Improved Survival Among HIV-Infected Individuals Following Initiation of Antiretroviral Therapy

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Context.—Clinical trials have established the efficacy of antiretroviral therapy with double- and triple-drug regimens for individuals infected with the human immunodeficiency virus (HIV), but the effectiveness of these regimens in the population of patients not enrolled in clinical trials is unknown.

Objective.—To characterize survival following the initiation of antiretroviral therapy among HIV-infected individuals in the province of British Columbia.

Design.—Prospective, population-based cohort study of patients with antiretroviral therapy available free of charge (median follow-up, 21 months).

Setting.—Province of British Columbia, Canada.

Patients.—All HIV-positive men and women 18 years of age or older in the province who were first prescribed any antiretroviral therapy between October 1992 and June 1996 and whose CD4 cell counts were less than 0.350 x 10^9/L.

Main Outcome Measures.—Rates of progression from initial antiretroviral therapy to death or a primary acquired immunodeficiency syndrome (AIDS) diagnosis for subjects who initially received zidovudine-, didanosine-, or zalcitabine-based therapy (ERA-I) and for those who initially received therapy regimens including lamivudine or stavudine (ERA-II).

Results.—A total of 1178 patients (951 ERA-I, 227 ERA-II) were eligible. A total of 390 patients died (367 ERA-I, 23 ERA-II), yielding a crude mortality rate of 33.1%.

ERA-I group subjects were almost twice as likely to die as ERA-II group subjects, with a mortality risk ratio of 1.86 (95% confidence interval [CI], 1.21-2.86; P = .005). After adjusting for Pneumocystis carinii and Mycobacterium avium prophylaxis use, patients without AIDS when treatment was started, ERA-I participants were 1.93 times (95% CI, 1.25-2.97; P = .003) more likely to die than ERA-II participants. Among patients without AIDS when treatment was started, ERA-I participants were 2.50 times (95% CI, 1.59-3.93; P < .001) more likely to progress to AIDS or death than ERA-II participants.

Conclusion.—The HIV-infected individuals who received initial therapy with regimens including stavudine or lamivudine had significantly lower mortality and longer AIDS-free survival than those who received initial therapy with regimens limited to zidovudine, didanosine, and zalcitabine.

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ANTIRETROVIRAL therapy has been shown to prolong survival in persons with acquired immunodeficiency syndrome (AIDS) and those with intermediate-stage human immunodeficiency virus (HIV) infection. Between 1990 and 1995, didanosine and zalcitabine were increasingly used in combination with zidovudine. The available options for combination antiretroviral therapy expanded further when positive results were reported in clinical trials involving lamivudine and stavudine and, more recently, in trials involving protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Recently, viral load–driven therapy has been adopted, as a growing body of evidence has established plasma viral load as a meaningful predictor of disease progression. Overall, these developments have resulted in significant changes to the therapeutic management of this disease and have led to a dramatic increase in the use of double- and, more recently, triple-combination antiretroviral therapy regimens among HIV-infected persons.

Through clinical trials, much evidence has been generated in support of newer treatment strategies. However, such evidence has not yet been obtained from population-based studies. Therefore, we characterized the treatment regimens and survival rates of HIV-infected individuals over time in the province of British Columbia, building on previous research that showed a substantial decline in AIDS-related mortality in British Columbia in recent years.

METHODS

Drug Treatment Program

Since the introduction of zidovudine monotherapy in British Columbia in 1986, antiretroviral drugs have been centrally distributed at no cost to eligible HIV-

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infected individuals. In October 1992, the Drug Treatment Program became the responsibility of the British Columbia Centre for Excellence in HIV/AIDS (the Centre). From 1986 to 1997, a total of 4775 HIV-positive British Columbians received antiretroviral therapy in British Columbia. Of these, 3935 had ever been enrolled in the Drug Treatment Program, and 2192 were currently receiving antiretroviral therapy at the time of this report. The Centre’s Drug Treatment Program remains the only free source of antiretroviral medications in the province.

The Centre distributes antiretroviral drugs based on specific guidelines generated by the Centre’s Therapeutic Guidelines Committee. These guidelines as well as treatment updates are distributed to all physicians participating in the Drug Treatment Program. In 1992, the therapeutic guidelines recommended double-combination therapy for individuals with CD4+ cell counts lower than 0.350 × 10^9/L. In December 1995, this recommendation was expanded to make double-combination therapy available to everyone with CD4+ cell counts lower than 0.500 × 10^9/L.

A total of 5 antiretroviral agents were available in the province of British Columbia during the study period. The nucleoside analogue zidovudine has been available since 1986. The other 4 nucleoside analogues were made available over a period of 3 years: didanosine and zalcitabine in October 1992, lamivudine in February 1994, and stavudine in April 1995. The dates for lamivudine and stavudine reflect the availability of these therapies through compassionate release; lamivudine did not become widely available as first-line therapy until December 1995 and stavudine until July 1996. Protease inhibitors and nonnucleoside reverse transcriptase inhibitors did not become available through the program until the summer of 1996.

Data Collection

Physicians enrolling an HIV-positive individual into the Centre’s Drug Treatment Program must complete a drug request enrollment form. The enrollment request form acts as a legal prescription and compiles information on the HIV-positive applicant’s address and enrolling physician, HIV-specific drug history, CD4+ cell counts, and current drug requests. Each request is reviewed by a qualified practitioner to ensure that it meets the Centre’s established therapeutic guidelines. Approved prescriptions are filled every 2 months. At the time of the initial refill, each participant is asked to complete an enrollment survey and a program consent form, while the physician is asked to complete a clinical staging form. Patients complete the survey and physicians complete the clinical staging forms annually. The clinical staging form records participant-specific information on HIV- and AIDS-related conditions according to the World Health Organization clinical staging system.

This analysis was restricted to all HIV-positive men and women who were antiretroviral naive and were first prescribed any antiretroviral therapy between October 1, 1992, and June 30, 1996. To limit the effect of changing therapeutic guidelines, we restricted our analysis to persons who had CD4+ cell counts less than 0.350 × 10^9/L, thereby ensuring that they were eligible for combination therapy throughout the study period. Study subjects were divided into those who initially received therapy with zidovudine, didanosine, and zalcitabine, denoted as ERA-I, and those who initially received therapy regimens including lamivudine or stavudine, denoted as ERA-II.

Outcome Measures

The primary and secondary end points in this analysis were death and a primary AIDS diagnosis, respectively. Deaths and AIDS diagnoses during the follow-up period were identified on a continuous basis from physician reports and through record linkages carried out with the British Columbia provincial AIDS registry and Division of Vital Statistics. All-cause mortality was used since more than 90% of deaths among participants were directly attributable to HIV-related causes. Baseline clinical information, including primary AIDS diagnosis and use of *Pneumocystis carinii* pneumonia and *Mycobacterium avium* prophylaxis, was obtained directly from the Drug Treatment Program records.

Information on clinical illnesses defined according to the 1993 Centers for Disease Control and Prevention AIDS definition was collected from physician reports and record linkages carried out in collaboration with the provincial and national AIDS registries.

Statistical Analysis

For the purposes of analysis, statistical methods followed the intent-to-treat principle, with subjects retained in their initial treatment groups (ERA-I or -II) irrespective of whether ERA-I participants subsequently switched to regimens available in ERA-II. The outcomes examined were time from the start of antiretroviral therapy to the diagnosis of any primary AIDS diagnosis. Cumulative mortality and AIDS-free survival rates were estimated using Kaplan-Meier methods. Survival functions were compared using a log-rank test. Event-free subjects were right-censored as of June 30, 1997. Persons unavailable for follow-up were censored at the date of last known contact with the Drug Treatment Program.

Statistical comparisons were conducted using distribution-free methods. Categorical variables and ordinal and skewed continuous variables were compared using the Mantel-Haenszel and Wilcoxon rank sum tests, respectively.

Cox proportional hazard models were used to estimate the hazard of death and to estimate AIDS-free survival for the ERA-I group relative to the ERA-II group, with associated 95% confidence intervals (CIs).

In this analysis, we adjusted for a number of salient prognostic variables at baseline, including use of *P carinii* pneumonia and *M avium* prophylaxis, CD4+ cell count, AIDS diagnosis, age, and sex. A diagnosis of AIDS, sex, and use of *P carinii* pneumonia and *M avium* prophylaxis at entry were treated as fixed binary variables (yes vs no). Age (in years) and CD4+ cell count (per 0.100 × 10^9/L) at baseline were modeled as continuous variables. All reported P values are 2-sided.

RESULTS

A total of 1687 individuals in British Columbia were first prescribed antiretroviral therapy between October 1, 1992, and June 30, 1996. We excluded 446 subjects from this analysis because they did not meet the inclusion criteria, ie, had baseline CD4+ cell counts of 0.350 × 10^9/L or greater (408 participants) or because they were less than 18 years old (38 participants). A further 63 subjects were excluded because CD4+ cell counts were not available within 1 year prior to the start of antiretroviral treatment. The total study sample was based on the remaining 1178 subjects (951 ERA-I, 227 ERA-II).

Compared with study participants, individuals excluded because CD4+ cell counts were not available within 1 year prior to the start of antiretroviral treatment were more likely to be women (25% vs 9%; P = .001). However, these groups did not differ with respect to age (P = .63), *P carinii* pneumonia (P = .63) or *M avium* (P = .19) prophylaxis use, or a diagnosis of AIDS (P = .38) at baseline.

The overall median follow-up was 21 months (interquartile range, 14–34 months), with median follow-up of 20 months (interquartile range, 17–38 months) and 15 months (interquartile range, 13–16 months), respectively, for subjects in groups ERA-I and -II (P < .001). A total
of 27 (26 ERA-I and 1 ERA-II) study subjects (2%) were unavailable for follow-up in this analysis. In addition, 473 subjects (49.7%) in the ERA-I group switched to ERA-II regimens prior to the end of the study period.

Of the 951 ERA-I subjects, 488 (51%) initially received monotherapy and 463 (49%) received double therapy. Among the ERA-I subjects, 422 (44%) were treated with zidovudine monotherapy, 206 (22%) with zidovudine and didanosine, 197 (21%) with zidovudine and zalcitabine, and 66 (7%) with other mono-therapy regimens. As shown in Figure 1, the majority of ERA-I subjects started therapy before 1996: 124 (13%) in 1992, 325 (34%) in 1993, 204 (21%) in 1994, 231 (24%) in 1995, and 67 (7%) in 1996.

Of the 227 subjects in the ERA-II group, 205 (90%) were treated with zidovudine and lamivudine, 10 (4%) with lamivudine and stavudine, and 10 (4%) with other regimens, including lamivudine with didanosine or zalcitabine. In the ERA-II group, 225 (99%) initially received antiretroviral therapy with a regimen including lamivudine, 206 (91%) zidovudine, 2 (1%) stavudine, 5 (2%) didanosine, and 5 (2%) zalcitabine. A total of 27 ERA-II subjects (12%) commenced therapy in 1995, and 200 (88%) in 1996.

A total of 301 study subjects had AIDS at baseline (250 ERA-I, 51 ERA-II). The numbers and percentages of the AIDS-defining illnesses in both groups were Pneumocystis carinii pneumonia, 150 (50%); other opportunistic infections, 74 (25%); Kaposi sarcoma, 37 (12%); wasting syndrome, 19 (6%); neurologic disease, 14 (5%); and other malignant neoplasms, 7 (2%). There was no statistical difference between the 2 groups in the proportion having Kaposi sarcoma (P = .42) or other opportunistic infections (P = .87). However, more subjects in the ERA-I group than the ERA-II group had Pneumocystis carinii pneumonia (53% vs 35%, P = .02).

As of June 30, 1997, a total of 390 deaths (367 ERA-I, 23 ERA-II) had been identified, yielding a crude mortality rate of 33.1%. Figure 2 displays the Kaplan-Meier survival curves for the ERA-I and ERA-II groups. Product-limit estimates (±SEs) of the cumulative mortality rate at 15 months were 17.1% (±1.2%) and 10.0% (±2.0%) for ERA-I and ERA-II groups, respectively (P = .004). ERA-I subjects were almost twice as likely to die as ERA-II subjects, with a mortality risk ratio of 1.86 (95% CI, 1.21-2.86; P = .005).

The final multivariate model for the baseline factors associated with mortality is presented in Table 2. Use ofERA-II regimens (P < .003), a higher CD4+ cell count (P < .001), absence of AIDS (P < .001), younger age (P < .001), and the use of Mavium prophylaxis (P = .009) at baseline were independently associated with longer survival after adjusting for sex and for use of Pneumocystis carinii pneumonia prophylaxis. The adjusted mortality risk ratio from this multivariate model indicates that study subjects in the ERA-I group were 1.93 times (95% CI, 1.25-2.97) more likely to die following the initiation of antiretroviral therapy than subjects in the ERA-II group.

We also restricted our analysis of survival to the 690 subjects who were initially prescribed dual-nucleoside regimens. After adjusting for other salient prognostic variables (use of Pneumocystis carinii pneumonia and Mavium prophylaxis, AIDS diagnosis, CD4+ cell count, sex, and age), ERA-I participants were 1.73 times (95% CI, 1.09-2.74; P = .02) more likely to die than ERA-II participants.

Finally, we repeated all relevant analyses with the time from the start of antiretroviral therapy to diagnosis of AIDS or death as the outcomes of interest. These analyses were restricted to the 877 subjects (701 ERA-I, 176 ERA-II) who were free of AIDS at baseline. As of June 30, 1997, a total of 300 events had been identified, 219 primary AIDS diagnoses (208 ERA-I, 11 ERA-II) and 81 deaths (71 ERA-I, 10 ERA-II). The numbers and percentages of AIDS-defining illnesses in both groups were Pneumocystis carinii pneumonia, 63 (29%); candida infections, 23 (11%); Mavium complex infection, 21 (10%); cytomegalovirus infection, 13 (6%); other opportunistic infections, 25 (11%); Kaposi sarcoma, 35 (16%); wasting syndrome, 23 (11%); neurologic disease, 8 (4%) and other malignant neoplasms, 8 (4%). Figure 3 displays the Kaplan-Meier curves for cumulative mortality or progression to AIDS for the ERA-I and ERA-II groups. Product-limit estimates (±SEs) of the rate of progression to AIDS or death at 15 months were 23.8% (±1.6%)
and 10.7% (+2.4%) for ERA-I and ERA-II subjects, respectively (P <.001). After adjusting for other prognostic variables (use of PCP pneumonia and M avium prophylaxis, CD4+ cell count, sex, and age), ERA-I participants were 2.50 times (95% CI, 1.51-3.96; P <.001) more likely than ERA-II participants to die or progress to AIDS. These results were not altered by removing those AIDS-free participants (risk ratio, 2.45; 95% CI, 1.51-3.96; P <.001) who were receiving monotherapy at baseline or by adjusting for an estimated AIDS reporting delay of 9 months (risk ratio, 2.23; 95% CI, 1.33-3.74; P =.002). When our analyses were based on the time from the start of antiretroviral therapy to diagnosis of AIDS, after adjusting for other prognostic variables, (use of PCP pneumonia and M avium prophylaxis, CD4+ cell count, sex, and age), ERA-I participants were 3.61 times (95% CI, 1.95-6.67; P <.001) more likely than ERA-II participants to progress to AIDS.

**COMMENT**

This analysis demonstrated a statistically significant improvement in survival and AIDS-free survival among HIV-infected men and women who received initial antiretroviral therapy using ERA-II regimens vs ERA-I regimens. Individuals in the ERA-I group were nearly twice as likely to die as those in the ERA-II group. This result remained statistically significant even after adjusting for PCP pneumonia and M avium prophylaxis use, CD4+ cell count, AIDS diagnosis, sex, and age at baseline. Furthermore, ERA-I participants who were free of AIDS at baseline were nearly 3 times more likely to progress to AIDS or die than those in the ERA-II group.

Definitive evidence regarding the relative efficacy of various treatment strategies can only be gathered in the context of randomized clinical trials. However, it is also important to monitor the reproducibility of the benefits obtained in controlled settings when therapies are applied to populations. Our findings are likely to reflect, to a substantial extent, the effect of the introduction of lamivudine, as recently established in clinical trials. The recently reported CAESAR trial showed that adding lamivudine to regimens including zidovudine reduced the 1-year progression to AIDS or death by 55%. This effect was maintained when subgroup analyses by various CD4+ cell count ranges and prior exposure to antiretroviral agents were performed among the CAESAR trial. In our study, the vast majority of subjects in the ERA-II group received initial therapy with a regimen containing lamivudine, and nearly all these subjects received both zidovudine and lamivudine.

In a population-based study, differences in outcomes between treatment groups might result from nonrandom assignment to therapies or from differential use of conterventions between groups. In this context, it is reassuring to note that no statistical differences were observed between the 2 treatment arms at entry in PCP pneumonia and M avium prophylaxis use, prior diagnosis of AIDS, and CD4+ cell count. Another possible concern is that subjects with more advanced disease or symptoms may have chosen to initiate treatment sooner or to use more aggressive therapy options. Those who survive a short time from enrollment have less opportunity to select subsequent treatment and are less likely to use any one treatment. In other words, rather than treatment influencing progression to AIDS-free survival or death, survival may lead to treatment use, thus overestimating the calculated treatment effect. We have attempted to control these possible biases in several ways. As noted above, comparisons of indicators of disease severity at baseline demonstrated no significant differences between groups. Furthermore, our analysis avoids any potential bias caused by individuals with more advanced disease discontinuing treatment due to more severe illness. In this type of analysis, those who switch treatment arms are retained in their original treatment group. Thus, the fact that they have remained event-free long enough to initiate new treatment becomes moot. Finally, as noted above, we used multivariate regression techniques to adjust or control simultaneously for the effects of multiple baseline clinical and demographic factors on mortality and AIDS-free survival. This approach, commonly used in observational studies, eliminates potential survival bias be-
cause the model compares only persons in the different treatment groups who survive to the same time point.

Measurements of our study include the provision of antiretroviral treatment at no cost, the intent-to-treat analysis, complete follow-up for 98% of the cohort, and the extent of active reporting of deaths (n=175 [98%]; median follow-up from date of death to date of reporting, 7 days [interquartile range, 4-12 days]).

In summary, our analysis demonstrated a significant improvement in mortality and AIDS-free survival for men and women who received initial therapy with regimens including stavudine or lamivudine compared with those who received initial therapy with regimens restricted to zidovudine, didanosine, or stavudine-monotherapy. Our results remained statistically significant even after adjusting for P. carinii pneumonia and M. avium prophylaxis use, CD4+ cell count, AIDS diagnosis, sex, and age at baseline. We therefore attribute this improvement to the introduction of new antiretroviral therapy strategies. While the observational cohort study is subject to a number of inherent constraints, adjustment for salient prognostic covariates, such as age, sex, CD4+ cell count, and use of prophyxaxis for P. carinii pneumonia and M. avium, as well as restriction to antiretroviral-naïve participants with CD4+ cell counts lower than 200 per cubic millimeter, reflects the efficacy of combinations including lamivudine and stavudine. Our results confirm the importance of including data from large-scale observational studies in the evaluation of the many available therapeutic strategies for persons with HIV disease. The long-term impact of these and newer treatment strategies remains to be explored.

References