Rates of Disease Progression by Baseline CD4 Cell Count and Viral Load After Initiating Triple-Drug Therapy

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TRIPLE-DRUG COMBINATION ANTIRETROVIRAL therapy has been shown to dramatically decrease morbidity and mortality in symptomatic and asymptomatic human immunodeficiency virus type 1 (HIV) infected individuals. As a result, triple-drug regimens have been widely adopted for the treatment of HIV infection starting in 1996. Recommendations for the initiation of antiretroviral therapy are largely based on CD4 T lymphocyte cell count and plasma HIV RNA levels. The relative prognostic value of each marker following initiation of therapy has not been fully characterized.

Objective To describe rates of disease progression to death and AIDS or death among patients starting triple-drug antiretroviral therapy, stratified by baseline CD4 cell count and HIV RNA levels.


Main Outcome Measure Cumulative mortality rates from the initiation of triple-drug antiretroviral therapy to September 30, 2000, determined using various CD4 cell and plasma HIV RNA thresholds.

Results As of September 30, 2000, 82 patients had died of AIDS-related causes, for a crude AIDS-related mortality rate of 6.7%. The product limit estimate (SE) of the cumulative mortality rate at 12 months was 2.9% (0.5%). In univariate analyses, a prior diagnosis of acquired immunodeficiency syndrome (AIDS), CD4 cell count, use of protease inhibitors, and HIV RNA level were associated with mortality. There was no difference in mortality by age or sex. Only CD4 cell count remained statistically significant in the multivariate analysis. After controlling for AIDS, protease inhibitor use, and plasma HIV RNA level at baseline, patients with CD4 cell counts of less than 50/µL were 6.67 (95% confidence interval [CI], 3.61-12.34) times and those with counts of 50/µL to 199/µL were 3.41 (95% CI, 1.93-6.03) times more likely to die than those with counts of at least 200/µL.

Conclusion Our data demonstrate uniformly low rates of disease progression to death and AIDS or death among patients starting antiretroviral therapy with CD4 cell counts of at least 200/µL. In our study, disease progression to death and AIDS or death was clustered among patients starting therapy with CD4 cell counts less than 200/µL.

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sion to AIDS or death as a function of baseline CD4 cell counts and HIV RNA levels in a population-based cohort of HIV-infected individuals initiating triple-drug antiretroviral therapy regimens. We further sought to identify a possible threshold at which the short-term clinical benefit derived from triple-drug regimens became compromised.

METHODS

HIV/AIDS Drug Treatment Program

The distribution of antiretroviral therapy in the province of British Columbia has been described. In short, antiretroviral medications have been centrally distributed at no cost to eligible HIV-infected individuals since 1986. In October 1992, the distribution of antiretroviral agents became the responsibility of the HIV/AIDS Drug Treatment Program of the British Columbia Centre for Excellence in HIV/AIDS. This antiretroviral drug distribution program remains the only free source of antiretroviral medications in the province. The center's HIV/AIDS drug treatment program, including mandated analyses such as those presented herein, has received ethical approval from the University of British Columbia ethics review committee at its St Paul's Hospital site. The program also conforms with the province's Freedom of Information and Protection of Privacy Act.

The center distributes antiretroviral drugs based on specific guidelines generated by the therapeutic guidelines committee. Since 1992, the HIV/AIDS drug treatment program has made available double combination therapy for individuals with CD4 cell counts of 350/µL or less. In December 1995, double-combination therapy was made available to everyone with CD4 cell counts of 500/µL or less. In June 1996 the center adopted plasma viral load-driven antiretroviral therapy guidelines, consistent with those put forward by the International AIDS Society—USA. In brief, antiretroviral therapy-naive individuals with plasma viral load higher than 100 000 copies/mL were offered triple-drug regimens (ie, 2 nucleosides plus a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor) while those with plasma viral loads from 5000 to 100 000 copies/mL were offered dual nucleoside therapy. If the plasma viral load was lower than 5000 copies/mL, quarterly monitoring was advised. Consistent with contemporary practice, the center guidelines were revised in July 1997 to recommend triple-combination therapy for all antiretroviral-naive individuals with plasma HIV RNA levels higher than 5000 copies/mL or CD4 cell counts less than 500/µL. The center recommends that plasma HIV RNA levels be monitored at baseline, at 4 weeks after starting antiretroviral therapy, and every 3 months thereafter. Plasma viral loads were measured using the Ampli
cor HIV-1 Monitor (Roche Diagnostic Systems, Branchburg, NJ).

All 3 classes of antiretroviral agents are currently available through the program including nucleoside reverse transcriptase inhibitors, zidovudine, lamivudine, didanosine, zalcitabine, stavudine, and abacavir; protease inhibitors, indinavir, nelfinavir, saquinavir, and ritonavir; and nonnucleoside reverse transcriptase inhibitors, delavirdine, nevirapine, and efavirenz. Zidovudine has been available since 1986. The other 4 nucleoside analogs were made available over a 4-year period: didanosine and zalcitabine in 1992, stavudine in 1993, and lamivudine in 1994. The dates for lamivudine and stavudine reflect the availability of these therapies through compassionate release. Saquinavir, the first protease inhibitor licensed in Canada, has been available since 1996. Indinavir and ritonavir became available later in the same year and nelfinavir was licensed in 1998. Delavirdine and nevirapine were licensed in Canada in 1998. Efavirenz became available a year later in 1999. Nelfinavir, delavirdine, and nevirapine have also been available through expanded access programs to participants in the HIV/AIDS drug treatment program.

Data Collection

All HIV-positive men and women in the current study were entered into the center's HIV/AIDS drug treatment program when they were first prescribed antiretroviral agents by any physician practicing within the province of British Columbia. Physicians enrolling an HIV-positive individual are required to complete a drug request enrollment form. The form acts as a legal prescription and is used to compile baseline information including past HIV-specific drug history, CD4 cell counts, plasma HIV RNA levels, current drug requests, and enrolling-physician data. Each request is reviewed by a qualified practitioner to ensure that it meets the center's guidelines. Typically, persons receiving antiretroviral therapy in the province are monitored by physicians at intervals no longer than 3 months at which time prescriptions are renewed or modified. At the time of the initial refill, participants are asked to provide informed consent for accessing electronic medical records (which may be used in studies of medical care utilization [not relevant to the analyses given herein]), and to complete a participant survey, which elicits information on sociodemographic characteristics, clinical and health status, and alternative therapy use. Both the consent form and participant survey are optional and a participant's refusal to do either will in no way limit his/her access to antiretroviral medications. At the same time, the treating physicians are asked to complete a clinical staging form using the World Health Organization (WHO) clinical staging system. For all program participants, a complete prospective profile of antiretroviral therapy is maintained, including the medications prescribed, the amount dispensed, the dose, and the prescription-fill dates.

Outcome Measures

The primary end point in this analysis was death. Deaths occurring during the follow-up period were identified on a continuous basis from physician reports and through record linkages carried out with the British Columbia Division of Vital Statistics. Deaths from accidental causes were censored at time of death and classified as nonevents in
this primary analysis. However, our results remained unchanged when all-cause mortality was considered.

Statistical Analysis
This analysis was restricted to HIV-positive men and women who were antiretroviral naive and were first prescribed triple-drug antiretroviral therapy between August 1, 1996, and September 30, 1999. Study subjects were initially prescribed triple-drug combination therapy with regimens consisting of 2 nucleoside reverse transcriptase inhibitors in addition to a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor. For the purposes of analysis, we followed the intent-to-treat principle; thus, all eligible subjects were included when they were first dispensed antiretroviral agents regardless of whether they later discontinued or modified their therapeutic regimen.

Cumulative mortality rates were estimated using Kaplan-Meier methods. Event-free subjects were right censored as of September 30, 2000. Participants were not followed up after this date and those lost to follow-up were censored at the date of last known contact with the HIV/AIDS drug treatment program. The CD4 cell count and HIV RNA levels were arbitrarily divided into 7 levels. The log-rank test was then used to compare between pairs of survival curves at consecutive levels of CD4 cell count and HIV RNA. In addition, we used the relative hazards from the Cox proportional hazard models and visual inspection to examine whether consecutive CD4 cell count and HIV RNA groups could be pooled when not significantly different.

Two plasma HIV RNA levels (<100000 copies/mL) and 3 CD4 cell counts (<50, 50-199, ≥200/μL) were obtained after systematically collapsing groups that were not significantly different. Cox proportional hazards regression was then used to calculate univariate and adjusted relative hazards and 95% confidence intervals (CIs). Time since the initiation of therapy was measured in days. A forward stepwise technique was used in the selection of covariates. The final fixed model also adjusted for AIDS diagnosis, use of protease inhibitor, and HIV RNA level, which were all significant univariately. The testing of interactions and nonproportionality of hazards were explored in our modeling. The assumption of proportional hazards was validated by inspection of log (-log [survival function]) estimates against log time plots. No interactions were entered into the final model because they did not improve fit of the model.

A multivariate model including all significant variables in the univariate analysis was used to estimate adjusted relative hazards. A number of salient baseline prognostic variables were examined in this analysis including: plasma HIV RNA levels, CD4 cell count, protease inhibitor use in the initial regimen, time of initiation of therapy, a prior diagnosis of AIDS, age, and sex. Protease inhibitor use (yes vs no), sex (man vs woman), time of initiation of therapy (after vs before July 1997), and a prior diagnosis of AIDS (yes vs no) were treated as fixed binary variables. The time of July 1997 was used as a temporal cutoff in our analysis because this reflected the time when the therapeutic guidelines for antiretroviral therapy were changed to the current standard of care in this province. Only patients who initiated antiretroviral therapy with triple-drug regimens were eligible in this study. Age (in years) was treated as a continuous variable. Plasma HIV RNA levels and CD4 cell counts were categorized into the groupings of 2 and 3 levels that were described above.

Analyses were performed using SAS software version 6.0 (SAS, Cary, NC). All tests of significance were 2 sided, with a P value of less than .05 indicating that an association was statistically significant.

RESULTS
Between August 1, 1996, and September 30, 1999, a total of 1353 antiretroviral-naive participants aged 18 years and older started taking triple-combination therapy consisting of 2 nucleoside reverse transcriptase inhibitors in addition to a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor. Of these, 134 (9.9%) were excluded in this analysis for not having both baseline CD4 cell count and plasma HIV RNA level measures available within 6 months prior to the start of antiretroviral therapy. No difference in age, sex, AIDS at baseline, and subsequent mortality was observed between the study sample and those excluded. However, persons excluded from this analysis were more likely to be taking protease inhibitors (85.9% vs 74.6%; P = .004). The total study sample was based on the remaining 1219 subjects (1031 [84.6%], men; 188 [15.4%], women). Of these subjects, 858 (70.4%) initiated triple-combination antiretroviral therapy after July 1997. The overall median follow-up time of the 1219 study subjects was 27.7 months (interquartile range [IQR], 17.9-37.6 months). At baseline, the median age of participants was 37.0 years (IQR, 31.9-43.5 years); median CD4 cell count, 280/μL (IQR, 130-420/μL); and median plasma HIV RNA level, 120000 copies/mL (IQR, 40 000-310 000 copies/mL).

Differences were observed in those participants who initiated triple-antiretroviral therapy prior to and after the change in the center’s therapeutic guidelines in July 1997. Most expected was the significant difference in follow-up times (P < .001). Those enrolled up until July 1997 had considerably longer median follow-up times compared with those who enrolled after this date (40.8 months [IQR, 38.2-44.5 months] vs 22.5 months [IQR, 16.1-30.7 months]). Also expected were the differences in HIV RNA plasma viral loads between the 2 groups. The median HIV RNA plasma viral load determinations were 170 000 copies/mL (IQR, 110 000-380 000 copies/mL) vs 85 700 copies/mL (IQR, 27 600-260 000 copies/mL), respectively, for those who started before or after July 1997 (P < .001). Finally, we observed
Disease progression by CD4 cell count

A total of 8555 CD4 cell count and 9372 HIV RNA level determinations were collected for study participants over the study period. The median number of CD4 cell count and HIV RNA level determinations per participant were 6 (IQR, 3-10) and 7 (IQR, 4-11), respectively. Over the study period, the proportion of participants contributing CD4 cell counts ranged from 76% to 78% for each 6-month period and for HIV RNA levels it ranged from 88% to 89% over the same 6-month interval.

A total of 158 study subjects (13.0%) had a prior diagnosis of AIDS at baseline. The total number and proportion of the AIDS-defining illnesses were Pneumocystis carinii pneumonia, 51 (32.3%); other opportunistic infections, 65 (41.1%); wasting syndrome, 9 (5.7%); neurologic disease, 6 (3.8%); Kaposi sarcoma, 21 (13.3%); and other malignancies, 6 (3.8%).

Study participants were first prescribed 27 different triple-combination antiretroviral regimens. The most frequently prescribed regimen was a stavudine-lamivudine-indinavir combination prescribed for 361 participants (29.6%), followed by a zidovudine-lamivudine-indinavir combination for 295 (24.2%), and a stavudine-lamivudine-nevirapine combination for 145 (11.9%). Of the participants, 909 (74.6%) initiated therapy with a protease inhibitor. The protease inhibitors used in the initial regimen included: 688 (75.7%), indinavir; 106 (11.7%), nelfinavir; 79 (8.7%), saquinavir; and 36 (4.0%), ritonavir. The rest of the 310 study participants (25.4%) had a regimen that included a non-nucleoside reverse transcriptase inhibitor. Among these subjects, 290 (93.5%) were taking nevirapine while 10 (3.2%) used efavirenz, and 10 (3.2%) used delavirdine. A total of 130 (10.7%) commenced therapy in 1996, 436 (35.8%) in 1997, 368 (30.2%) in 1998, and 285 (23.4%) in 1999.

As of September 30, 2000, a total of 104 deaths were identified in the study population. Twenty-two of these were not attributed to HIV and were censored as non-events at the time of death. These 22 deaths included 5 suicides and 17 accidental drug overdoses. The remaining 82 deaths gave a crude AIDS-related mortality rate of 6.7%. The product limit estimate (SE) of the cumulative mortality rate at 12 months was 2.9% (0.5%). As expected, the crude mortality rates were higher among those who initiated triple therapy prior to July 1997. The crude mortality rates for the 2 periods were 10.8% vs 5.0%, respectively. The product limit estimate (SE) of the cumulative mortality rate at 12 months was 3.9% (0.5%) for those who initiated up until July 1997, and 2.5% (0.5%) for those started after this date (log rank test, P = .11).

In Figure 1, we divided CD4 cell count and HIV RNA levels into 7 arbitrary categories to examine whether any consecutive CD4 cell count or HIV RNA level strata could be pooled. Among 1219 participants, 94 (7.7%) had CD4 cell counts less than 25; for 48 (3.9%), 25 to 49; for 102 (8.4%), 50 to 99; for 199 (16.3%), 100 to 199; for 327 (26.8%), 200 to 349; for 257 (21.1%), 350 to 499; and for 192 (15.8%) 500/µL or more. The product limit estimates (SE) of the cumulative mortality rate at 12 months for these 7 categories were 1.1% (1.1%), 1.6% (0.7%), 4.0% (0.4%), and 0% (0.0%), respectively.

Log rank tests and Cox proportional hazard risk ratios were examined to determine if baseline CD4 cell count could be pooled in the current study population as observed in Figure 1. These new groupings have 142 participants (11.6%) with CD4 cell counts less than 50, 301 (24.7%) from 50 to 199, and 776 (63.7%) of 200 cells/µL or more (Figure 2). The product limit estimates (SE) of the cumulative mortality rate at 12 months for these 3 categories were 8.6% (2.4%), 5.8% (1.4%), and 0.8% (0.3%), respectively.

With regards to the plasma HIV RNA levels, similar techniques were used to pool 7 consecutive HIV RNA level strata from Figure 1 into 2 new groups. As shown in Figure 2, these 2 groups were made up of 541 participants (44.4%) with levels less than 100000 copies/mL and 678 (55.6%) with levels of at least 100000 copies/mL. The product limit estimates (SE) of the cumulative mortality rate at 12 months for these 2 categories were 1.9% (0.5%) and 4.0% (0.8%), respectively. Statistically significant differences in survival were noted among the 3 CD4 strata (all log rank, P < .05) and the 2 HIV RNA level strata (log rank, P < .001).

Table 1 and Table 2 summarize the relative hazards from the Cox proportional hazard models to determine whether consecutive CD4 cell count and HIV RNA level strata could be pooled when not significantly different. For example, as shown in Table 1 (baseline strata), there was significant difference in survival between CD4 cell count groups of 100 to 199 and 200 to 299 9999; for 83 (6.8%), 300 000 to 399 9999; and for 231 (18.9%), 400 000 copies/mL or more. The product limit estimates (SE) of the cumulative mortality rate at 12 months for these 7 categories were 1.1% (1.1%), 2.0% (0.9%), 1.2% (0.8%), 4.8% (1.3%), 2.9% (1.6%), 2.4% (1.7%), and 4.4% (1.4%), respectively.
served these regroupings to be statistically different. As shown in Table 2, we conducted a similar analysis for HIV RNA levels and obtained groupings higher and lower than 100,000/mL.

To examine how survival probabilities vary with certain combinations of CD4 cell count and plasma HIV RNA level groupings, participants were stratified into 6 different groups, dividing each of the 3 CD4 cell count groupings from Figure 2 into a stratum with low (<100,000 copies/mL) and high (≥100,000 copies/mL) baseline HIV RNA levels. Figure 3 shows 6 survival curves representing those 6 combinations of CD4 cell count and HIV RNA level. There was no statistically significant difference in survival for the low and high HIV RNA level subgroups within the low CD4 cell count group (log rank, \( P = .71 \)). Likewise, there was no statistical significance between the survival curves for those with CD4 cell counts from 50 to 199/µL (log rank, \( P = .21 \)) and 200/µL or more (log rank, \( P = .07 \)). The results were also unchanged if we used a plasma HIV RNA cutoff level of 50,000 or 200,000 copies/mL.

The univariate and multivariate analyses of the baseline factors associated with the time to death are presented in Table 3. Only a prior diagnosis of AIDS, use of protease inhibitors, HIV RNA levels, and CD4 cell counts were found to be baseline predictors of survival in the...
univariate analysis. Participants who initiated therapy with a protease inhibitor were 2.02 (95% CI, 1.01-4.07; P < .05) times more likely to die than those who did not start therapy with this class of drug while persons with a prior AIDS diagnosis were 2.57 (95% CI, 1.58-4.15; P < .001) times more likely to die than those without a diagnosis of AIDS. In comparison with subjects with HIV RNA levels of less than 100,000 copies/mL, participants who initiated therapy with 100,000 copies/mL or more were 2.58 (95% CI, 1.53-4.35; P < .001) times more likely to die. In regards to CD4 cell count, those who initiated therapy with CD4 cell counts of less than 50/µL were 7.97 (95% CI, 4.58-13.88; P < .001) times more likely to die and those with CD4 cell counts between 50 to 199/µL were 3.84 (95% CI, 2.22-6.63; P < .001) times more likely to die than persons with baseline counts of at least 200/µL.

In a multivariate model, CD4 cell count at baseline remained the only statistically significant factor associated with shorter survival. Protease inhibitor use, AIDS, and plasma HIV RNA level at baseline were not significant in the adjusted analyses. After controlling for the 3 variables that were significant in the univariate analysis but not in the multivariate one, those with CD4 cell counts of less than 50/µL were 6.67 (95% CI, 3.61-12.34; P < .001) times more likely to die and those with counts of 50 to 199/µL were 3.41 (95% CI, 1.93-6.03; P < .001) times more likely to die than those with CD4 cell counts of 200/µL or more. We repeated our analysis adjusting for a proxy measure of adherence to antiretroviral

Figure 2. Cumulative Progression to Death for Treatment-Naive Subjects Starting Antiretroviral Therapy by Combined Strata of CD4 Cell Counts and Viral Load Levels

Kaplan-Meier product limit estimates of cumulative progression to death for 1219 subjects starting antiretroviral therapy between August 1, 1996, and September 30, 1999. The diminishing number of patients at risk at each subsequent time interval is due to death, being lost to follow-up, or being censored as of September 30, 2000.

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agents. For this exercise, we limited our measure of adherence to the first year of therapy and estimated it by dividing the number of months of medication dispensed by the number of months of follow-up in the first year. In these analyses, CD4 cell count at baseline was again found to be the only independent predictor of shorter survival. Those with CD4 cell counts of less than 50/µL were 8.30 (95% CI, 4.44-15.54; P<.001) times more likely to die and those with counts of 50 to 199/µL were 3.85 (95% CI, 2.17-6.81; P<.001) times more likely to die than those with CD4 cell counts of 200/µL or more.

In another subanalysis, we repeated our univariate and multivariate survival analyses to investigate the influence of time-dependent covariates on mortality in this population. In this analysis, a number of prognostic variables were treated as time-dependent variables including plasma HIV RNA levels, CD4 cell count, initial protease inhibitor use, and a prior diagnosis of AIDS. Protease inhibitor use (yes vs no) and a prior diagnosis of AIDS (yes vs no) were treated as binary time-dependent variables. Plasma HIV RNA level (<100000 and ≥100000 copies/mL) and CD4 cell count (<50, 50-199, ≥200/µL) were treated as categorical time-dependent variables. The last 3 variables of age (in years), sex (men vs women), and time of initiation of therapy (before vs after July 1997) were treated as fixed covariates. Table 4 shows the univariate and multivariate variables significant in this time-dependent analysis. This time-dependent analysis shows that CD4 cell count and HIV RNA levels are prognostic factors associated with HIV-related mortality. For both CD4 cell count and HIV RNA levels, the relationship is more pronounced in time-dependent analysis than when only baseline values were used in the model. Those with CD4 cell counts of <50/µL were 15.74 (95% CI, 8.83-28.04; P<.001) times more likely to die, and those with counts of 50 to 199/µL were 2.27 (95% CI, 1.20-4.29; P=.01) times more likely to die than those with CD4 cell counts of at least 200/µL. In comparison, those with HIV RNA levels of 100000 copies/mL or more were 2.17 (95% CI, 1.33-3.54; P=.002) times more likely to die than those with HIV RNA levels less than 100000 copies/mL.

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 1061 subjects who were AIDS-free at baseline. As of September 30, 2000, a total of 82 events were identified, 25 primary AIDS diagnoses and 57 deaths. After adjusting for protease inhibitor use and plasma HIV RNA levels, those with CD4 cell counts of less than 50/µL were 8.40 (95% CI, 4.67-15.12; P<.001) times more likely to progress to AIDS or to die and those with counts of 50 to 199/µL were 4.55 (95% CI, 2.71-7.63; P<.001) times more likely to progress to AIDS or to die than those with CD4 cell counts 200 cells/µL or more. It is reassuring to note that our findings were unchanged in this subanalysis in which patients with a baseline diagnosis of AIDS were excluded. Like in the original multivariate analysis, CD4 cell count was the only statistically significant prognostic factor in the final model. All risk ratios were similar when we restricted our analyses to patients initiating therapy after July 31, 1997.

**COMMENT**

Our results demonstrate uniformly low rates of disease progression to AIDS and

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**Table 1. Cox Proportional Hazard Analysis to Determine CD4 Cell Count Groupings**

<table>
<thead>
<tr>
<th>CD4 Cell Count /µL</th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
<th>Risk Ratio (95% CI)</th>
<th>Cox-Model P Value</th>
<th>Log Rank P Value†</th>
<th>Overall Log Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline strata</td>
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<tr>
<td>&lt;50</td>
<td>94</td>
<td>21</td>
<td>24.54 (5.75-104.67)</td>
<td>&lt;.001</td>
<td>.59</td>
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<tr>
<td>25 to 49</td>
<td>48</td>
<td>8</td>
<td>19.28 (4.09-90.80)</td>
<td>&lt;.001</td>
<td>.20</td>
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<tr>
<td>50 to 99</td>
<td>102</td>
<td>11</td>
<td>11.00 (2.44-49.61)</td>
<td>.002</td>
<td>.99</td>
<td></td>
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<tr>
<td>100 to 199</td>
<td>199</td>
<td>20</td>
<td>10.80 (2.52-46.23)</td>
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<td>.003</td>
<td>.001</td>
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<tr>
<td>200 to 349</td>
<td>327</td>
<td>12</td>
<td>3.77 (0.84-16.86)</td>
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<td>.68</td>
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<tr>
<td>350 to &lt;500</td>
<td>257</td>
<td>8</td>
<td>3.10 (0.66-14.62)</td>
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<td>.11</td>
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<td>≥500</td>
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<td>2</td>
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<td>&lt;50</td>
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<td>29</td>
<td>7.97 (4.58-13.88)</td>
<td>&lt;.001</td>
<td>.003</td>
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<tr>
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<td>301</td>
<td>31</td>
<td>3.84 (2.22-6.63)</td>
<td>&lt;.001</td>
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<tr>
<td>≥200</td>
<td>776</td>
<td>22</td>
<td>1.00</td>
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*Among 1219 persons first prescribed any triple-combination antiretroviral therapy between August 1, 1996, and September 30, 1999. CI indicates confidence interval; ellipses, not applicable.
†Comparisons for each pair of consecutive categories.

**Table 2. Cox Proportional Hazard Analysis to Determine Human Immunodeficiency Virus Type 1 (HIV) RNA Groupings**

<table>
<thead>
<tr>
<th>HIV RNA Level, Copies/mL</th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
<th>Risk Ratio (95% CI)</th>
<th>Cox-Model P Value</th>
<th>Log Rank P Value†</th>
<th>Overall Log Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline strata</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>&lt;10000</td>
<td>97</td>
<td>3</td>
<td>1.00</td>
<td></td>
<td>.82</td>
<td>.03</td>
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<tr>
<td>10000-49999</td>
<td>259</td>
<td>7</td>
<td>0.85 (0.22-3.30)</td>
<td>.82</td>
<td>.32</td>
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<td>50000-99999</td>
<td>185</td>
<td>8</td>
<td>1.40 (0.37-5.29)</td>
<td>.62</td>
<td>.16</td>
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<tr>
<td>100000-199999</td>
<td>258</td>
<td>23</td>
<td>2.53 (0.76-8.44)</td>
<td>.13</td>
<td>.84</td>
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</tr>
<tr>
<td>200000-299999</td>
<td>106</td>
<td>10</td>
<td>2.73 (0.75-9.22)</td>
<td>.13</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>300000-399999</td>
<td>83</td>
<td>8</td>
<td>2.71 (0.72-10.24)</td>
<td>.14</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>≥400000</td>
<td>231</td>
<td>23</td>
<td>3.02 (0.91-10.05)</td>
<td>.07</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Combined strata</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100000</td>
<td>541</td>
<td>18</td>
<td>1.00</td>
<td></td>
<td>.82</td>
<td>.03</td>
</tr>
<tr>
<td>≥100000</td>
<td>678</td>
<td>64</td>
<td>2.58 (1.53-4.35)</td>
<td>&lt;.001</td>
<td>.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Among 1219 persons first prescribed any triple-combination antiretroviral therapy between August 1, 1996, and September 30, 1999. CI indicates confidence interval; ellipses, not applicable.
†Comparisons for each pair of consecutive categories.
death over a median of 28 months among patients starting antiretroviral therapy with CD4 cell counts 200/µL or more. Disease progression to AIDS and death clustered among patients starting therapy with CD4 cell counts less than 200/µL in our cohort. Rates of disease progression and death, in this cohort of individuals receiving antiretroviral therapy, were independent of age, sex, prior AIDS diagnosis, protease inhibitor use, and plasma HIV RNA levels.

Our study confirms that low CD4 cell count is an important marker of disease progression, especially death. In this analysis, we identified 3 strata for which differences in mortality were statistically significant in our population: less than 50, 50 to 199, and 200/µL or more. As noted, CD4 cell count was the only independent predictor of mortality in the final multivariate model. Our data also indicate that plasma HIV RNA level alone was not an independent predictor of survival among patients initiating triple-combination antiretroviral therapy. We identified 2 strata for which a survival benefit could be distinguished statistically in individuals in the univariate analysis: less than 100,000, and 100,000 copies/mL or more. When all prognostic factors that were found to be statistically significant in the univariate analysis were put into a multivariate model, plasma HIV RNA level was not independently associated with survival. These findings would appear to be in conflict with the results of natural history studies and published guidelines for the use of antiretroviral therapy. In fact, our results are easy to reconcile with natural history studies, which were conducted in untreated cohorts. When such cohorts are analyzed, HIV RNA levels are an important independent predictor of disease progression and death, as well as CD4 cell counts. In contrast, in a clinical environment in which triple-therapy regimens are used, plasma HIV RNA levels lose their prognostic effect given that the treatment itself is uniformly able to decrease HIV RNA levels independent of sex, age, or whether the regimen was protease inhibitor–based or nonnucleoside reverse transcriptase inhibitor–based. Subjects who initiated therapy with a protease inhibitor were more likely to die in the univariate analysis, but the use of protease inhibitor was based on the worst prognosis. This is later confirmed by the fact that protease inhibitor use was not significant after adjustment. The fact that the CD4 cell count remains the single independent predictor of survival in this population-based cohort of treated individuals would suggest that there is a threshold beyond which immune reconstitution may be compromised. In our time-dependent subanalysis, CD4 cell count remained an important predictor of mortality while AIDS diagnosis did not; HIV RNA level was also shown to be a prognostic factor associated with HIV-related mortality. This would be expected because both CD4 cell count and plasma HIV RNA level are markers of disease progression. A possible limitation of these observations relates to the fact that patients are not randomly assigned to immediate or deferred therapy and, thus, it is at least possible that the same factors promoting later initiation of therapy may be com-

**Figure 3. Cumulative Progression to Death for Treatment-Naive Subjects Starting Antiretroviral Therapy by Combinations of CD4 Cell Counts and Viral Load Levels**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>CD4 Cell Count, Cells/µL</th>
<th>HIV RNA, Copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥200</td>
<td>&lt;100,000</td>
<td>416 403 389 362 314 243 166 88</td>
</tr>
<tr>
<td></td>
<td>≥100,000</td>
<td>360 348 334 288 244 206 155</td>
</tr>
<tr>
<td>50-199</td>
<td>&lt;100,000</td>
<td>97 90 87 62 38 30 17</td>
</tr>
<tr>
<td></td>
<td>≥100,000</td>
<td>204 193 186 161 120 93 68</td>
</tr>
<tr>
<td>&lt;50</td>
<td>&lt;100,000</td>
<td>28 24 22 17 10 10 6</td>
</tr>
<tr>
<td></td>
<td>≥100,000</td>
<td>114 104 100 80 55 47 34</td>
</tr>
</tbody>
</table>

Kaplan-Meier product limit estimates of cumulative progression to death for 1219 subjects starting antiretroviral therapy between August 1, 1996, and September 30, 1999. The diminishing number of patients at risk at each subsequent time interval is due to death, being lost to follow-up, or being censored as of September 30, 2000.
promising its effectiveness. In this regard, we have not been able to identify an independent effect of sex, age, AIDS diagnosis, or initial therapy use. Also, we have previously shown that CD4 cell count remains an important predictor of mortality even after adjusting for adherence levels over the first year of triple-combination antiretroviral treatment.27

It is important to emphasize that the optimal time for initiation of therapy cannot be elucidated from this work. It is at least conceivable that differences in treatment effectiveness may develop among subgroups of patients with CD4 counts higher than 200/µL if followed up for a longer time. Our results do indicate that there is a critical threshold below which the short-term clinical effectiveness of antiretroviral therapy is at least partially compromised. Specifically, we found that those participants who initiated triple-drug therapy with CD4 cell counts lower than 200/µL were at least 3 times more likely to die than those whose cell counts were higher than this limit. Although these data cannot be used to establish the optimal time to start therapy, our results do clearly argue that deferral of treatment beyond a CD4 cell count of 200/µL would be associated with an increased short-term rate of disease progression to AIDS or death.

There are several features of our study that should be highlighted. Our study was carried out within a province-wide treatment program in which all individuals had access to medical attention, combination antiretroviral therapy, and laboratory monitoring free of charge. We are confident, therefore, that our results are not influenced by access to therapy-related issues, which have often compromised the interpretation of similar population-based or cohort-based studies. Secondly, this study was based on treatment-naive individuals; thus, our results are not confounded by previous therapy use. Third, delayed reporting was not likely a factor because the vast majority of deaths were reported within 3 months of death through active follow-up with physicians and hospitals and regular linkages.23,24 Fourth, our results were consistent whether we used death or progression to AIDS or death as an end point. Fifth, our study results were not affected by changes in the therapeutic guidelines that had occurred during the study period. Our findings remained the same if the analysis was restricted to patients who started after July 31, 1997, when triple-drug antiretroviral therapy became the standard of care for all HIV-infected individuals in the province. Finally, we were not able to explore the possible lead-time biases associated with the decision of starting therapy at various CD4 cell count strata in this population-based study. For most individuals in this study, we do not know their exact date of seroconversion. The lead time between HIV seroconversion and antiretroviral treatment may also vary considerably among patients. Therefore, the overall effect of treatment on the natural history of the disease cannot be determined. As a result, our data cannot characterize the full impact of antiretroviral therapy on the total survival time after HIV seroconversion. However, estimates of disease progression in seroprevalent cohorts of untreated individuals have been published, and they are strikingly different from those seen in our treated cohort. For example, data from the Multicenter AIDS Cohort Study demonstrated that 85% of gay men with CD4 cell counts lower than 200/µL and plasma viral loads higher than 110,000 copies/mL at or near entry into the study would progress to AIDS or death within 28 months.10 In com-

Table 3. Univariate and Multivariate Cox Proportional Hazard Analysis of Baseline Factors Associated With Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio (95% Confidence Interval)</th>
<th>Crude</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>1.02 (1.00-1.04)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1.45 (0.70-3.02)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Start of 3-drug therapy (after July 1997 vs before)</td>
<td>0.70 (0.44-1.09)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Protease inhibitor use (yes vs no)</td>
<td>2.02 (1.01-4.07)</td>
<td>1.44 (0.71-2.94)</td>
<td>. . .</td>
</tr>
<tr>
<td>AIDS diagnosis (yes vs no)</td>
<td>2.57 (1.58-4.15)</td>
<td>1.04 (0.62-1.75)</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*Among 1219 persons first prescribed any triple-combination antiretroviral therapy between August 1, 1996, and September 30, 1999. Ellipses indicate not applicable; HIV, human immunodeficiency virus type 1; and AIDS, acquired immunodeficiency syndrome.
†Excludes all prognostic variables that were not statistically significant in the univariate analysis.

Table 4. Univariate and Multivariate Cox Proportional Hazard Analysis of Time-Dependent Factors Associated With Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio (95% Confidence Interval)</th>
<th>Crude</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever had an AIDS diagnosis before or during the study period (yes vs no)</td>
<td>2.58 (1.61-4.13)</td>
<td>1.09 (0.66-1.79)</td>
<td></td>
</tr>
<tr>
<td>Continuous CD4 cell count per µL</td>
<td>2.68 (1.44-4.98)</td>
<td>2.27 (1.20-4.29)</td>
<td></td>
</tr>
<tr>
<td>Continuous plasma viral load, copies/mL</td>
<td>22.35 (13.61-36.71)</td>
<td>15.74 (8.83-28.04)</td>
<td></td>
</tr>
</tbody>
</table>

*Among 1219 persons first prescribed any triple-combination antiretroviral therapy between August 1, 1996, and September 30, 1999. AIDS indicates acquired immunodeficiency syndrome; HIV, human immunodeficiency virus type 1; and triple-combination antiretroviral treatment.27
parison, only 22% of men and women in our study with the same baseline parameters would progress to AIDS or death. Our data are also consistent with those from Lee et al 28 who demonstrate a progressive improvement in survival time after a diagnosis of AIDS from 1984 to 1997 in the United States. 28 

Our results have been recently confirmed by 3 independent cohorts from the University of Alabama, the Johns Hopkins University, and the Centers for Disease Control and Prevention. 29-31 In each of these cohorts, disease progression to AIDS or death was clustered among patients initiating antiretroviral therapy with CD4 cell counts lower than 200/µL. Similar to our results, in the 2 cohorts in which plasma HIV RNA levels were available, these were not found to independently predict clinical outcomes after the initiation of therapy. Taken together these data have important implications for clinical management of HIV-infected individuals. First, the emphasis for monitoring of HIV-infected individuals prior to initiation of antiretroviral therapy should be placed on CD4 cell counts. Second, a greater effort should be made to encourage HIV-infected individuals to start antiretroviral therapy before their CD4 cell count reaches 200/µL. Third, although the optimal time to start treatment cannot be derived from these data, the lower strata beyond which short-term survival becomes compromised is clearly defined by these results, and as such, our results should contribute to narrow this important debate. Finally, these results provide rates of disease progression to AIDS or death in treated individuals that compare favorably with those generated in the era prior to availability of triple-combination therapy. Such information should be quite valuable when counseling HIV-infected individuals when their therapy is initiated. 

In summary, our data demonstrate uniformly low rates of disease progression to AIDS and death at a median of 28 months among patients starting antiretroviral therapy with CD4 cell counts of at least 200/µL. Disease progression to AIDS and death clustered among patients starting therapy with CD4 cell counts less than 200/µL in our cohort. Rates of disease progression and death were independent of age, sex, prior AIDS diagnosis, protease inhibitor use and plasma HIV RNA levels. 


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REFERENCES 

30. Sterling TR, Chaisson RE, Bartlett LG, Moore RD. CD4+ lymphocyte level is better than HIV-1 plasma viral load in determining when to initiate HAART. From: 8th Conference on Retroviruses and Opportunistic Infections; February 4-8, 2001; Chicago, Ill. Abstract 519. 
31. Kaplan J, Hanson D, Karon J, et al. Late initiation of antiretroviral therapy (at CD4+ lymphocyte count <200 cells/µL) is associated with increased risk of death. From: 8th Conference on Retroviruses and Opportunistic Infections; February 4-8, 2001; Chicago, Ill. Abstract 520.