The Incidence and Spectrum of AIDS-Defining Illnesses in Persons Treated with Antiretroviral Drugs

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The incidence and spectrum of primary AIDS-defining illnesses in human immunodeficiency virus–positive patients receiving antiretroviral drugs may have changed since the introduction of newer antiretroviral agents. We performed a retrospective analysis of patients enrolled in the British Columbia Drug Treatment Program who were ever prescribed antiretroviral drugs between 1 January 1994 and 31 December 1996. Rates were calculated on a 6-month basis. There were 344 AIDS cases diagnosed among 2,533 participants between 1994 and 1996. The incidence of primary AIDS diseases decreased from 1994 to 1996, with a sharp decline in 1995 and 1996. There was no statistically significant change in the incidence of primary AIDS diagnoses relative to one another, and Pneumocystis carinii pneumonia and Kaposi's sarcoma remain the most common AIDS index diagnoses. In patients receiving antiretroviral therapy in the modern era, the incidence of AIDS-defining illnesses has decreased substantially, but the spectrum of AIDS-defining illnesses remains unchanged.

In recent years, the natural course of HIV infection has changed dramatically [1]. Before 1995 the incidence of AIDS and AIDS-defining illnesses increased or remained static [2, 3], but since then stabilization in the incidence of AIDS-related opportunistic infections has been followed by a reduction in the rate of new AIDS cases in the United States [1, 4, 5]. Progress in the management and prevention of the complications of HIV disease had considerable impact on the clinical manifestations of AIDS in the era prior to the advent of highly active antiretroviral therapy [6–9]. However, it is unclear how the clinical course of HIV infection will evolve in patients receiving highly active antiretroviral therapy, particularly given the possibility that clinically significant immune reconstitution will be induced by such therapy [10–16].

The purpose of this study was to assess the evolution in the incidence of AIDS-defining opportunistic infections and tumors as primary diagnoses among HIV-positive patients prescribed antiretroviral drugs during a 3-year period prior to and since the introduction of newer antiretroviral agents, from 1 January 1994 through 31 December 1996. The second objective of this study was to determine whether there was a change in the spectrum or relative incidence of AIDS-defining illnesses during this period.

Methods

Since 1986, antiretroviral agents in the province of British Columbia, Canada, have been distributed at no cost to eligible HIV-infected individuals through the HIV/AIDS Drug Treatment Program, centrally administered through the British Columbia Center for Excellence in HIV/AIDS [17]. For physicians to prescribe antiretroviral drugs, they must complete a participant enrollment form that acts as the drug prescription. This permits tracking of enrolled participants, determination of the timing of development of AIDS, and identification of index AIDS diagnoses. In this way, manifestations of complications of HIV disease in individuals in British Columbia who are prescribed antiretroviral agents can be ascertained.

From 1986 to 1997, a total of 3,968 HIV-positive British Columbians received antiretroviral therapy. Between 1994 and 1997, a total of 2,456 patients began receiving antiretroviral therapy. The present analysis was restricted to HIV-positive, AIDS-free patients who were ever prescribed any antiretroviral therapy between January 1994 and December 1996. The primary endpoint was the first AIDS-defining illness. Opportunistic infections and other AIDS-defining events, defined according to the 1993 Centers for Disease Control and Prevention AIDS definition [18], were identified during the follow-up...
period on a continuous basis with use of physician reports and through record linkages with the British Columbia provincial AIDS registry and Division of Vital Statistics.

Rates were expressed as the number of primary AIDS diagnoses among those previously treated with antiretroviral drugs per 1,000 AIDS-free participants receiving antiretrovirals in a 6-month period. All rates were calculated on a 6-month basis over a 3-year period, from 1 January 1994 through 31 December 1996. Patients with a first AIDS-defining illness were excluded from analysis in subsequent semesters. Incidences were recorded for all primary AIDS diagnoses (principally, Pneumocystis carinii pneumonia [PCP], Kaposi’s sarcoma [KS], candidal infection, Mycobacterium avium complex [MAC] infection, cytomegalovirus infection, dementia and other AIDS-defining neurological illnesses, and wasting syndrome), and the rates of decline for each were calculated and compared. The relative proportion of different AIDS-defining illnesses was compared for 1995 and 1996, relative to the baseline in 1994.

For further analysis, PCP, candidal infection, infection with Mycobacterium tuberculosis, and herpes simplex virus infection were grouped and analyzed separately from other AIDS-defining illnesses. This group of HIV-related complications is amenable to therapy, and if treated successfully, these complications do not contribute to limitation of life expectancy. In contrast, other AIDS-defining illnesses such as toxoplasmosis, MAC infection, progressive multifocal leukoencephalopathy, and lymphoma more often cannot be treated successfully and often limit survival. The former group has been designated amenable, while all others were considered nonamenable [19, 20]. Analyzing these groups of diagnoses separately was important to determine if changes in the incidence of AIDS-defining illnesses and spectrum of disease were associated with changes in the extent to which the terminal stage of HIV infection (AIDS) was amenable to therapy during the study period.

Statistical Analysis

Categorical variables and ordinal and skewed continuous variables were compared with the Mantel-Haenszel test and Wilcoxon’s rank-sum test, respectively. Fisher’s exact test was used for 2 × 2 contingency tables in which any of the expected cell frequencies was <5. Linear regression analysis was used to assess the rate of change in AIDS cases diagnosed over time. All reported P values are two-sided, and P < .05 was considered statistically significant.

Results

From January 1994 through December 1996 there were 2,533 participants (2,238 [88.4%] men and 295 [11.6%] women) receiving antiretroviral medications who were AIDS-free at enrollment in the HIV/AIDS Drug Treatment Program. A total of 344 (13.6%) of these 2,533 participants (325 men and 19 women) had AIDS diagnosed after the initiation of antiretroviral therapy. The median age of these 344 participants at the time of diagnosis of primary AIDS was 38 years (interquartile range, 34–44 years). The median age at diagnosis of AIDS did not differ significantly between the 3 study years (P = .908). The median value for the last CD4+ cell counts obtained within 12 months prior to the AIDS diagnosis was 0.070 × 10^9/L (interquartile range, 0.030–0.130 × 10^9/L). The median value did not differ significantly during the study period (0.080 × 10^9/L in 1994 vs. 0.060 × 10^9/L in 1996; P = .377).

Infection with HIV was attributable to homosexual contact in 268 cases (78%), heterosexual contact in 35 (10.2%), intravenous drug abuse in 38 (11%), transfusion of packed RBCs in 6 (1.7%), and transfusion of other blood products in 11 (3.2%). Over the study period there was an increase in the diagnosis of AIDS among injection drug users (10% in 1994 vs. 11% in 1996; P = .894) and a decrease among homosexual and bisexual men (81% in 1994 vs. 66% in 1996; P = .023). There was no substantial change in the AIDS case rate among patients who acquired disease through heterosexual transmission (8.97% in 1994 vs. 7.69% in 1996; P = .761). The distribution of patients with varying levels of immunodeficiency, as reflected by CD4+ cell count, did not change through the period of study (P = .133; figure 1).

During the study period, the incidence rates of primary AIDS diseases peaked in the first months of 1994 and reached their lowest values in the last 6 months of 1996. There were 80 primary AIDS cases diagnosed per 1,000 antiretroviral-treated participants in the first 6 months of 1994. This number dropped to 22 per 1,000 in the last 6 months of 1996. The overall number of primary AIDS cases decreased at a rate of 18 cases

![Figure 1. AIDS-free participants prescribed antiretroviral therapy between 1 January 1994 and 31 December 1996, stratified by CD4+ cell count (□ = <0.050 × 10^9/L; □ = 0.050–0.199 × 10^9/L; ■ = ≥0.200 × 10^9/L). The distribution of participants by major CD4+ cell groups did not change over time (P = .133).](image-url)
per 1,000 every 6 months from 1994 to 1996 (P < .001). The overall rate of decrease was related primarily to the sharp decline during the last 2 years (1995 and 1996). The primary AIDS diagnoses in this population treated with antiretroviral drugs decreased at a rate of 24 cases per 1,000 participants every 6 months during this 2-year period (P = .004).

Figure 2 represents the decline in AIDS incidence among participants receiving antiretroviral therapy before diagnosis, by major diagnosis category. The rate of decline in AIDS incidence was highest for PCP, at five cases per 1,000 every 6 months from 1994 to 1996 (P = .004). The KS incidence rate declined at a rate of three cases per 1,000 every 6 months from 1994 to 1996 (P < .001). Incidence of all other primary AIDS diagnoses combined decreased at a rate of 11 cases per 1,000 every 6 months (P < .001) during the study period. Changes in other AIDS disease categories, such as infections due to Candida species, cytomegalovirus, and MAC, neurological disorders (progressive multifocal leukoencephalopathy and dementia), and wasting disease, are noted in figure 3. Declines in AIDS incidence were most marked for infections due to Candida species (two cases per 1,000 participants; P = .010). However, the small numbers in each of these categories impairs meaningful analysis of individual diseases. The AIDS incidence rate decreased significantly in all categories of immunosuppression, as reflected by CD4+ cell counts (P < .001 overall; figure 4).

Despite a decrease in the overall incidence rate of primary AIDS diagnoses among Drug Treatment Program participants, there was no statistically significant difference in the proportion of PCP, KS, and other AIDS index diagnoses from 1994 to 1996 (P = .082; figure 5). PCP accounted for 28% of all primary AIDS diagnoses in 1994 and 42% of those in 1996 (P = .048). Fifteen percent of individuals who developed AIDS in 1994 had KS as their primary diagnosis, while 11% did in 1996 (P = .442).

Finally, we completed a separate analysis, grouping AIDS index diagnoses as amenable or nonamenable to treatment. As shown in figure 6, from 1995 to 1996 the incidence of primary AIDS in the amenable group decreased at a rate of 9 cases per 1,000 participants every 6 months (P = .010), and the incidence in the nonamenable group decreased at a rate of 15 cases per 1,000 participants every 6 months (P = .011). There is no statistically significant difference between the proportions of AIDS index diseases considered amenable to treatment (44% in 1994 vs. 58% in 1996; P = .062).
decline in incidence of AIDS-de®ning illnesses observed in our study. In British Columbia, the change in death rate due to AIDS has been related to the availability of newer antiretroviral agents, especially lamivudine (3TC) [21, 22]. Continued monitoring of AIDS index disease incidence and survival rates will allow us to characterize fully the impact of more recent therapeutic advances on a populational basis. For example, the substantial reduction in the AIDS case rate in 1996 is unlikely due to the advent of protease inhibitors; therefore, the impact of antiretroviral regimens containing such agents cannot be assessed from the current data set.

Certainly, the decrease in AIDS-de®ning illnesses parallels changes in the availability of and strategy applied in using antiretroviral agents over the period of study. Since 1992, the therapeutic guidelines of the British Columbia Center for Excellence in HIV/AIDS for the use of antiretroviral therapy have recommended double combination therapy for individuals with a CD4 cell count of $\leq 0.350 \times 10^9/L$. This recommendation was expanded in December 1995 to make double combination therapy available to everyone with a CD4 cell count of $\leq 0.500 \times 10^9/L$. In July 1996, individuals naive to antiretroviral therapy were prescribed triple-drug therapy if their viral load was $\leq 100,000$ copies/mL, while those with a plasma viral load of $5,000-100,000$ copies/mL received two drugs [17].

**Discussion**

Our data demonstrate that there was a substantial decrease in the incidence of AIDS-de®ning illnesses in the province of British Columbia, Canada, from 1994 to 1996 among HIV-positive patients prescribed antiretroviral agents. This decrease accelerated in 1995. A similar decrease was noted among AIDS-de®ning illnesses amenable and nonamenable to therapy. Furthermore, these results indicate that the spectrum of AIDS-de®ning illnesses, their incidence relative to one another among patients prescribed antiretroviral therapy, and the level of immunosuppression at which AIDS develops have not changed substantially, despite the overall decline in incidence of AIDS-de®ning illnesses. PCP and KS remain the most common AIDS index illnesses in HIV-infected patients prescribed antiretroviral therapy in the modern era.

The finding of a decline overall in the incidence of primary AIDS-de®ning illnesses con®rms earlier work demonstrating a decline in AIDS-related death rates in British Columbia [21, 22] and supports others’®ndings of a declining AIDS incidence in recent years [1, 5, 23]. Similarly, a decline in AIDS-de®ning illnesses was found over a 5-year period in the series of Moore and Chaisson and was felt to be attributable to increased use of prophylactic medications for opportunistic infections [24]. However, it is not clear that such changes account for the decline in incidence of AIDS-de®ning illnesses observed in our study.

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**Figure 4.** Change in AIDS incidence among AIDS-free participants prescribed antiretroviral therapy between 1 January 1994 and 31 December 1996, stratified by CD4+ cell count ($\bigcirc = <0.050 \times 10^9/L; \blacktriangle = 0.050-0.199 \times 10^9/L; \blacktriangleleft = \geq 0.200 \times 10^9/L$). There was a significant decrease in AIDS incidence in all three CD4+ cell count groups ($P < .001$ for CD4+ cell counts $<0.050$ and $0.050-0.199 \times 10^9/L; P = .0134$ for CD4+ cell counts $\geq 0.200 \times 10^9/L$).

**Figure 5.** Proportion of AIDS index diseases attributed to *Pneumocystis carinii* pneumonia (PCP; $\Box$), Kaposi’s sarcoma (KS; $\square$), and other AIDS-de®ning illnesses ($\blacksquare$), among participants with AIDS diagnosed and antiretroviral drugs prescribed between 1 January 1994 and 31 December 1996. There was no signi®cant difference in the proportion of participants who developed AIDS due to PCP ($P = .048$ for 1994 vs. 1996), KS ($P = .442$ for 1994 vs. 1996), or another AIDS-de®ning illness ($P = .190$ for 1994 vs. 1996).
the pattern of AIDS-defining diseases has been very mutable, of the nature of the study design [1]. The main disadvantage with a change in the spectrum or proportion of AIDS-defining against all AIDS-defining illnesses.

improvements in antiretroviral therapy might explain our obser- In this context, it is noteworthy that there was no signiﬁcant
decrease during the study period in AIDS-defining illnesses to PCP and KS, it remains uncertain that this will continue in
and thus most participants had uniform access to preventive Hence, while no signiﬁcant change was observed in the inci-
doses of the British Columbia Center for Excellence, which months after the start of combination antiretroviral therapy, in
our study. Second, most patients enrolled in the Drug Treatment disease [41]. For example, retinitis due to cytomegalovirus
related to initiation of aggressive combination antiretroviral

Figure 6. Change in AIDS incidence among AIDS-free participants prescribed antiretroviral therapy between 1 January 1994 and 31 December 1996, stratified by whether the condition was considered to be amenable (■) or nonamenable (○) to treatment. There was no signiﬁcant difference between the proportions of AIDS index diseases considered amenable to therapy in 1994 vs. 1996 (P = .062).

Thus, particularly since 1995, double and subsequently triple combination drug therapy (especially with newer agents) has been widely available for those patients participating in the Drug Treatment Program.

There are several other reasons to implicate changes in anti-
retroviral therapy in the observed decline in AIDS-defining illnesses. First, most prophylactic regimens for HIV-related opportunistic infections were introduced in the late 1980s [24, 25] and did not change substantially over the 3-year period of our study. Second, most patients enrolled in the Drug Treatment Program are managed in accordance with the therapeutic guidelines of the British Columbia Center for Excellence, which include clear recommendations regarding use of prophylaxis, and thus most participants had uniform access to preventive therapies throughout the study period. Finally, the dramatic decrease during the study period in AIDS-defining illnesses not amenable to treatment provides compelling evidence that improvements in antiretroviral therapy might explain our observations. Most important, however, a recent similar cohort study demonstrated deﬁnitively the impact of more intensive combination antiretroviral regimens on HIV-related mortality rates [23].

The second important finding of this study is that a decline in incidence of AIDS-defining illnesses was not coincident with a change in the spectrum or proportion of AIDS-defining illnesses observed. Since the beginning of the AIDS epidemic, the pattern of AIDS-defining diseases has been very mutable, owing to a variety of factors [6–9, 26–28]. Thus, the incidence of PCP as a primary AIDS diagnosis declined after the advent of prophylactic therapies in the late 1980s and constituted the first major shift in the pattern of AIDS-defining illnesses described [9, 29]. Yet, although the eficacy of prophylactic regimens has been well documented [30], PCP remains the most frequent opportunistic infection present at AIDS diagnosis in developed countries [26, 29]. Our results indicate that PCP continues to be the predominant AIDS-defining illness in the modern era of antiretroviral therapy. Hence, prophylaxis for PCP remains of primary importance [31, 32].

Given increasing evidence that KS is related to infection with a sexually transmissible herpesvirus [33–35], change in incidence of KS as an AIDS-defining illness can be anticipated to parallel changes in the behaviors and demographics of HIV-infected individuals. Indeed, a substantial shift in the occurrence of KS has been reported widely, with a decreasing trend as a primary AIDS diagnosis and more frequent development at a later stage of HIV disease [34, 36, 37]. Previous data indicate a substantially stable incidence of KS as an AIDS index disease among Canadian HIV-positive patients since 1987 [28, 38]. Data from the present study suggest a decreasing incidence of KS but no change in its relative frequency among AIDS-defining illnesses.

There was a reduction in incidence of all other index AIDS-
defining illnesses, but the proportion of patients developing these illnesses as index AIDS-related diseases relative to other AIDS-defining illnesses did not change over the 3 years of study. Given the small numbers of index AIDS-defining illnesses, it is unclear to what extent the observed changes may be related to prophylaxis (e.g., for infection related to Toxoplasma gondii [39] or MAC) or to the impact of newer antiretroviral strategies. The effect of prophylaxis in reducing the incidence of infection with MAC has been shown in a recent study [23]. Indeed, there is a suggestion that early immunologic rebound related to initiation of aggressive combination antiretroviral therapy may be incomplete [40] or may unmask subclinical disease [41]. For example, retinitis due to cytomegalovirus infection has been reported to occur in patients in the first months after the start of combination antiretroviral therapy, in association with CD4+ cell counts of >100 × 10^9/L [42]. Hence, while no signiﬁcant change was observed in the incidence overall of these other AIDS-defining illnesses relative to PCP and KS, it remains uncertain that this will continue in the modern era of antiretroviral therapy.

In this context, it is noteworthy that there was no signiﬁcant change in CD4+ cell count at the time of AIDS diagnosis. Furthermore, the incidences of amenable and nonamenable AIDS-defining illnesses decreased at similar rates. This implies that the improvement in CD4+ cell count occurring as a result of aggressive antiretroviral treatment is sufﬁcient to protect against all AIDS-defining illnesses.

Caution is advised in the interpretation of these data, because of the nature of the study design [1]. The main disadvantage
with this type of analysis is the delay in the reporting of AIDS cases: the median reporting delay in Canada is 9 months [43]. There are also uncertainties about area boundaries at the time of AIDS diagnosis and thus uncertainty about the reporting of AIDS diagnoses for men and women who did not receive medical care at their usual place of residence. We also may have underestimated the rate of migration, because geographic information was given greater weight in the matching process. Finally, specific data regarding prophylactic therapies are not available through our database. In addition, analysis of specific antiretroviral regimens is not meaningful because of the lack of an adequate sample size, inability to control for confounding variables (including adjustments in regimens in accordance with guidelines and availability of newer agents), and heterogeneity of the population studied. However, this does not detract from the conclusions of our study; indeed, we feel it strengthens it as an analysis of the effects of recommended combination antiretroviral therapy on a populational basis in real-world application in clinical practice.

In summary, then, in a 3-year retrospective analysis (from 1994 to 1996) of patients in British Columbia, Canada, who were prescribed antiretroviral drugs, the incidence of AIDS-defining illnesses decreased substantially, especially since 1995, coincident with the introduction of newer antiretroviral agents and more widespread use of aggressive combination therapy. PCP and KS remain the most common AIDS index illnesses for the population studied. However, this does not detract from the conclusions of our study; indeed, we feel it strengthens it as an analysis of the effects of recommended combination antiretroviral therapy on a populational basis in real-world application in clinical practice.

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References


