infection [30, 31]. Downregulation of IL-7R is also associated with T-cell activation and immune recovery following HAART [32]; we recently described that CD127 expression on CD4+ T cells was the only marker associated with a reduced risk of incomplete immune response under HAART [33]. Loss of IL-7R on T cells seems to determine an impairment of these cells to response to IL-7 with subsequent inability to differentiation or reversion to resting central memory phenotype and a generalized immune activation with increased susceptibility to apoptosis [29]. In fact, LP and AHD subjects were characterized also by higher CD8+ expression of the death receptor Fas (CD95+), activated CD38+CD8+ T cells, and terminally differentiated CD45R0+CD38+CD8+ T cells, compared to N-LP and N-AHD. It has been previously demonstrated how

CD38+CD8+ phenotype has predictive value for progression to AIDS, even after adjustment for CD4+ levels, and it has been proposed as surrogate marker to clinical monitoring of HIV infection [34, 35]. Again, in our previous work [33], the proportion of CD38+CD8+ T cells resulted a feature of patients introducing late HAART together with higher levels of CD8+ cells with increased vulnerability to apoptosis (i.e., CD95+) and lower CD127+CD4+ T cells. Indeed, increased numbers of primed activated CD8+CD38+CD45R0+ T cells have been shown to predict the decline of CD4+ T cells in HIV-1-infected patients [36, 37] and can be considered a marker of immune exhaustion reflecting a history of elevated rounds of proliferation [38]. Although Fas expression on peripheral T cells are not indicative of an active apoptotic process, we believe that our data suggest an increased sensitivity of circulating CD8+ T lymphocytes to Fas-mediated cells death.

On the basis of previous literature findings, we could hypothesise that HIV-infected patients with a first HIV diagnosis late in the course of infection display a highly dysregulated immunity with expansion of activated/senescent T-cell phenotypes and contraction of central memory cells; in this context, loss of CD127 on T cells following immune activation determines a proapoptotic signal with reinforcement of CD4 declining and disease progression.

Furthermore, multivariate analysis confirmed reduction of CD127 on CD4+ T cells as the main marker of late presentation; given the positive effects of IL-7 on homeostatic survival and proliferation of T cells, lower CD127+CD4+ percentages could be used as additional marker, together with CD4+ counts, to identify HIV-positive patients in a particular advanced stage of disease and at higher risk of clinical progression and death.

Finally, we studied the demographic factors and immune phenotypes characterizing patients presenting with AIDS-defining conditions. Among LP/AHD, the proportion of AIDS presenters has increased over time and the immunological status at presentation is severely compromised with a CD4+ count frequently <50 cells/μL [3]. Overall, also in our population, almost 20% (49/275, 18%) of patients were AIDS presenters. As expected, they were older and more frequently heterosexuals than patients without an AIDS event. In this case, patients with AIDS resulted also more commonly male, but globally our population presented a higher prevalence of male subjects.

From an immunological standpoint, these patients showed again a deeply compromised immune system: in addition to lower CD4+ and higher CD8+ levels, we observe a downregulation of CD127 on CD4+ T cells, higher expression of CD95+ on CD8+ T cells and higher activated CD38+CD8+, and terminal-differentiated CD45R0+CD38+ CD8+ T cells, probably reflecting the same perturbations of immunological homeostasis registered in late presentation. In multivariate analysis, however, besides declining CD4+ cells, the main association with AIDS presentation was the presence of higher immune activation, consistent with the notion that in AIDS patients a profound immunodeficiency strongly correlates with generalized immune activation.

5. Conclusion

A broader definition of immunological features of late presenters could permit a better identification of patients subsets at high risk of clinical progression and reduced immunological response to HAART. Besides CD4+ levels, CD127+ expression on CD4+ T lymphocytes, and T-cell activation could be proposed as novel additional markers of late presentation and advanced HIV disease. Further studies on larger population are needed to confirm immunological patterns associated with late presentation.

Acknowledgments

The authors are grateful to all patients and their families for the participation in the study. They would like to acknowledge all the staff people for their precious help in the conduct of the study, in particular Tiziana Formenti for creating dataset and data management. Authors' Contribution A. d'Arminio Monforte and G. Marchetti developed the concept of this study. F. Bai and C. Pacioni performed the data entry. F. Bai did the statistical analysis. G. Carpani and E. Sinigaglia analyzed immune-phenotypes. F. Bai, C. Tincati, E. Merlini, G. Marchetti and A. d'Arminio Monforte contributed to the final text.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 757135, 8 pages
doi:10.1155/2012/757135

Research Article

The Direct Medical Costs of Late Presentation (<350/mm^3) of HIV Infection over a 15-Year Period

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Received 12 May 2011; Revised 28 June 2011; Accepted 1 July 2011

Academic Editor: Enrico Girardi

We describe the immediate- and longer-term direct medical costs of care for individuals diagnosed with HIV at CD4 counts <350/mm^3 ("late presenters"). We collected and stratified by initial CD4 count all inpatient, outpatient, and drug costs for all newly diagnosed patients accessing HIV care within Southern Alberta from 1/1/1995 to 1/1/2010. 59% of new patients were late presenters. We found significantly higher costs for late presenters, especially inpatient costs, during the first year after accessing care. Direct medical costs remained almost twice as high for late presenters in subsequent years compared to patients presenting with CD4 counts >350/mm^3 despite significantly their improved CD4 counts. The sustained high cost for late presenters has implications for recent recommendations for wider routine HIV testing and the earlier initiation of cART. Earlier diagnosis and treatment, while increasing the immediate expenditures within a population, may produce both direct and indirect cost savings in the longer term.

1. Introduction

The medical and social aspects of the HIV/AIDS epidemic have been extensively studied since the first cases of AIDS were described in 1981. The medical cost and economic burden to society of the HIV/AIDS epidemic have attracted some but substantially less attention. Early costing studies in the pre-cART (combination antiretroviral therapy) era examined the direct medical costs associated with the morbidity and mortality of AIDS focusing mainly on the costs of hospitalizations [1–7]. These studies also often mentioned that the total economic impact of the epidemic was likely substantially higher than that being measured by direct medical costs when one included the "indirect costs" (i.e., costs not directly attributable to the direct medical cost of HIV/AIDS such as loss of income due to work stoppage) to family members of those living with HIV/AIDS, and the opportunity costs incurred by society from the loss of life from AIDS in a younger, still productive population [8–11].

In the pre and early cART eras, costing studies attempted to determine the immediate and lifetime direct costs of HIV disease from the costs associated with various clinically determined stages such as AIDS or CD4+ lymphocyte count. They then predicted the duration that any given patient would be expected to remain in for each one of the stages using a standardized downward trajectory towards eventual death and then generated an estimate of lifetime directs costs for HIV/AIDS [12–17]. This methodology was viewed as generally being valid as few, if any, effective treatments were available to slow disease progression.

With the arrival in 1996 and subsequent widespread implementation of cART, the HIV epidemic changed significantly. Morbidity and mortality from HIV decreased increasing patients' health, survival, and overall lifespan [18, 19]. The economic burden measured by direct medical costs has shifted from inpatient costs (i.e., hospitalizations) to outpatient costs primarily reflected as the cost of the ARV (antiretroviral) drugs, outpatient visits, and laboratory tests [20–26]. The success of cART is likely even to be greater than measured in direct costs as it has allowed most patients to live not only longer and healthier lives, but to maintain the individual's productivity thereby decreasing the indirect

and opportunity costs to family members and to society in general.

Costing of the HIV epidemic has become far more complex in the cART era as the disease trajectory is no longer a predictable decline. Many patients experience a CD4 increase after starting cART, some maintain stable CD4 counts while on cART, and some remain with low CD4 counts but suppressed viremia [27–29]. As such, it has become increasingly difficult to determine how long any patient would remain in a particular disease "stage" using the CD4 count as the stage marker. Costs within any CD4 stratum may vary widely depending upon the mix of patients with untreated disease or with disease recovering on cART. This heterogeneity makes this methodology no longer easily usable on large populations [30–32].

Individuals infected with HIV may also access care for the first time at different stages of their HIV infection (based on their CD4+ lymphocyte counts). These stages at presentation carry both health and economic implications. The term "*late presenters*" was originally used to indicate a person who initiates HIV care at a "late" stage of their disease or with a lower CD4 count (i.e., <200/mm^3) indicating poorer health and poorer health outcomes [33–39]. These studies indicated that these "late" patients had not only higher mortality and morbidity than patients presenting "early" but also incurred substantially more direct medical costs [17, 31, 32]. With cART, however, mortality and morbidity rates as well as costs and the distribution of costs have changed for late presenters. It has also been proposed that the term "late presenter" be modified [40] to reflect "late for care" with the CD4 threshold moving to CD4 <350/mm^3 and the term "advanced disease" introduced to reflect CD4 <200/mm^3. These adjustments will make comparisons between historical and current studies difficult unless the definition of a "late presenter" is clearly presented.

Using our costing database, we examined in this paper the cost of late presentation (CD4 < 350/mm^3) over a 15-year period describing past and current trends. We determined the cost of care of both late and "early" presenters (i.e., patients who access initial HIV care with CD4 counts >350/mm^3) over time comparing costs after accessing HIV care. We discuss the impact of late presentation on current recommendations for more widespread and routine HIV screening and testing, and on the proposed "test and treat" strategies under discussion. Late presentation has not only clinical and public health implications within the HIV epidemic but also has financial and costing implications.

2. Methods

The Southern Alberta Clinic Cohort (SAC) includes all HIV-infected patients receiving HIV care and living within southern Alberta, Canada. Patients are automatically included in the cohort when they initiate HIV care within a centralised outpatient program. SAC provides exclusive, comprehensive interdisciplinary care to all HIV patients living in southern Alberta including pharmaceuticals, outpatients, and laboratory tests. All individuals testing positive for HIV are referred to SAC located in Calgary, Alberta. Over 90% of patients reside within the immediate Calgary region. Inpatient services are provided in one of 3 local hospitals.

Administrative data including demographic, clinical characteristics as well as the direct cost of care are collected on all individuals on a routine basis during every clinical contact. Use of this administrative data was approved by the University Conjoint Medical committee on medical bioethics.

We include all newly infected HIV individuals diagnosed within the region who accessed their initial HIV treatment at SAC ("locally diagnosed patients"). Individuals who were diagnosed elsewhere were included if they were initiated care within 6 months of their diagnosis and had not accessed HIV elsewhere prior to their 1st SAC visit. We include all individuals initiating care between 1 Jan 1995 and 1 Jan 2010. To be included, patients must have had at least one regular clinic visit. Patients were followed until they moved, were lost to followed, died or until 1 April 2010.

We use the definition of "late presenters" as those patients who initiated care with a CD4 count <350/mm^3 although we also subdivide this group by CD4 count > or < than 200/mm^3 for comparisons with earlier uses of the term "late presenters." We collected the patient's gender, age at clinic visit, risk factor (MSM, MSW, IVDU, other) and self-reported ethnicity (Caucasian/non-Caucasian) at the initial visit. We recorded the patient's initial CD4 count taken within 30 days of the initial visit and any recorded AIDS defining condition at diagnosis.

The Southern Alberta Clinic Cohort has been continuously tracking the direct cost of care for all HIV-infected patients followed at the regionalized Southern Alberta Clinic. SAC established a "costing search engine" that routinely captures all the direct costs of care including ARV (antiretroviral) and non-ARV drug costs, all outpatient clinic visits including laboratory texts and referrals to non-HIV specialists, and the cost of inpatient (i.e., hospitalizations) visits for both HIV and non-HIV-related admissions. Costs are collected per patient, per demographic population, or per a number of other variables including the CD4 status of the individual patient.

For this study, the direct costs of care were collected between 1/1/1995 and 12/31/2009. Costs were collected from the original costing source or agency using a methodology previously described [16]. Briefly, we collected the direct costs of drugs (antiretroviral (ARV) and nonantiretroviral drugs), outpatient clinical care (including physician and laboratory costs), and inpatient (hospital) care. ARV and non-ARV drug costs, lab utilization, and outpatient care costs were derived directly from the SAC pharmacy, Calgary Laboratory Services, and the SAC-costing database whereas inpatient costs (i.e., unit service costs) were supplied by the regional health service providers. The unit costs used are market values charged to the regional payer (Alberta Health Services). All costs were obtained directly from the costing agencies and reported in Canadian dollars adjusted for inflation to 2009.

Annual costs for patients who initiate HIV care at SAC are reported from the date of initiating year to December

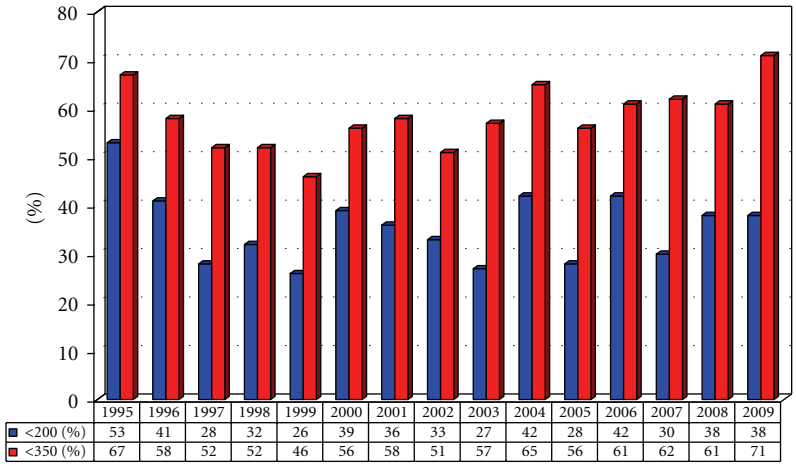


Figure 1: Proportions of newly diagnosed HIV patients accessing care with CD4 counts <200/mm^3 ("advanced disease") and/or <350/mm^3 ("late presenters").

Table 1: Demographic and clinical characteristics of patients followed within the Southern Alberta Clinic Cohort from 1995 to 2009 (selected years only) accessing initial HIV care with CD4 counts <350/mm^3 ("late presenters").

	1995	2000	2005	2009
Total no. of late presenters (%)	47 (67)	34 (56)	45 (56)	67 (71)
Male (%)	42 (89)	39 (87)	36 (80)	49 (73)
Median age (yrs)	30	32	33	34
[IQR]	[26–37]	[27–39]	[27–40]	[28–41]
Risk factor				
MSM (%)	31 (66)	20 (58)	24 (54)	30 (45)
Heterosexual	8 (17)	5 (16)	11 (24)	29 (43)
IVDU	7 (15)	7 (22)	9 (20)	7 (10)
Other	1 (2)	2 (4)	1 (2)	1 (2)
Caucasian (%)	37 (79)	24 (70)	25 (55)	32 (48)
Median initial CD4	123	55	159	193
[IQR]	[36–211]	[10–214]	[80–261]	[63–263]

31st of that particular year. Costs are then adjusted as mean cost per patient per month (PPPM) in 2009 Cdn$ over the time followed in that year, and cumulatively for patients initiating care ±350/mm^3. The annual cost for "late presenters" is reported as a proportion of all costs for newly diagnosed HIV patients accessing care for the first time. Long-term or "lifetime" costs are determined from the date of initiating HIV care to the date they moved, were LTFU (lost to followup), died, or 4/1/2010 and, are reported as mean PPPM or PPPY (per patient per year) costs.

Health care utilization data is based on number of clinic visits, laboratory tests, visits to HIV, and non-HIV physicians (i.e., outpatient visits), and the number of hospital admissions (inpatient visits/length of stay (LOS)). Administrative data were obtained directly from the SAC database and hospitalization admission records. Visits for physicians for non-HIV related conditions were self reported by the patients and may be underreported. Clinical protocols on recommended frequency of clinic visits, ART options, and laboratory testing algorithms for patients remained stable during the study period.

We compare the PPPM cost of care for late presenters initiating care at SAC to that of early presenters over the same time period and under the same clinical protocols. We provide descriptive statistics (i.e., mean, standard deviations, medians) to describe the data. We use Student t-tests for normally distributed data and Mann Whitney U-test for non normally distributed variables to compare the populations. Chi-square tests were used to compare proportions. $P < .05$ was set for the level of significance.

3. Results

The demographic and clinical characteristics of late presenters are listed in Table 1. Between 1995 and 2010, 59% of all locally diagnosed patients initiated care with a CD4 <350/mm^3 (36% with CD4 counts <200/mm^3) as shown in Figure 1. We found a change in the demographics of late presenters during this period. In 1995, 89% were male, 66% were MSM (men who have sex with men), and 79% were Caucasian; in 2009, 73% were male, 45% MSM (43% were MSW), and 48% were Caucasian. The median CD4 count for late presenters was 149/mm^3 (IQR [47-253]); 26% of late presenters had an AIDS defining condition at time of accessing care. 9.6% of late presenters died within 60 months of accessing care.

Over the past 15 years, locally diagnosed "late presenters" account for 56% of the total patient months followed at SAC compared to 44% for early presenters (>350/mm^3); however, they account for >68% of all costs (Figure 2(a)). Overall, 70% of all drug costs (69% of ARV drug costs, 84% of all non-ARV drug costs), 61% of all outpatient costs, and 64% of hospital costs (92% of HIV-related hospital costs and 51% of non-HIV-related hospital costs) were attributable to late presenters (Figure 2(b)).

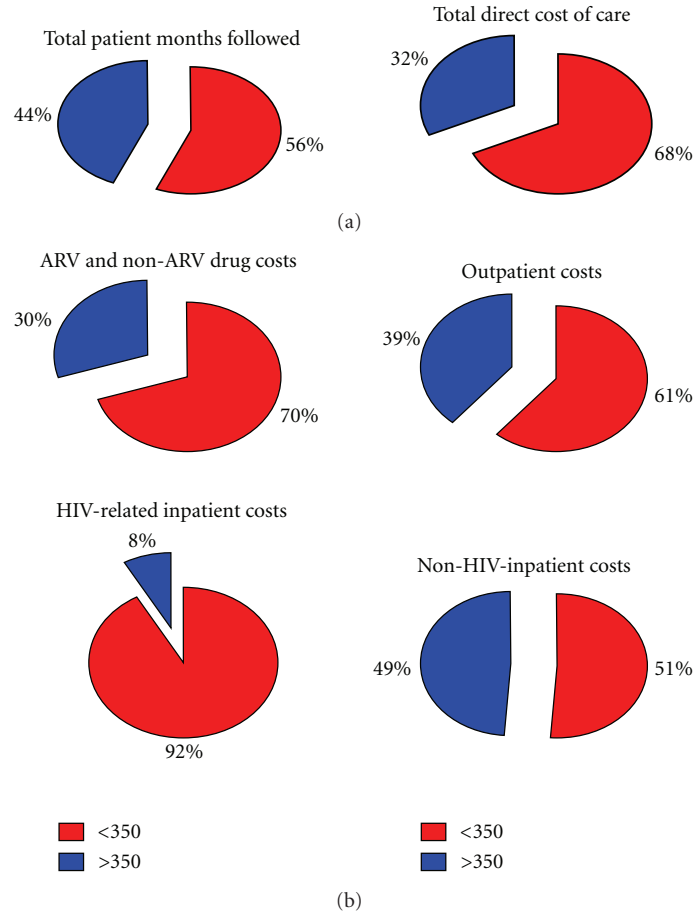


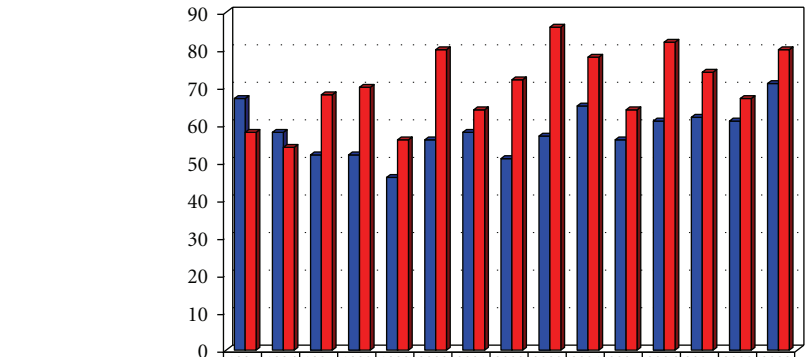
Figure 2: (a) Proportional costs of direct medical care with for newly diagnosed HIV patients accessing care from 1995 to 2010, (b) catergorized by cost category.

The proportional annual cost of care for late presenters versus early presenters for the year the person was diagnosed is presented in Figure 3. With the increased use of cART and with the trend at initiating cART at higher CD4 counts, we found that the proportional costs for late presenters increased substantially over the past 15 years—from 60% between 1995 and 1999 to over 75% between 2000 and 2009. Inpatient costs account for nearly two thirds (i.e., 64%) of all the costs incurred during the first year after accessing HIV for late presenters.

Patients who present late continue to cost more despite a recovery in their health in subsequent years beyond their initial year of diagnosis (Figure 4). Overall, late presenters cost a mean of $\$1419 \pm \$378$ per month ($\$17,028 \pm \$5,031$ per year) compared to $\$914 \pm \$452$ per month ($\$10,968 \pm \$5,677$ per year) for early presenters. Although there is yearly variation, mean PPPM costs remain substantially higher every year throughout the past 15 years. This substantial difference is also seen for patients who have been continuously followed at SAC from initial time of access care to the end of 2009. The mean initial CD4 count for late presenters was 122/mm^3 at first visit and 437/mm^3 at their latest CD4 count in 2009 compared to 470/mm^3 and 566/mm^3, respectively, for early presenters yet mean PPPM cost for these "late presenters" for the year 2009 remained almost twice as high (i.e., $\$1477 \pm \$402$ versus $\$896 \pm \$366$) despite significant improvements in CD4 counts.

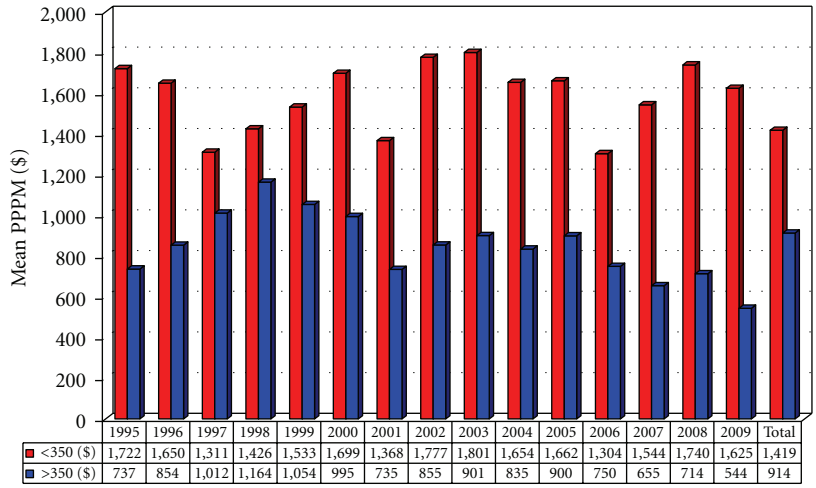
4. Discussion

We have documented that over the past 15 years the direct cost of care has remained significantly higher (>50%) for HIV-infected patients who present with a CD4 count <350/mm^3. These costs are not exclusively derived from the use of cART but reflect all direct medical costs. We have also shown that these increased direct costs are sustained beyond the initial year of care after presentation and persist despite CD4-rebound and -improved health. Late presenters continue after presentation to use not just more cART and outpatient care but more inpatient care, and, more non-ARV drugs. These costs may not only reflect lifelong legacy costs of the residual morbidities from some AIDS conditions but also may reflect the costs of complex social and medical issues that contributed to late presentation (e.g. denial, psychiatric illness, substance use). The rate of hospital admissions in late presenters is higher for both HIV and non-HIV-related conditions both at initial presentation and in subsequent years suggestive of the importance of legacy morbidity



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
<350 (%)	67	58	52	52	46	56	58	51	57	65	56	61	62	61	71
Total direct medical costs (%)	58	54	68	70	56	80	64	72	86	78	64	82	74	67	80

Figure 3: Proportions of the total direct medical costs incurred by "late presenters" (<350/mm^3) as a percentage of all direct medical costs for newly diagnosed HIV patients accessing care.



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Total
<350 ($)	1,722	1,650	1,311	1,426	1,533	1,699	1,368	1,777	1,801	1,654	1,662	1,304	1,544	1,740	1,625	1,419
>350 ($)	737	854	1,012	1,164	1,054	995	735	855	901	835	900	750	655	714	544	914

Year patient initially accessed HIV care

Figure 4: Mean cumulative PPPM (per patient per month) total cost of care for HIV patients accessing care in the year listed and followed until the patient moved, died, or 12/31/2009 in 2009 Cdn$.

and comorbidities. Fleishman et al. [32] also documented substantially higher continuing direct medical costs in the United States for late entrants to HIV care even after 7 to 8 years in care. They state that earlier entry into HIV care at relatively less costly disease stages could reduce aggregate expenditures. Our findings concur.

The center for disease control [41] recommended in 2006 more widespread and routine HIV testing as a means to detect more of the 20% to 33% of individuals who currently unaware they are HIV infected. The findings from this and other similar costing studies, carry implications with regard to assessing the economic impact of these recommendations as well as for the associated increased cART use for patients successfully engaged in HIV care.

It is anticipated that a substantial number of individuals identifying earlier with lower CD4 counts through this wider testing process will successfully engage in care, receive cART, decrease their infectivity (and the rate of secondary infections), and improve their own health. The costs of wider testing and the increased use of cART may be defrayed by decreasing the substantial and sustained direct medical costs from later presentation, the indirect costs to family from an avoidable illness (i.e., presentation with HIV/AIDS), and the opportunity costs to society by minimising lost productivity and reducing secondary infections [42, 43].

It is argued that the largest societal cost impact of earlier and more widespread detection of HIV and engagement to care will be the public health effect of "infections prevented." Proponents of the "test and treat" strategies for HIV prevention stated that expanded testing and earlier treatment could markedly decrease ongoing HIV infection and, in time, stem the HIV epidemic [44–46]. Those on treatment will have decreased viral loads and be less infectious and, in principle, should decrease to some degree new infections. The precise reduction in new infections from such a strategy within a population remains highly speculative along with its predicted savings both in actual costs and in reduced HIV transmission [47–49].

On a population level beyond the costs of wider testing, the cost of HIV care will increase as the number of individuals diagnosed with HIV and on treatment will increase. We have previously shown that the overall cost of care for HIV-infected individuals will increase within a population as more individuals are detected and begin to access HIV care and ARV drugs [50]. We estimated that wider screening and initiated HIV care would increase HIV costs by 21 to 28% if over half of the currently unidentified individuals with HIV infection were identified and accessed care. However, on an individual basis, patients who access care at a higher CD4 count have much lower cost PPPM over the course of their condition compared to individuals who access care at lower CD4 counts. We have shown how costs remain high over at least 7 years or more of followup despite improved health. As both early and late presenters now live longer and require sustained treatment and management of their condition, the difference in the cost PPPM between these groups will continue to be disproportional.

Our study, while comprehensive, does have limitations. Many factors including the ease and availability of accessing care, the composition of the HIV community, the location of the HIV care site or sites, the cost of direct or indirect health care within the community, the use and preference by ARV's by health care providers, and other aspects of care delivery may influence mean cost PPPM over time and between geographic locations. Collection of costing data itself may increase or decrease actual costing estimates. We have attempted to reduce many of the factors by concentrating on only those patients diagnosed and accessing care at a centralized care center within a defined geographic population over the course of 15 years in which there was a continuity in clinic protocols and management philosophy driven by international guidelines. Costing collection and the methodologies applied have remained the same over the study period. Although the actual costs of ARV medicine, outpatient and inpatient care may be higher or lower than other centers due to differences in health care systems across and inside any country, the proportional differences we identified are remarkably similar to those reported by others in costing studies, and, thus, the analysis and discussion should be widely applicable. Our study also only reports on costs in a developed country and as such is not directly relevant to costing studies in developing nations where clinical, demographic, and economic issues are significantly different [51–54], at least to a degree. The underlying aspects and costing principles presented in our study can be applied to other situations albeit with differing cost estimates.

Two other considerations will need to be addressed in future costing studies. More and more ARV drugs will be coming off patent in the near future and will be available in generic form. This most likely will directly or indirectly reduce the cost of ARV drugs and regimens and should reduce long-term costs of care for HIV-infected individuals. How much and how quickly these costs change will increasingly make future costing projections less precise. Another important aspect to be addressed is the cost savings in indirect costs and opportunity costs from cART therapy. Improving the health of HIV patients and increasing their longevity not only is beneficial to the patient's health but its major impact is likely in minimising indirect cost to patients family for caring and in reducing opportunity cost to society form lost productivity. Future studies need to explore such issues to further measure the economic impact of early identification and treatment with cART.

5. Conclusion

HIV/AIDS has been and continues to be an expensive disease to manage. Early detection and treatment of the HIV infection has been shown to produce very positive clinical and public health effects; however, at the same time, direct medical care costs increase as patients initiate cART earlier and over longer-time periods. Increased initial costs can be defrayed over time by more stable and lower costs of care as health improves. Many costly hospitalizations may be avoided with proper disease management. Earlier detection and access to HIV care may also reduce indirect costs as patients maintain productive lifestyles to the best of their abilities thus also reducing societal costs. The high initial and sustained costs of late presentation in HIV disease is a factor in discussions on more widespread testing and treatment of HIV disease.

Acknowledgments

The authors wish to thank Ian Cosman and Danette Mohagen for maintaining and updating the SAC database. They thank Mike Henry for constructing our powerful and useful cost search engine. They also thank the staff and patients at SAC for their ongoing support of their research.

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