



CHANGES IN BOTH CD4 CELL COUNTS AND HIV-1 RNA LEVELS PREDICT SUBSEQUENT DISEASE

PROGRESSION AMONG HIV-1 INFECTED PERSONS INITIATING ANTIRETROVIRAL THERAPY

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OBJECTIVE

To describe the impact of changes in CD4 cell count and HIV-1 RNA levels on disease progression among HIV-1 infected persons initiating antiretroviral therapy.

METHODS

This analysis was restricted to HIV-positive men and women who were antiretroviral naïve 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 including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. In this study all eligible subjects were included as they were first dispensed antiretrovirals 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 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. Cox proportional hazards regression was then used to calculate univariate and adjusted relative hazards and 95% confidence intervals. 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-1 RNA, which were all significant univariately. The testing of interactions and non-proportionality of hazards were explored in our modelling. The assumption of proportional hazards was validated by inspection of log (-log (survival function)) estimates against log time plots.

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-1 RNA levels, CD4 cell count, protease-inhibitor use in the initial regimen, time of initiation of therapy, a prior diagnosis of AIDS, age, and gender. Protease-inhibitor use (yes versus no), gender (male versus female), time of initiation of therapy (after versus before July 1997), and a prior diagnosis of AIDS (yes versus no) were treated as fixed binary variable. The time point 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 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. Two plasma HIV-1 RNA (<100,000 and 100,000 copies/ml) and three CD4 cell count (< 50, 50 to 199, 200 cells/mm³) levels were used in this analysis.

RESULTS

Between August 1st, 1996 and September 30th, 1999, a total of 1,353 antiretroviral naïve participants aged 18 years and over started on triple combination therapy. Of these, 134 (9.9%) were excluded in this analysis for not having both baseline CD4 and plasma HIV-1 RNA levels measures available within six months prior to the start of antiretroviral therapy. The study was based on the remaining 1,219 subjects [1,034 (84.8%) men and 185 (15.2%) women]. Of these subjects 858 (70.4%) initiated triple combination antiretroviral therapy after July 1997. The overall median follow-up time of the 1,219 study subjects was 27.7 months (inter quartile range = 17.9 - 37.6 months).

At baseline, the median age of participants was 37.0 years (inter quartile range: 31.9 - 43.5), median CD4 cell count 280 cells/mm³ (inter quartile range: 130 - 420 cells/mm³) and median plasma HIV-1 RNA level was 120,000 copies per mL (inter quartile range: 40,000 to 310,000 copies per mL). Study participants were first prescribed 27 different triple combination antiretroviral regimens. Over half of these participants (909 [74.6%]) initiated therapy with a protease-inhibitor. The rest of the study participants (310 [25.4%]) had a regimen that included a non-nucleoside reverse transcriptase inhibitor. 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-1 and were censored as non-events at the time of death. The remaining 82 deaths gave a crude mortality rate of 6.7%. The product limit estimate of the cumulative mortality rate at 12 months was 2.9% (±0.5%).

In univariate analyses, only a prior diagnosis of AIDS, use of protease inhibitors, HIV-1 RNA levels and CD4 cell counts were found to be baseline predictors of survival in the univariate analysis. Participants who initiate therapy with a protease inhibitor were 2.02 (95% CI: 1.01, 4.07; p = 0.048) 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 < 0.001) times more likely to die than those without a diagnosis of AIDS. In comparison to subjects with HIV-1 RNA levels of <100,000 copies per mL, participants who initiated therapy with 100,000 copies per mL were 2.58 (95% CI: 1.53, 4.35; p < 0.001) times more likely to die. In regards CD4 cell count, those who initiated therapy with CD4 cell counts < 50 cells/mm³ were 7.97 (95% CI: 4.58, 13.88; p < 0.001) times more likely to die and those with CD4 cell counts between 50 to 199 cells/mm³ were 3.84 (95% CI: 2.22, 6.63; p < 0.001) times more likely to die than persons with baseline counts of 200 cells/mm³ or more.

In multivariate analyses, only CD4 cell count at baseline remained the only statistically significant factor associated with shorter survival. After controlling for the three variables that were significant in the univariate analysis but not in the multivariate one, those with CD4 cell counts of <50 cells/mm³ were 6.67 (95% CI: 3.61, 12.34; p < 0.001) times more likely to die and those with counts of 50 to 199 cells/mm³ were 3.41 (95% CI: 1.93, 6.03; p < 0.001) times more likely to die than those with CD4 cell counts 200 cells/mm³.

In the time dependent analysis, both plasma HIV-1 RNA levels and CD4 cell count were independent predictors of mortality. In this analysis, a number of prognostic variables were treated as time-dependent variables including: plasma HIV-1 RNA levels, CD4 cell count, initial protease-inhibitor use, and a prior diagnosis of AIDS. Protease-inhibitor use (yes versus no and a prior diagnosis of AIDS (yes versus no) were treated as binary time-dependent variables. Plasma HIV-1 RNA (<100,000 and 100,000 copies/ml) and CD4 cell count (< 50, 50 to 199, 200 cells/mm³) were treated as categorical time-dependent variables. The last three variables age (in years), gender (male versus female), and time of initiation of therapy (before versus after July 1997), were treated as fixed covariates.

Table 1 shows the univariate and multivariate variables significant in this time-dependent analysis. This time dependent analysis shows that CD4 cell count and HIV-RNA are prognostic factors associated with HIV-related mortality. For both CD4 and HIV-RNA 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 cells/mm³ were 15.74 (95% CI: 8.83, 28.04; p < 0.001) times more likely to die and those with counts of 50 to 199 cells/mm³ were 2.27 (95% CI: 1.20, 4.29; p < 0.001) times more likely to die than those with CD4 cell counts 200 cells/mm³. In comparison, those with HIV-1 RNA levels 100,000 copies/ml were 2.17 (95% CI: 1.33, 3.54; p < 0.001) were likely to die than those with HIV-1 RNA levels < 100,000 copies/ml.

Table 1: Univariate and multivariate Cox proportional hazard analysis of the time dependent factors associated with survival among 1,219 persons first prescribed any triple combination antiretroviral therapy between August 1, 1996 and September 30, 1999.

Variable	Risk Ratios (RR)	
	Crude [RR, (95% CI)]	Adjusted* [RR, (95% CI)]
Ever had an AIDS diagnosis		
Before or during the study period		
[Yes versus no]	2.58 (1.61, 4.13)	1.09 (0.66, 1.79)
Continuous CD4 cell count (cells/mm³)		
≥200	1.00	1.00
50 to 199	2.68 (1.44, 4.99)	2.27 (1.20, 4.29)
<50	22.35 (13.61, 36.71)	15.74 (8.83, 28.04)
Continuous plasma viral load (copies/ml)		
<100,000	1.00	1.00
≥100,000	5.17 (3.30, 8.11)	2.17 (1.33, 3.54)

CONCLUSION

Our data demonstrated a continued clustering of deaths among persons initiating therapy with CD4 cell counts <200 cells/mm³. In this time-dependent analysis we show that changes in CD4 counts and HIV-1 RNA levels are markers of disease progression independent of therapeutic class and AIDS diagnosis. This finding should be expected as both CD4 cell count and plasma HIV-1 RNA level are markers of disease progression.