Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens

Evidence

Études

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Abstract

Background: The efficacy of triple-drug antiretroviral regimens in the treatment of patients infected with HIV has been established in several randomized clinical trials. However, the effectiveness of these new regimens in patient populations outside clinical trials remains unproven. This study compares mortality and AIDS-free survival among HIV-infected patients in British Columbia who were treated with double- and triple-drug regimens.

Methods: The authors used a prospective, population-based cohort design to study a population of HIV-positive men and women 18 years or older for whom antiretroviral therapy was first prescribed between Oct. 1, 1994, and Dec. 31, 1996; all patients were from British Columbia. Rates of progression from the initiation of antiretroviral therapy to death or to diagnosis of primary AIDS were determined for patients who initially received an ERA-II regimen (2 nucleoside analogue reverse transcriptase inhibitors [NRTIs] including lamivudine or stavudine, or both) and for those who initially received an ERA-III regimen (triple-drug regimen consisting of 2 NRTIs and a protease inhibitor [indinavir, ritonavir or saquinavir] or a non-NRTI [nevirapine]).

Results: A total of 500 men and women (312 receiving an ERA-II regimen and 188 an ERA-III regimen) were eligible. Patients in the ERA-III group survived significantly longer than those in the ERA-II group. As of Dec. 31, 1997, 40 patients had died (35 in the ERA-II group and 5 in the ERA-III group), for a crude mortality rate of 8.0%. The cumulative mortality rates at 12 months were 7.4% (95% confidence interval [CI] 5.9% to 8.9%) for patients in the ERA-II group and 1.6% (95% CI 0.7% to 2.5%) for those in the ERA-III group (log rank $p = 0.003$). The likelihood of death was more than 3 times higher among patients in the ERA-II group (mortality risk ratio 3.82 [95% CI 1.48 to 9.84], $p = 0.006$). After adjustment for prophylaxis for *Pneumocystis carinii* pneumonia or *Mycobacterium avium* infection, AIDS diagnosis, CD4+ cell count, sex and age at initiation of therapy, the likelihood of death among patients in the ERA-II group was 3.21 times higher (95% CI 1.24 to 8.30, $p = 0.016$) than in the ERA-III group. Cumulative rates of progression to AIDS or death at 12 months were 9.6% (95% CI 7.7% to 11.5%) in the ERA-II group and 3.3% (95% CI 1.8% to 4.8%) in the ERA-III group (log rank $p = 0.006$). After adjustment for prognostic variables (prophylaxis for *P. carinii* pneumonia or *M. avium* infection, CD4+ cell count, sex and age at initiation of treatment), the likelihood of progression to AIDS or death at 12 months among patients in the ERA-II group was 2.37 times higher (95% CI 1.04 to 5.38, $p = 0.040$) than in the ERA-III group.

Interpretation: This population-based cohort study confirms that patients initially treated with a triple-drug antiretroviral regimen comprising 2 NRTIs plus a protease inhibitor or a non-NRTI have a lower risk of morbidity and death than patients treated exclusively with 2 NRTIs.

Résumé

Contexte : Plusieurs études cliniques randomisées ont établi l'efficacité de régimes antirétroviraux à trois médicaments dans le traitement de patients infectés par le VIH. L'efficacité de ces nouveaux régimes dans les populations de patients autres que celles d'études cliniques reste toutefois à prouver. Cette étude compare la mortalité et la survie sans SIDA chez des patients infectés par le VIH en Colombie-Britannique qui ont été traités au moyen de régimes à deux et à trois médicaments.

Méthodes : Les auteurs ont utilisé une étude prospective de cohortes représentatives portant sur une population d'hommes et de femmes infectés par le VIH, âgés de 18 ans ou plus, auxquels on a prescrit pour la première fois une thérapie aux antirétroviraux entre le 1er octobre 1994 et le 31 décembre 1996. Tous les patients étaient de la Colombie-Britannique. Les taux d'évolution du début de la thérapie aux antirétroviraux jusqu'à la mort ou au diagnostic de SIDA primitif ont été établis dans le cas des patients qui ont reçu au début un traitement ERA-II (deux inhibiteurs de la transcriptase inverse analogues aux nucléosides [ITIN], y compris la lamivudine ou la stavudine, ou les deux), et dans le cas de ceux qui ont reçu au début un traitement ERA-III (régime à trois médicaments comportant deux ITIN et un inhibiteur de la protéase [indinavir, ritonavir ou saquinavir] ou un non-ITIN [névirapine]).

Résultats : Au total, 500 hommes et femmes (312 qui suivaient un traitement ERA-II et 188, un traitement ERA-III) étaient admissibles. Les patients du groupe ERA-III ont survécu beaucoup plus longtemps que ceux du groupe ERA-II. Au 31 décembre 1997, 40 patients étaient morts (35 du groupe ERA-II et 5 du groupe ERA-III), ce qui donne un taux de mortalité brut de 8,0 %. Les taux de mortalité cumulatifs à 12 mois étaient de 7,4 % (intervalle de confiance [IC] à 95 % de 5,9 % à 8,9 %) chez les patients du groupe ERA-II et de 1,6 % (IC à 95 % de 0,7 % à 2,5 %) chez ceux du groupe ERA-III (rang log $p = 0,003$). La probabilité de décès était plus que trois fois plus élevée chez les patients du groupe ERA-II (coefficient de probabilité de mortalité de 3,82 [IC à 95 % de 1,48 à 9,84], $p = 0,006$). Après rajustement pour tenir compte d'une prophylaxie à cause d'une pneumonie à *Pneumocystis carinii* ou d'une infection par *Mycobacterium avium*, d'un diagnostic de SIDA, de la numération des leucocytes CD4+, du sexe et de l'âge au début du traitement, la probabilité de mort chez les patients du groupe ERA-II était 3,21 fois plus élevée (IC à 95 % de 1,24 à 8,30, $p = 0,016$) que chez les sujets du groupe ERA-III. Les taux cumulatifs d'évolution vers le SIDA ou la mort à 12 mois étaient de 9,6 % (IC à 95 % de 7,7 % à 11,5 %) chez les patients du groupe ERA-II et de 3,3 % (IC à 95 % de 1,8 % à 4,8 %) chez ceux du groupe ERA-III (rang log $p = 0,006$). Après rajustement en fonction de variables liées au pronostic (prophylaxie contre une pneumonie à *P. carinii* ou une infection à *M. avium*, numération des leucocytes CD4+, sexe et âge au début du traitement), la probabilité de mort ou d'évolution vers le SIDA chez les patients du groupe ERA-II était 2,37 fois plus élevée (IC à 95 % de 1,04 à 5,38, $p = 0,040$) que chez les sujets du groupe ERA-III.

Interprétation : Cette étude de cohorte représentative confirme que chez les patients traités au début au moyen d'un régime antirétroviral à trois médicaments comportant deux ITIN plus un inhibiteur de la protéase ou un non-ITIN, le risque de morbidité et de mort est moins élevé que chez les patients traités exclusivement avec deux ITIN.

Triple-drug antiretroviral therapy has been shown to increase short-term survival, decrease morbidity, improve CD4+ cell counts and decrease plasma viral loads in HIV-infected patients.[1–5] As a result, current guidelines recommend a triple-drug regimen as the standard first-line therapy.[6–9] To date, however, most of the evidence favouring this approach has come from randomized controlled trials rather than from population-based studies.

We previously described an improvement in survival among HIV-infected people after combination antiretrovi-

ral therapy became available in British Columbia.[10] We further demonstrated that the rate of progression from initiation of combination therapy to a diagnosis of primary AIDS or to death among patients who initially received an ERA-I regimen (double-drug regimen with zidovudine, didanosine or zalcitabine) was nearly 2-fold greater than the rate among those who initially received an ERA-II regimen (2 nucleoside analogue reverse transcriptase inhibitors [NRTIs] including lamivudine or stavudine, or both).[10,11] We report here a further improvement in survival among HIV-infected patients after initiation of therapy with triple-drug regimens in British Columbia.

Methods

HIV/AIDS Drug Treatment Program

The distribution of antiretroviral therapy in British Columbia has been described in detail elsewhere.[10,12] In brief, antiretroviral drugs have been centrally distributed at no cost to eligible HIV-infected patients since 1986. In October 1992 the HIV/AIDS Drug Treatment Program became the responsibility of the British Columbia Centre for Excellence in HIV/AIDS. From 1986 to 1998 a total of 5005 HIV-positive people in the province received antiretroviral therapy. Of these, 4171 have been enrolled in the HIV/AIDS Drug Treatment Program and, as of December 1998, 2384 were receiving antiretroviral therapy. The HIV/AIDS Drug Treatment Program remains the only free source of antiretroviral medications in the province.

The British Columbia Centre for Excellence in HIV/AIDS distributes antiretroviral drugs on the basis of specific guidelines generated by the Therapeutic Guidelines Committee. Since 1992 the guidelines have made available double-drug antiretroviral therapy for people with a CD4+ cell count of 0.35×10^9/L or less. In December 1995 double-drug therapy was made available to everyone with a CD4+ cell count of 0.50×10^9/L or less. In June 1996 the centre adopted antiretroviral therapy guidelines based on plasma viral load, consistent with those put forward by the International AIDS Society — USA.[7] In brief, people who had never received antiretroviral therapy and who had a plasma viral load of more than 100 000 HIV-1 RNA copies/mL were offered triple-drug regimens (i.e., 2 NRTIs plus a protease inhibitor or a non-NRTI), whereas those with a plasma viral load of 5000 to 100 000 HIV-1 RNA copies/mL were offered 2 NRTIs. If the plasma viral load was less than 5000 HIV-1 RNA copies/mL, quarterly monitoring was advised. If the load was 20 000 HIV-1 RNA copies/mL or more while the patient was receiving therapy, a change to a new triple-drug regimen was recommended. In July 1997 the guidelines were revised to allow access to triple-drug therapy for all patients who had never received antiretroviral drugs and had a plasma viral load of 5000 HIV-1 RNA copies/mL or more. The British Columbia Centre for Excellence in HIV/AIDS recommends that viral load be monitored at baseline, at 4 weeks following the initiation of antiretroviral therapy and every 3 months thereafter.

Data collection

Physicians enrolling an HIV-positive person into the HIV/AIDS Drug Treatment Program must complete a drug request enrolment form. The form acts as a legal prescription and compiles information on the patient's address and enrolling physician, past 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 therapeutic guidelines.[9] Approved prescriptions are renewed every 2 months. At the time of enrolment each participant is asked to complete a survey and program consent form, and the physician is asked to complete a clinical staging form. Participant surveys and clinical staging forms are completed annually. The clinical staging form records participant-specific information on HIV/AIDS-related conditions according to the World Health Organization's clinical staging system.[13]

We restricted our analysis to HIV-positive men and women who had never received antiretroviral therapy and were first prescribed such therapy between Oct. 1, 1994, and Dec. 31, 1996. The antiretroviral drugs available during the study period are listed in Table 1. Study subjects were divided into 2 groups: those who initially received a double-drug regimen with 2 NRTIs including lamivudine or stavudine, or both (ERA-II regimen) and those who initially received a triple-drug regimen containing 2 NRTIs plus a protease inhibitor or a non-NRTI (ERA-III regimen). We did not include patients initially prescribed ERA-I therapy (monotherapy or double-drug combination therapy with zidovudine, didanosine or zalcitabine). In order to limit the effect of changing therapeutic guidelines and management, we restricted our analysis to ERA-II subjects whose antiretroviral therapy began between Oct. 1, 1994, and May 31, 1996, and to ERA-III subjects whose therapy began between Oct. 1, 1994, and Dec. 31, 1996. The timeframe for ERA-II subjects represents a period when double-drug therapy was generally recommended; the timeframe for ERA-III subjects reflects the availability of nevirapine through compassionate release, small research protocols or open-access programs.

Table 1: Antiretroviral drugs available during the study period

Drug	Year first available
Nucleoside analogue reverse transcriptase inhibitors (NRTIs)	
Zidovudine	1986
Didanosine	1992
Zalcitabine	1992
Stavudine	1993*
Lamivudine	1994*
Protease inhibitors	
Saquinavir	1996
Indinavir	1996
Ritonavir	1996
Nelfinavir	1997*
Non-NRTIs	
Nevirapine	1994*
Delavirdine	1997*

*Available through compassionate release, small research protocols or open-access programs.

Outcome measures

The primary and secondary outcome measures in our analysis were death and a primary AIDS diagnosis respectively. Deaths and diagnoses of AIDS during the follow-up period were identified on a continual basis from physician reports and through record linkages carried out with the British Columbia AIDS registry and Division of Vital Statistics. We used all-cause mortality in this analysis because more than 90% of deaths among participants were directly attributable to HIV-related causes. Baseline clinical information, including primary AIDS diagnosis and use of prophylaxis for *Pneumocystis carinii* pneumonia and *Mycobacterium avium* infection, was obtained directly from the HIV/AIDS Drug Treatment Program records. Information on clinical illnesses defined according to the 1993 case definition for AIDS of the US Centers for Disease Control and Prevention[14] were collected from physician reports and record linkages carried out in collaboration with the provincial and national AIDS registries.

Statistical analysis

We followed the intent-to-treat principle — subjects were retained in their initial treatment groups irrespective of whether ERA-II participants subsequently switched to regimens available in ERA-III — because it provided us with the most conservative estimate of true treatment effect. We did not adjust for ERA-II patients who switched to ERA-III therapies. Cumulative mortality and AIDS-free survival rates were estimated using Kaplan–Meier methods. These methods provide estimates of survival probabilities, product-limit estimates and graphical presentation of survival distribution. Survival functions were compared with a log-rank test. Study subjects were followed up until Dec. 31, 1997. Those lost to follow-up were censored as of the date of last known contact with the HIV/AIDS Drug Treatment Program.

Statistical comparisons were conducted using distribution-free methods.[15] Categorical variables and ordinal and skewed continuous variables were compared with the Mantel–Haenszel and the Wilcoxon rank sum tests respectively. The Fisher's exact test was used for 2×2 contingency tables in which any of the expected cell frequencies was less than 5.

Cox-proportional hazard models were used to estimate the hazard of death and AIDS-free survival in the ERA-II group relative to the ERA-III group, with associated 95% confidence intervals (CIs).[16] We adjusted for a number of prognostic variables at baseline: prophylaxis for *P. carinii* pneumonia or *M. avium* infection, AIDS diagnosis, CD4+ cell count, sex and age. The variables prophylaxis for *P. carinii* pneumonia or *M. avium* infection, AIDS diagnosis and sex were treated as fixed binary variables (Yes or No). Age (in years) and CD4+ cell count (per 0.10 cell count $\times 10^9$/L) at initiation of therapy were modelled as continuous variables. All reported p values are 2-tailed.

Results

A total of 504 people in British Columbia were given antiretroviral therapy for the first time between Oct. 1, 1994, and Dec. 31, 1996. We excluded 4 subjects from our analysis because they were less than 18 years old. The remaining 500 subjects (312 receiving an ERA-II regimen and 188 an ERA-III regimen) were followed by 151 physicians and lived in 43 cities and towns across the province.

Data on how HIV infection had been acquired were available for 271 of the participants (165 in the ERA-II group and 106 in the ERA-III group). We found no difference between the ERA-II and ERA-III groups in the proportion who acquired HIV infection through homosexual contact (132 and 79 respectively), through injection drug use (29 and 20 respectively) or through heterosexual contact, blood transfusions or use of blood products (27 and 23 respectively). These categories were not mutually exclusive.

The overall median follow-up was 20 months (interquartile range 14 to 23 months); the median follow-up was 21 months (interquartile range 20 to 23 months) in the ERA-II group and 14 months (interquartile range 13 to 17 months) in the ERA-III group ($p < 0.001$). Two (0.4%) of the study subjects, both in the ERA-II group, were lost to follow-up. In addition, 156 (50.0%) of the subjects in the ERA-II group switched to ERA-III regimens before the end of the study period. The median time to switching from ERA-II to ERA-III regimens was 13 months (interquartile range 8 to 16 months).

Of the 312 subjects in the ERA-II group 298 (95.5%) were receiving zidovudine and lamivudine and 14 (4.5%) were receiving lamivudine along with stavudine, didanosine or zalcitabine. All ERA-II participants started antiretroviral therapy with lamivudine, and 4 (1.3%) started with lamivudine and stavudine. One (0.3%) of the ERA-II subjects started therapy in 1994, 50 (16.0%) in 1995 and 261 (83.7%) in 1996.

In the ERA-III group, 8 drug regimens were prescribed during the study period: lamivudine–stavudine–indinavir (49 [26.1%]), zidovudine–lamivudine–indinavir (42 [22.3%]), zidovudine–lamivudine–saquinavir (39 [20.7%]), zidovudine–zalcitabine–saquinavir (26 [13.8%]), zidovudine–didanosine–nevirapine (19 [10.1%]) and another regimen containing 2 NRTIs plus indinavir or saquinavir (13 [6.9%]). For almost half of the ERA-III subjects (93 [49.5%]) the initial regimen included indinavir, for 76 (40.4%) it included saquinavir, and for 19 (10.1%) it contained nevirapine. None of the initial ERA-III regimens contained ritonavir. Eight (4.3%) of the ERA-III subjects started therapy in 1994, 33 (17.6%) in 1995 and 147 (78.2%) in 1996.

Table 2 shows the baseline demographic and clinical characteristics of the study subjects. The only significant difference between the 2 groups was the proportion of women (12.8% in the ERA-II group v. 5.9% in the ERA-III group, $p = 0.013$).

Overall, 97 subjects (61 in the ERA-II group and 36 in

the ERA-III group) had AIDS at baseline. The AIDS-defining illnesses in the 2 groups were: *P. carinii* pneumonia, 33 subjects (34.0%); other opportunistic infections, 25 (25.8%); wasting syndrome, 5 (5.2%); neurologic disease, 3 (3.1%); Kaposi's sarcoma, 16 (16.5%); and other malignant diseases, 4 (4.1%). The remaining 11 people (11.3%) had reported having 2 or more AIDS-defining illnesses. There was no statistical difference between the 2 groups in the proportion of subjects with Kaposi's sarcoma, *P. carinii* pneumonia or other opportunistic infections.

As of Dec. 31, 1997, 40 patients had died (35 in the ERA-II group and 5 in the ERA-III group), for a crude mortality rate of 8.0%. The cumulative mortality rates at 12 months were 7.4% (95% CI 5.9% to 8.9%) in the ERA-II group and 1.6% (95% CI 0.7% to 2.5%) in the ERA-III group (log rank $p = 0.003$) (Fig. 1). The likelihood of death was more than 3 times higher among the patients in the ERA-II group than among those in the ERA-III group (mortality risk ratio 3.82 [95% CI 1.48 to 9.84], $p = 0.006$).

Table 3 presents the univariate and multivariate analyses of baseline factors associated with death in the 500 subjects. In the final multivariate model, use of an ERA-III regimen ($p = 0.016$) and a higher CD4+ cell count ($p = 0.002$) at baseline were independently associated with longer survival after adjustment for age, sex, baseline AIDS diagnosis and prophylaxis for *P. carinii* pneumonia or *M. avium* infection. The adjusted mortality risk ratio from this multivariate model indicated that the likelihood of death was 3.21 times higher (95% CI 1.24 to 8.30, $p = 0.016$) among the subjects in the ERA-II group than among those in the ERA-III group.

We repeated our analysis of survival excluding subjects who were initially prescribed triple-drug regimens containing a non-nucleoside reverse transcriptase inhibitor. This was done to determine the effect on survival of protease inhibitor use only. After adjustment for the prognostic variables (prophylaxis for *P. carinii* pneumonia or *M. avium* infection, AIDS diagnosis, CD4+ cell count, sex and age at baseline) the likelihood of death was 3.62 times higher (95% CI 1.27 to 10.33, $p = 0.016$) among patients in the ERA-II group than among those in the ERA-III

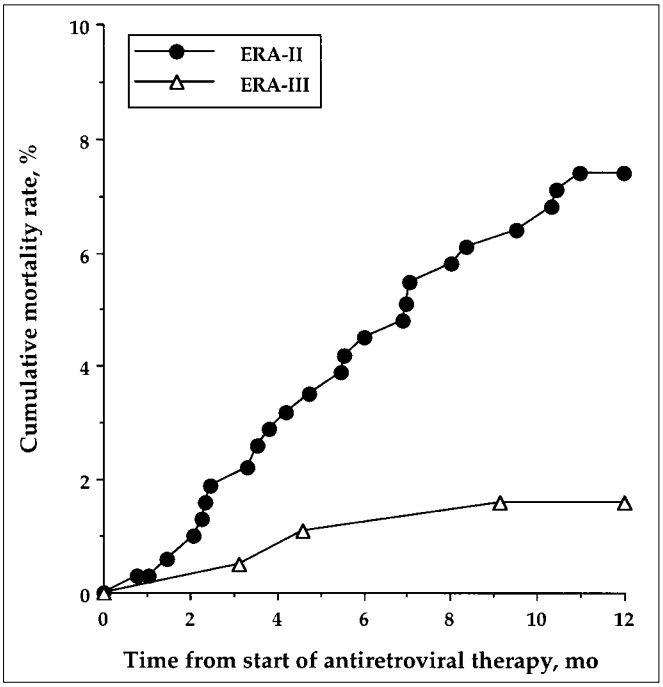

Fig. 1: Cumulative mortality at 12 months among 500 HIV-positive patients for whom antiretroviral therapy with a double- or triple-drug regimen was initiated between Oct. 1, 1994, and Dec. 31, 1996. ERA-II = double-drug regimen with 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs) including lamivudine or stavudine, or both; ERA-III = triple-drug regimen with 2 NRTIs plus a protease inhibitor or a non-NRTI.

Table 2: Characteristics of HIV-positive subjects, by treatment group*

Characteristic	ERA-II therapy	ERA-III therapy	*p* value
Age, yr			
Median	38	37	0.852
Range	33–43	32–44	
Sex, no. (and %)			
Female	40 (12.8)	11 (5.9)	0.013
Male	272 (87.2)	177 (94.1)	
CD4+ cell count, $\times 10^9$/L)			
Median	0.230	0.250	0.055
Interquartile range	0.100–0.355	0.130–0.420	
Prophylaxis for *Pneumocystis carinii* pneumonia or *Mycobacterium avium* infection			
No	284 (91.0)	170 (90.4)	0.822
Yes	28 (9.0)	18 (9.6)	
AIDS diagnosis at baseline			
No	251 (80.5)	152 (80.9)	0.912
Yes	61 (19.5)	36 (19.1)	

*ERA-II = double-drug regimen with 2 NRTIs including lamivudine or stavudine, or both; ERA-III = triple-drug regimen with 2 NRTIs plus a protease inhibitor or a non-NRTI.

Table 3: Univariate and multivariate analyses of the baseline factors associated with death among the 500 HIV-positive subjects

Variable	Crude risk ratio (and 95% CI)	Adjusted risk ratio* (and 95% CI)
Antiretroviral therapy (ERA-II v. ERA-III)	3.82 (1.48–9.84)	3.21 (1.24–8.30)
AIDS diagnosis (yes v. no)	2.19 (1.13–4.25)	1.17 (0.56–2.47)
Age, yr (continuous)	1.02 (0.99–1.05)	1.02 (0.98–1.05)
Prophylaxis for *P. carinii* pneumonia or *M. avium* infection (yes v. no)	1.92 (0.81–4.58)	0.90 (0.35–2.31)
Sex (male v. female)	0.82 (0.32–2.09)	0.83 (0.32–2.13)
CD4+ cell count (per 0.10 cell count $\times 10^9$/L)	0.62 (0.49–0.79)	0.65 (0.49–0.85)

*Multivariate analysis.

group. We conducted a further analysis restricted to the 438 subjects (293 in the ERA-II group and 145 in the ERA-III) who had never participated in a clinical trial of antiretroviral therapy. After adjustment for the prognostic variables specified earlier, the likelihood of death was 4.43 times higher (95% CI 1.34 to 14.64, $p = 0.014$) among the ERA-II subjects than among the ERA-III subjects.

Finally, we repeated all relevant analyses with the time from the start of antiretroviral therapy to AIDS diagnosis or death as the outcomes of interest. These analyses were done to determine the effect of triple-drug therapy on AIDS-free survival and were restricted to the 403 subjects (251 in the ERA-II group and 152 in the ERA-III group) who were AIDS-free at baseline. As of Dec. 31, 1997, 19 people had a diagnosis of AIDS (15 in the ERA-II group) and 24 people had died (21 in the ERA-II group). The AIDS-defining illnesses were: *P. carinii* pneumonia (3 [15.8%]), *Candida* infections (2 [10.5%]), cytomegalovirus infection (4 [21.1%]), other opportunistic infections (4 [21.1%]), Kaposi's sarcoma (2 [10.5%]), neurologic disease (1 [5.3%]), and other diagnoses (3 [15.8%]). The cumulative rates of progression to AIDS or death at 12 months were 9.6% (95% CI 7.7% to 11.5%) of patients in the ERA-II group and 3.3% (95% CI 1.8% to 4.8%) of patients in the ERA-III group (log rank $p = 0.006$) (Fig. 2). After adjustment for the prognostic variables, the likelihood of progression to AIDS or death at 12 months was 2.37 times higher (95% CI 1.04 to 5.38, $p = 0.040$) among patients in the ERA-II group than among those in the ERA-III group. The results were unchanged when subjects who initiated therapy with a non-nucleoside transcriptase inhibitor were removed from the analysis. In this case, the likelihood of progression to AIDS or death was 2.41 times higher (95% CI 1.00 to 5.78, $p = 0.050$) among subjects in the ERA-II group. Similar findings were observed when all 58 AIDS-free participants (18 receiving an ERA-II regimen and 40 an ERA-III regimen) who had ever participated in a clinical trial of antiretroviral therapy were removed from this analysis: the likelihood of progression to AIDS or death was 4.26 times higher (95% CI 1.30 to 14.03, $p = 0.017$) among the ERA-II subjects.

Interpretation

Our study demonstrated a statistically significant decrease in mortality and increase in AIDS-free survival at 12 months among HIV-infected men and women who received a triple-drug antiretroviral regimen. Subjects receiving an ERA-II regimen were more than 3 times more likely to die than those receiving an ERA-III regimen. These results remained statistically significant even after adjustment for the prognostic variables prophylaxis for *P. carinii* pneumonia or *M. avium* infection, CD4+ cell count, AIDS diagnosis, sex and age at initiation of antiretroviral therapy. Of the participants who were free of AIDS at baseline, the likelihood of progression to AIDS or death was at least twice as high among those receiving an ERA-II regimen than among subjects receiving an ERA-III regimen.

It is reassuring that the magnitude of the clinical benefit observed in our population-based study is comparable to that found in randomized clinical trials. In our study, 95% of the subjects in the ERA-II group received a regimen containing lamivudine in combination with zidovudine; 48% of the subjects in the ERA-III group received indinavir and lamivudine along with either zidovudine or stavudine. The clinical benefit seen in our study was of the same magnitude as that described in a major randomized trial in which the addition of indinavir and lamivudine to zidovudine or stavudine led to significantly slower progression to AIDS or death (risk ratio 0.50; 95% CI 0.33 to 0.76) and death (risk ratio 0.43; 95% CI 0.19 to 0.99).[3]

The results of our study are also in agreement with those from a recently reported clinic-based study that demonstrated reduced morbidity and mortality after including a protease inhibitor in a triple-drug regimen.[17] However, unlike our study, this one only enrolled patients from 8 selected specialized infectious disease clinics within large urban centres. We included individuals followed by 151 physicians in 43 cities and towns across British Columbia. Also, antiretroviral therapy in our study was given to all participants free of charge within a setting of universal health care. Furthermore, in order to characterize the

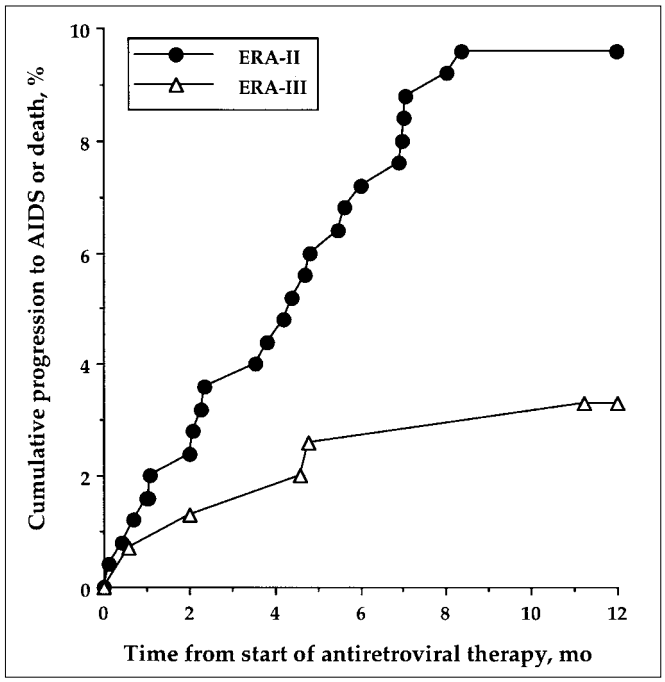

Fig. 2: Cumulative rates of progression to AIDS or death at 12 months among 403 patients who were AIDS free at baseline and for whom antiretroviral therapy was first prescribed between Oct. 1, 1994, and Dec. 31, 1996.

population-based impact of the revised therapeutic guidelines, we limited our study to patients who had never had antiretroviral therapy before enrolment.[7] Finally, in contrast to the clinic-based study, we had complete follow-up information for more than 99% of our subjects through the various linkages to provincial and federal databases established within our program.

Given the population-based nature of our study, no statistical differences were observed between the 2 treatment groups at baseline in terms of prophylaxis for *P. carinii* pneumonia or *M. avium* infection, AIDS diagnosis, CD4+ cell count or age. Although women were underrepresented in the ERA-III group, sex was not a significant risk factor in our multivariate analysis after we controlled for the other prognostic factors. The difference in access to ERA-III regimens among men and women in British Columbia may reflect the fact that women are more likely to be recently infected and that women who are injection drug users are less likely to seek antiretroviral therapy than male injection drug users in BC.[18] However, given the nature of our health care system, with antiretroviral therapy, laboratory monitoring and medical follow-up provided at no cost, access to care is not likely an important confounding variable.[19]

We used the intent-to-treat principle in all of our analyses. Since half of the patients initially receiving an ERA-II regimen switched to an ERA-III regimen during the study period, the magnitude of the clinical benefit demonstrated in our analysis for ERA-III regimens over ERA-II regimens is likely an underestimate.

Nelfinavir and the non-nucleoside reverse transcriptase inhibitors were available only through randomized controlled trials or expanded access programs, which typically did not allow for the use of these agents as first-line therapy during the study period. This explains the underrepresentation of these drugs as first-line therapy in our study. To what extent wider availability of these drugs will contribute to further decreases in morbidity and mortality among HIV-positive people remains to be established.

In summary, our results have demonstrated a significant improvement in short-term survival and decrease in morbidity among HIV-infected men and women whose first-line therapy was a triple-drug regimen containing 2 NRTIs plus a protease inhibitor or a non-NRTI. This finding remained statistically significant even after adjustment for prognostic factors. The magnitude of the clinical benefit associated with triple-drug regimens in our study is likely an underestimate of the true treatment effect. The long-term impact of triple-drug antiretroviral therapy on survival, however, remains to be fully characterized.

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