Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up

Robert S. Hogg[a,b], Katherine Heath[a,b], David Bangsberg[c], Benita Yip[a], Natasha Press[a], Michael V. O'Shaughnessy[a,d] and Julio S.G. Montaner[a,e]

Objective: To characterize the impact of intermittent use of triple drug antiretroviral therapy on survival.

Design, setting and participants: Population-based analysis of 1282 antiretroviral therapy naive HIV-positive individuals aged 18 years and older in British Columbia who started triple-combination therapy between August 1996 and December 1999. Therapy use was estimated by dividing the number of months of medications dispensed by the number of months of follow-up. Intermittent therapy was defined as the participant having obtained less than 75% of their medication in the first 12 months.

Main outcome measure: Cumulative all-cause mortality rates from the start of triple drug antiretroviral therapy to 30 September 2000.

Results: As of 30 September 2000, 106 subjects had died. Cumulative mortality was 3.9% ($\pm$ 0.5%) at 12 months. In a multivariate model, after controlling for other variables that were significant in the univariate analyses each 100 cell decrement in baseline CD4 cell count and the intermittent use of antiretroviral drugs were associated with increased mortality with risk ratios of 1.31 [95% confidence interval (CI), 1.16–1.49; $P < 0.001$] and 2.90 (95% CI, 1.93–4.36; $P < 0.001$), respectively. In order to control for downward drift, intermittent use of therapy was measured over the first year whereas other factors were measured at the end of year 1. After adjusting for all other factors, those participants who used antiretroviral drugs intermittently were 2.97 times (95% CI, 1.33–6.62; $P = 0.008$) more likely to die.

Conclusion: Our study demonstrates that even after adjusting for other prognostic factors intermittent use of antiretroviral therapy was associated with increased mortality.

AIDS 2002, **16**:1051–1058

Keywords: nucleoside reverse transcriptase inhibitors, protease inhibitors, non-nucleoside reverse transcriptase inhibitor, antiretroviral therapy, intermittent use of antiretrovirals, mortality, effectiveness, population based cohort

From the [a]BC Centre for Excellence in HIV/AIDS, the [b]Department of Health Care and Epidemiology, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada, the [c]Epidemiology and Prevention Interventions Center, Division of Infectious Diseases and the Positive Health Program, San Francisco General Hospital, California, USA, the [d]Department of Pathology and Laboratory Medicine, and the [e]Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada.

Requests for reprints to: R. Hogg, Division of Epidemiology and Population Health, BC Centre for Excellence in HIV/AIDS, 608-1081 Burrard Street, Vancouver, B.C. V6Z 1Y6, Canada.

Received: 12 July 2001; revised: 20 December 2001; accepted: 7 January 2002.

Introduction

The virologic and immunologic efficacy of triple-combination antiretroviral therapy currently used in the treatment of HIV infected patients has been shown in clinical trials [1–3]. Cohort and population based studies have now confirmed the impact of triple-combination therapy in terms of reductions in AIDS-related death rates, opportunistic infections, and hospitalization [4,5].

Despite these advances, the full benefit of antiretroviral regimens as reported in clinical trials remains difficult to achieve in clinical practice due in part to imperfect adherence [6]. Incomplete adherence to antiretroviral treatment has been shown to be an important cause of premature virologic failure [7]. Patients taking antiretroviral drugs intermittently or at reduced doses often experience suboptimal drug levels thus increasing the likelihood of drug resistance [8,9]. Moreover, resistance to one drug is frequently associated with cross-resistance to other members of the same class [10,11] thus limiting future treatment options. This problem is compounded by the possibility that multidrug resistant viruses can be transmitted from HIV-positive persons on antiretroviral therapy to sexual and injecting drug user networks [6,12].

While the clinical efficacy of triple-combination antiretroviral regimens and the importance of adherence in achieving viral suppression appear well established, the long term impact of intermittent use of antiretroviral therapy on disease progression in a previously untreated population of men and women remains unclear. We undertook the present study to ascertain the impact of intermittent use of antiretroviral therapy on survival within a population based cohort with free access to medical services, including antiretroviral therapy.

Methods

HIV/AIDS drug treatment program

The delivery of antiretroviral therapy in the province of British Columbia, Canada has been described elsewhere [5,13]. In this province, antiretroviral drugs have been centrally distributed at no cost to eligible HIV-infected individuals since 1986. In October 1992, the HIV/AIDS Drug Treatment Program became the responsibility of the British Columbia Centre for Excellence in HIV/AIDS (the Centre). The Centre's HIV/AIDS Drug Treatment Program remains the only free source of antiretroviral medications in the province and one of the few population-based HIV drug distribution systems in the world.

The Centre distributes antiretroviral medications based on specific guidelines generated by the Therapeutic Guidelines Committee. In June 1996 the Centre adopted plasma HIV-1 RNA driven antiretroviral therapy guidelines, consistent with those put forward by the International AIDS Society, USA [14]. Consistent with contemporary practice [15], the Centre guidelines were revised in July 1997 to recommend triple-combination therapy for all antiretroviral naive individuals with plasma HIV-1 RNA levels $\geqslant 5000$ copies/ml or CD4 cell count $< 500 \times 10^6$/l. The Centre recommends that plasma HIV-1 RNA levels be monitored at baseline, at 4 weeks after starting antiretroviral therapy and every 3 months thereafter.

All three classes of antiretroviral drug were available through the program during the study period including: nucleoside reverse transcriptase inhibitors, zidovudine, lamivudine, didanosine, zalcitabine, stavudine, and abacavir; protease inhibitors (PI), indinavir, nelfinavir, saquinavir, and ritonavir; and non-nucleoside reverse transcriptase inhibitors (NNRTI), delavirdine, nevirapine, and efavirenz. Plasma HIV-1 RNA was measured using the Amplicor HIV-1 Monito (Roche Diagnostic Systems, Branchburg, New Jersey, USA).

Data collection

HIV-positive men and women are entered into the Centre's HIV/AIDS Drug Treatment Program when they are first prescribed antiretroviral agents by any physician practicing within the province. Physicians enrolling an HIV-positive individual must complete a drug request enrolment form. The form acts as a legal prescription and compiles baseline information, including the applicant's address, past HIV-specific drug history, CD4 cell counts, plasma HIV-1 RNA, current drug requests, and enrolling physician data. Each request is reviewed by a qualified physician to ensure that the prescription meets the Centre's guidelines [14]. Typically, persons receiving antiretroviral therapy are monitored by physicians at intervals no longer than 3 months at which time prescriptions are renewed or modified. At the time of the first medication refill participants are asked to provide informed consent for accessing electronic medical records (which may be used for health utilization studies, but is not relevant to the analyses in this study), and complete a participant survey, which elicits information on sociodemographic characteristics, clinical and health status, and alternative therapy use. Both the consent form and the participant survey are optional and participant's refusal to do either will not limit his or her access to free antiretroviral therapy. At the same time, the treating physicians are asked to complete a clinical staging form using the World Health Organization (WHO) clinical staging system [16]. For all program participants a complete prospective profile of antiretroviral therapy is maintained, including the medications prescribed, the amount dispensed, and the prescription fill dates.

Outcome measures and explanatory variables

The primary endpoint in this analysis was all-cause mortality. 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. The secondary endpoint in this analysis was a primary diagnosis of AIDS and/or death in AIDS-free subjects. As with the primary endpoint, primary AIDS diagnoses occurring over the study period were obtained either from the physician or the provincial AIDS registry.

The following baseline explanatory variables were investigated: age, sex, CD4 cell count, plasma HIV-1 RNA levels, prior AIDS diagnosis, PI use, current or past history of injecting drug use, physician experience, and intermittent therapy use. Physician experience was defined as the number of HIV-positive patients the physician had previously treated at the time the study subject was enrolled into the HIV/AIDS Drug Treatment Program. Estimates of intermittent use of antiretroviral therapy are based on medications dispensed, not prescribed. Antiretrovirals are prescribed and dispensed according to approved therapeutic guidelines. Patients receive new prescriptions at various time intervals ranging from monthly to, at most, every 3 months. For this exercise we limit our measure of intermittent use of antiretroviral drugs to the first year of therapy and estimated it by dividing the number of months' worth of medications dispensed by the number of months of follow-up in the first 12 months, expressed as percent. Intermittent use of therapy in this study represents the gap between the time that the previous medication supply ran out until the next refill date, and/or until the last contact date with the program.

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 1 August 1996 and 31 December 1999. Study subjects were initially prescribed triple drug combination therapy with regimens including a PI or a NNRTI. For the purposes of analysis we followed the intent-to-treat principle; thus all eligible subjects were included as they were first dispensed antiretroviral drugs regardless of whether they later discontinued or modified their therapeutic regimen.

Cumulative mortality rates were estimated using Kaplan–Meier methods. Survival curves were compared between groups with the log-rank test. Event-free subjects were right censored as of 30 September 2000. Participants included in this analysis 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 hazard regression was used to model the simultaneous effect of prognostic variables on survival [17]. In this analysis, we adjusted for a number of salient prognostic explanatory variables at baseline. The variables sex, prior AIDS diagnosis, PI use, and current or past history of injecting drug use were treated as fixed binary variables (yes versus no), age (in years) was treated as a continuous variable, and CD4 cell count (per 100 cell decrement), HIV-1 RNA levels (per $\log_{10}$ increment), physician experience (per 100 patients followed) and intermittent use of antiretroviral therapy (less than 75% of their medication in the first 12 months) were treated as ordinal variables. The results of our analyses were unchanged when other cut-offs for physician experience were used in this study.

We then used the magnitude of the relative hazards and their statistical significance from the Cox proportional hazard models to search for any potential thresholds in intermittent use of antiretroviral therapy. Therapy use was first divided into nine levels: 15–24%, 25–34%, 35–44%, 45–54%, 55–64%, 65–74%, 75–84%, 85–94%, and finally, $\geqslant 95\%$ used as the control group. We then used the magnitude of the relative hazards and their statistical significance from the Cox proportional hazard models to search for any potential thresholds. As noted in Table 1, when this methodology was applied we observed a threshold in risk ratio at the 65–74% level of intermittent use of antiretroviral drugs, at which point the risk ratio ($P = 0.092$) was marginally significant when compared against the comparison group with $\geqslant 95\%$ use of antiretroviral therapy. In this analysis, participants with $< 75\%$ use of antiretroviral drugs in the first year were pooled and then compared against those $\geqslant 75\%$ use.

A subanalysis restricted to participants with at least 1 year of follow-up was conducted to adjust for the potential confounding of downward drift (i.e., that lesser use of antiretroviral drugs in the first year may be a marker for rapid progression in this study group). In this survival analysis the first 12-month period was used to determine intermittent use according to the above mentioned cut-off and the other baseline prognostic explanatory variables (age, CD4 cell count, plasma HIV-1 RNA levels, prior AIDS diagnosis, PI use and physician experience) were measured at the end of year 1. As in the first set of analyses, both the primary and secondary outcomes were examined prospectively.

Results

Between 1 August 1996 and 31 December 1999, a total of 1397 antiretroviral naive participants aged 18 years and over initiated triple-combination therapy consisting of two nucleoside reverse transcriptase in-

Table 1. Cox proportional hazard analysis to determine intermittent therapy groupings[a].

Therapy use in the first year (%)	Patients (n = 1282)	Deaths (n = 106)	Risk ratio	95% Confidence interval	*P*
Baseline					
15–24	83	10	2.04	1.03–4.04	0.041
25–34	66	9	2.46	1.20–5.02	0.014
35–44	47	6	2.45	1.05–5.73	0.039
45–54	38	7	3.29	1.49–7.28	0.003
55–64	52	7	2.37	1.07–5.25	0.033
65–74	41	5	2.21	0.88–5.55	0.092
75–84	118	9	1.28	0.63–2.61	0.497
85–94	108	6	0.88	0.38–2.05	0.761
⩾ 95	729	47	1.00	–	
Combined					
< 75	327	44	2.35	1.60–3.46	< 0.001
⩾ 75	955	62	1.00	–	

[a]Among 1282 persons first prescribed any triple-combination antiretroviral therapy between 1 August 1996 and 30 September 1999.

hibitors plus a PI or with a NNRTI. Of these, 115 (8.23%) were excluded from this analysis for not having both baseline CD4 cell counts and plasma HIV-1 RNA levels measures available within 6 months prior to the start of antiretroviral therapy. The total study sample was based on the remaining 1282 (91.8%) subjects. Study participants were less likely to be on PI (73.0%) and less likely to have a prior AIDS diagnosis (13.1%) or to be a past or current injecting drug user (21.5%) in comparison with those excluded from the analyses. The overall median follow-up time of these study subjects was 26.8 months [interquartile range (IQR), 16.5–37.2 months].

Table 2 provides the baseline characteristics of the 1282 study participants. The median age was 37 years (IQR, 32–44 years), CD4 cell count was 270×10^6/l (IQR, $130–420 \times 10^6$/l), plasma HIV-1 RNA level was 120 000 copies/ml (IQR, 38 800–310 000 copies/ml), physician experience was 45 patients per physician (IQR, 5–132 patients per physician), and therapy use was 100% (IQR, 67–100%) in the first 12 months. A total of 729 (56.9%) participants used antiretroviral therapy ⩾ 95% of the time in the first year.

Study participants were first prescribed 29 different triple-combination antiretroviral regimens. A total of 130 (10.1%) commenced therapy in 1996, 436 (34.0%) in 1997, 368 (28.7%) in 1998, and 348 (27.1%) in 1999. The vast majority of participants (936, 73.0%) initiated therapy with a PI. The PI used in the initial regimen included: indinavir (692, 73.9%), nelfinavir (128, 13.7%), saquinavir (79, 8.4%), and ritonavir (37, 4.0%). The rest of the study participants (346, 27.0%) had a regimen that included a NNRTI. Among these subjects, 324 (93.6%) were on nevirapine, whereas 11 (3.2%) used efavirenz and 11 (3.2%) used delavirdine.

As of 30 September 2000, a total of 106 deaths were identified in the study population; of these 22 were not attributed to AIDS. These 22 deaths included five suicides and 17 accidental drug overdoses. All-cause mortality rate was 8.3%. The product limit estimate of the cumulative mortality rate at 12 months was 3.9%

Table 2. Baseline characteristics of 1282 persons first prescribed any triple-combination antiretroviral therapy between August 1996 and December 1999.

Variable	
Age (years) [median (IQR)]	37 (32–44)
Sex [n (%)]	
Male	1081 (84.3)
Female	201 (15.7)
CD4 cell count ($\times 10^6$ cells/l) [median (IQR)]	270 (130–420)
Plasma viral load (copies/ml) [median (IQR)]	120 000 (38 800–310 000)
Protease inhibitor use [n (%)]	
Yes	936 (73.0)
No	346 (27.0)
Injecting drug use [n (%)]	
Yes	275 (21.5)
No	1007 (78.5)
Physician experience (number of previous patients) [median (IQR)]	45 (5–132)
Therapy use in the first year (%) [median (IQR)]	100 (67–100)

IQR, Interquartile range.

(± 0.5%). Among individuals who were AIDS free at baseline, a total of 103 events were identified, 25 primary AIDS diagnoses and 78 deaths. The total number and proportion of the AIDS-defining illnesses were: *Pneumocystis carinii* pneumonia, eight (32.0%); other opportunistic infections, 10 (40.0%); wasting syndrome, one (4.0%); malignancies, two (8.0%); others, four (16.0%). At 12 months the product limit estimate of the likelihood of progressing to AIDS or to death was 4.9% (± 0.7%).

The univariate and multivariate analyses of the baseline factors associated with all-cause mortality are presented in Table 3. Inclusion of PI in the initial regimen, a prior diagnosis of AIDS, HIV-1 RNA levels and CD4 cell count, physician experience and intermittent use of therapy were found to be prognostic predictors of survival in the univariate analysis. Participants with a prior AIDS diagnosis at baseline were 2.13 times (95% CI, 1.37–3.32; $P < 0.001$) more likely to die than those without a diagnosis of AIDS. For each 100 cell decrease in CD4 cell count study participants were 1.36 times (95% CI, 1.21–1.53; $P < 0.001$) more likely to die; while for each $\log_{10}$ increase in plasma HIV-1 RNA level there was a 1.78 times (95% CI, 1.26–2.50; $P < 0.001$) increased risk of mortality. Those who started therapy with a PI were 2.09 times more likely to die than those who did not (95% CI, 1.14–3.84; $P = 0.017$). Patients visiting a more experienced physician (by 100 HIV patient increments) had a reduced risk of mortality [relative risk (RR), 0.76; 95% CI, 0.59–0.98; $P = 0.037$). For intermittent use of therapy in the first year, those who used therapy < 75% of the time were 2.35 times (95% CI, 1.60–3.46; $P < 0.001$) more likely to die than those participants who used antiretroviral therapy ⩾ 75% of the time.

In the multivariate model, only CD4 cell count, and intermittent use of antiretroviral therapy were found to be independent predictors of survival. After controlling for other prognostic explanatory variables that were significant in the univariate analyses (plasma HIV-1 RNA levels, prior AIDS diagnosis, PI use and physician experience), each 100 cell decrement in CD4 cell count and intermittent use of antiretroviral therapy (< 75% of the time in the first year) were associated with increased mortality with risk ratios of 1.31 (95% CI, 1.16–1.49; $P < 0.001$) and 2.90 (95% CI, 1.93–4.36; $P < 0.001$), respectively.

All relevant analyses were repeated with the time from the start of antiretroviral therapy to a diagnosis of AIDS or death as the outcomes of interest. These analyses were restricted to 1114 participants who were AIDS free at baseline. After adjusting for all other prognostic factors the results were unchanged when AIDS-free survival was used as the primary outcome. In this case, participants who used antiretroviral drugs < 75% of the time in the first year were 2.99 times (95% CI, 2.00–4.47; $P < 0.001$) more likely to die or to get an AIDS-defining illness.

Finally, we repeated all relevant analyses restricted to participants with at least 1 year of follow-up. As noted above, the aim of this subanalysis was to adjust for the potential confounding of downward drift by measuring intermittent therapy use in the first year and measuring other prognostic baseline factors (age, sex, CD4 cell

Table 3. Univariate and multivariate analysis of the baseline factors associated with survival among 1282 persons first prescribed any triple-combination antiretroviral therapy.

	Risk ratio (95% CI)	
Variable	Crude	Adjusted[a]
Age (years) (continuous)	1.02 (1.00–1.04)	–
Sex (male versus female)	1.17 (0.66–2.10)	–
Protease inhibitor use (yes versus no)	2.12 (1.16–3.88)	1.52 (0.82–2.82)
Injecting drug use (yes versus no)	0.99 (0.63–1.54)	–
Physician experience (per 100 patients per physician)	0.77 (0.59–0.99)	0.86 (0.67–1.12)
AIDS diagnosis (yes versus no)	2.15 (1.38–3.34)	1.44 (0.88–2.35)
CD4 cell count (per 100×10^6 cells/l decrease)	1.36 (1.21–1.53)	1.31 (1.16–1.49)
Plasma viral load (per $\log_{10}$ copies/ml increase)	1.79 (1.28–2.52)	1.34 (0.95–1.87)
Intermittent antiretroviral use (< 75% of the time in the first year)	2.35 (1.60–3.46)	2.90 (1.93–4.36)

[a]Including all prognostic variables that were statistically significant in the univariate analysis. CI, Confidence interval.

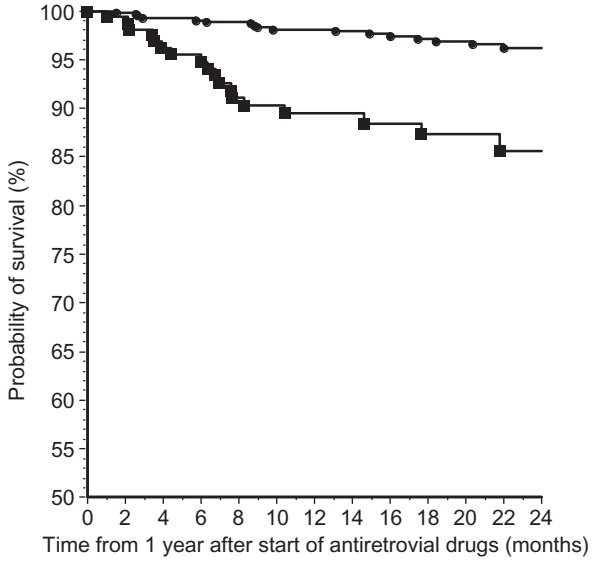

Fig. 1. Kaplan–Meier product limit estimates of cumulative progression to death among 847 HIV-positive subjects who had at least 12 months of follow-up and started naive on antiretroviral therapy between August 1996 and September 1999, stratified by intermittent use of antiretroviral therapy during the first year (closed circles, use of therapy $\geqslant 75\%$; n = 683; closed squares, use of therapy $< 75\%$; n = 164). Log-rank test $P < 0.001$. Note: baseline in this figure starts at month 12, so month 1 is actually month 13 from the start of antiretroviral therapy.

count, plasma HIV-1 RNA levels, prior AIDS diagnosis, PI use, current or past history of injecting drug use, and physician experience) at the end of the first year. A total of 1119 (87.3%) of the 1282 study participants had at least 1 year of follow-up. Of these, 272 (24.3%) were excluded from this subanalysis for not having both baseline CD4 cell count and plasma HIV-1 RNA level data available within 6 months prior to the start of year 1. Subjects excluded were younger (median, 36 versus 38 years; $P = 0.001$), less likely to be male (75.7% versus 87.8%; $P = 0.001$), and visited less experienced physicians (median experience, 23 versus 54 patients; $P < 0.001$) than those in the subanalysis. However, we did not observe any differences in the use of PI, injecting drug use, diagnosis of AIDS, baseline CD4 cell count or HIV-plasma viral load between these two groups. The total subanalysis study sample was based on the remaining 847 (75.7%) subjects. The overall median follow-up time of these study subjects, with time zero shifted to 1 year from the start of antiretroviral drugs, was 18 months (IQR, 8–26 months).

Kaplan-Meier product limit estimates of cumulative progression to death among 847 HIV-positive subjects who had at least 12 months of follow-up and started naïve on antiretroviral therapy are highlighted in Fig. 1. Of the 847 participants with at least 1 year of follow-up, 683 (80.6%) used antiretroviral drugs for $\geqslant 75\%$ of the time in the first year. The product limit estimate of all-cause mortality at 12 months was 1.91% ($\pm$ 0.57%) for those who used antiretroviral drugs for $\geqslant 75\%$ of the time and 10.57% ($\pm$ 2.6%) for those who did not (log rank $P < 0.001$). In univariate analyses, those who used antiretroviral drugs for $< 75\%$ of the time in this 12 month period were 4.83 times [95%

Table 4. Univariate and multivariate analysis of the baseline factors associated with survival among 847 persons with at least 1 year of follow-up first prescribed any triple-combination antiretroviral therapy.

	Risk ratio (95% CI)	
Variable	Crude	Adjusted[a]
Age in years (continuous)	1.01 (0.98–1.05)	–
Sex (male versus female)	1.34 (0.41–4.37)	–
Protease-inhibitor use (yes versus no)	3.52 (0.84–14.70)	–
Injecting drug use (yes versus no)	1.48 (0.76–2.89)	–
Physician experience (per 100 patients per physician)	1.00 (0.72–1.40)	–
AIDS diagnosis (yes versus no)	2.39 (1.19–4.81)	1.65 (0.79–3.47)
CD4 cell count (per 100×10^6 cells/l decrease)	1.70 (1.39–2.08)	1.49 (1.21–1.84)
Plasma viral load (per $\log_{10}$ copies/ml increase)	1.88 (1.47–2.39)	1.20 (0.88–1.62)
Intermittent antiretroviral use ($< 75\%$ of the time in the first year)	4.83 (2.57–9.06)	2.97 (1.33–6.62)

[a]Including all prognostic variables that were statistically significant in the univariate analysis. CI, Confidence interval.

confidence interval (CI), 2.57–9.06; $P < 0.001$] more likely to die than those participants who used therapy for $\geqslant 75\%$ of the time.

As indicated in Table 4, the results of our all-cause mortality survival analysis remained unchanged. After adjusting for all other prognostic factors, those participants who used antiretroviral drugs $< 75\%$ of the time in the first year were 2.97 times (95% CI, 1.33–6.62; $P = 0.008$) more likely to die. The results of the multivariate analyses remained unchanged when AIDS-free survival was used as the outcome.

Discussion

Our results demonstrate that intermittent use of antiretroviral therapy is associated with increased mortality. Similar results were found when we considered AIDS-free survival. After controlling for other prognostic explanatory variables that were significant in the univariate analyses each 100 cell decrement in CD4 cell count and intermittent use of antiretroviral drugs ($< 75\%$ of the time in the first year) were associated with increased mortality with risk ratios of 1.31 (95% CI, 1.16–1.49; $P < 0.001$) and 2.90 (95% CI, 1.93–4.36; $P < 0.001$), respectively. The results were similar when the analysis was restricted to persons with at least 1 year of follow-up and when intermittent use of therapy was measured in the first year while all other prognostic explanatory variables were measured at the end of year 1. Besides intermittent therapy use, CD4 cell counts at baseline were the only other significant independent predictors of mortality in this analysis.

A novel finding of our study was that intermittent use of antiretroviral therapy was positively associated with mortality. These results are consistent with what has been observed with durable response to therapy in clinical and observational settings among persons infected with HIV. The results of clinical trials and clinical studies indicate that near perfect adherence in the range of 90–100% may be necessary to achieve and maintain durable suppression of viral replication among persons using triple-combination antiretroviral therapy [18–20]. In our study population we have previously demonstrated a positive linear relationship between intermittent use as estimated in this fashion and achievement of viral suppression [21]. Similarly, in an indigent population in San Francisco the level of adherence to antiretroviral therapy was closely associated with longitudinal viral suppression and the rate of subsequent disease progression [22].

Our study confirms low CD4 cell count as a key marker of disease progression, especially death [23–26]. Our data also indicate that plasma HIV-1 RNA alone was not an independent predictor of survival among patients initiating triple-combination antiretroviral therapy. These findings appear to conflict with current published natural history studies and guidelines for the initiation of therapy. We would propose that these differences are easy to reconcile based on the fact that previous natural history studies were conducted in untreated cohorts [27–30]. Plasma HIV-1 RNA levels are likely to lose their prognostic value if treatment is similarly able to decrease plasma HIV-1 RNA levels across each CD4 cell count stratum. This is consistent with what we reported previously in Durban, South Africa [31] and has been confirmed by other cohort studies in the USA and Europe this year [32–34]. Finally, it was reassuring to observe no difference in survival according to age, sex, injecting drug use, physician experience and between those who initiated triple therapy with a PI versus those using a NNRTI.

There are several important aspects of this study that should be highlighted. First, our study was carried out within a province-wide treatment program where all individuals had free access to medical attention, combination antiretroviral therapy, and laboratory monitoring free of charge. Therefore, we believe that issues related to access to therapy do not compromise our results. Second, this study was based on treatment naive individuals, thus our results are not confounded by any past antiretroviral use. Also, all patients received triple drug therapy consistent with current guidelines. Third, delayed reporting does not play a role in these analyses as the vast majority of deaths are reported within 3 months of occurrence [5,13].

A potential limitation of our study relates to our measure of intermittent use of therapy: this was estimated based on refills and we cannot be sure that participants refilling their prescription actually took their medication. Our approach, based on incoming refills, can be judged as analogous to the community used-pill counts. However, pill counts were not measured directly. As such, our analyses probably overestimated the actual level of medication use in this population and thus underestimated its true impact on mortality. In other words, we would view this as a conservative bias. Several methods have been applied to evaluate adherence including pill count, computer-assisted electronic monitoring systems, physician assessment and patient self-report. The accuracy of these methods in estimating true levels of antiretroviral drug use remains controversial, and each has been shown to be unreliable in various settings [14,16,24].

In conclusion, our results demonstrate that intermittent use of antiretroviral therapy is associated with increased mortality. Our findings indicate that after adjusting for other important prognostic factors intermittent use of therapy was an important independent predictor of

mortality in this population. Similar results were seen when AIDS-free survival was considered. These findings have important implications for long-term management of persons with HIV disease. Those individuals using antiretroviral drugs intermittently (< 75% of the time in the first year) cannot be expected to achieve the full benefits of therapy including increased duration of survival. Regardless of future advances in treatment, protracted and near perfect use of antiretroviral drugs is likely to remain a requirement of successful antiretroviral therapy.

Acknowledgements

K. Heath is supported by a Walton Killam Memorial Pre-doctoral Fellowship, R. S. Hogg is supported by a Senior Scholar Award through the Michael Smith Foundation for Health Research and an Investigator Award through the Canadian Institutes of Health Research and D. R. Bangsberg is supported by The Doris Duke Charitable Foundation. We thank B. Devlin, D. Campbell, E. Ferris, N. Gataric, K. Hsu, M. Reginaldo and P. Vann for their research and administrative assistance.

References

1. Hammer SM, Squires KE, Hughes MD, *et al.* **A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less.** *N Engl J Med* 1997, **337**:725–733.
2. Cameron DW, Heath-Chiozzi M, Danner S, *et al.* **Prolongation of life and prevention of AIDS complications in a randomized controlled clinical trial of ritonavir in patients with advanced HIV disease.** *Lancet* 1998, **351**:543–549.
3. Montaner JSG, Reiss P, Cooper D, *et al.* **A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients. The INCAS Trial. Italy, The Netherlands, Canada and Australia Study.** *JAMA* 1998, **279**:930–937.
4. Palella FJ Jr, Delaney KM, Moorman AC, *et al.* **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.** *N Engl J Med* 1998, **338**:853–860.
5. Hogg RS, Yip B, Kully C, *et al.* **Improved survival among HIV-infected patients after the initiation of triple-drug antiretroviral regimens.** *Can Med Assoc J* 1999, **160**:659–665.
6. Hecht FM, Grant RM, Petropoulos CJ, *et al.* **Sexual transmission of HIV-1 variant resistant to multiple reverse-transcriptase and protease inhibitors.** *N Engl J Med* 1998, **339**:307–311.
7. Descamps D, Flandre P, Calvez V, *et al.* **Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy.** *JAMA* 2000, **283**:205–211.
8. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. **Patients compliance and drug failure in protease inhibitor monotherapy.** *JAMA* 1999, **276**:1955–1956.
9. Markowitz M, Saag M, Powderly WG, *et al.* **A preliminary study of ritonavir an inhibitor of HIV-1 protease, to treat HIV-1 infection.** *N Engl J Med* 1995, **333**:1534–1539.
10. Tisdale M, Myers RE, Maschera B, Parry NR, Oliver NM, Blair ED. **Cross-resistance analysis of human immunodeficiency virus type 1 variants individually selected for resistance to five different protease inhibitors.** *Antimicrob Agents Chemother* 1995, **39**:1704–1710.
11. Condra JH, Schleif WA, Blahy OM, *et al.* **In vivo emergency of HIV-1 variants resistant to multiple protease inhibitors.** *Nature* 1995, **374**:569–571.
12. Imrie A, Beveridge A, Genn W, Vizard J, Cooper D. **Transmission of HIV-1 resistant to nevirapine and zidovudine: Sydney Primary HIV Infection Study Group.** *J Infect Dis* 1997, **175**:1502–1506.
13. Hogg RS, Heath KV, Yip B, *et al.* **Improved survival among HIV-infected individuals following initiation of antiretroviral therapy.** *JAMA* 1998, **279**:450–454.
14. *Therapeutic Guidelines for the Treatment of HIV/AIDS and Related Conditions.* Vancouver, Canada: BC Centre for Excellence in HIV/AIDS; 1999.
15. Carpenter CC, Fischl MA, Hammer SM, *et al.* **Antiretroviral therapy for HIV infection in 1997. Updated recommendations of the International AIDS Society – USA.** *JAMA* 1997, **277**: 1962–1969.
16. World Health Organization. **Acquired immune deficiency syndrome (AIDS): interim proposal for a WHO staging system for HIV infection and disease.** *Wkly Epidemol Rec* 1990, **65**: 221–228.
17. Cox DR. **Regression models and life tables (with discussion).** *J Royal Stat Soc B* 1972, **34**:187–202.
18. de Jong MD, de Boer RJ, de Wolf F, *et al.* **Overshoot of HIV-1 viraemia after early discontinuation of antiretroviral treatment.** *AIDS* 1997, **11**:F79–F84.
19. Fatkenheuer G, Theisen A, Rockstroh J, *et al.* **Virologic treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients.** *AIDS* 1997, **11**:F113–F116.
20. Chesney A, Ickvics J, Hecht M, Sikipa G, Rabkin J. **Adherence: a necessity for successful HIV combination therapy.** *AIDS* 1999, **13**(suppl A):S271–S278.
21. Low-Beer SC, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JSG. **Adherence to triple therapy and viral load response.** *J Acquir Immune Defic Syndr* 2000, **23**:360–361.
22. Bangsberg DR, Perry S, Charlebois ED, Clark Robertson M, Moss AR. **Adherence to HAART predicts progression to AIDS.** *AIDS* 2001, **15**:1181–1183.
23. Pedersen C, Gerstoft J, Tauris P, Lundgren JD, Gotzsche PC, Buhl M, *et al.* **Trends in survival of Danish AIDS patients from 1981 to 1989.** *AIDS* 1990, **11**:1111–1116.
24. Lemp GF, Payne SF, Neal D, Temelso T, Rutherford GW. **Survival trends for patients with AIDS.** *JAMA* 1990, **263**:402–406.
25. Saah AJ, Hoover DR, He Y, Kingsley LA, Phair JP. **Factors influencing survival after AIDS: report from the multicentre AIDS cohort study (MACS).** *J Acquir Immune Defic Syndr* 1994, **7**:287–295.
26. Bindels PJ, Krol A, Roos M, *et al.* **The predictive value of T cell function in vitro and pre-AIDS zidovudine use for survival after AIDS diagnosis in a cohort of homosexual men in Amsterdam.** *J Infect Dis* 1995, **172**:97–104.
27. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. **Prognosis in HIV-1 infection predicted by the quantity of virus in plasma.** *Science* 1996, **272**:1167–1170.
28. Marschner IC, Collier AC, Coombs RW, *et al.* **Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy.** *J Infect Dis* 1998, **177**:40–47.
29. O'Brien WA, Hartigan PM, Martin D, *et al.* **Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS.** *N Engl J Med* 1996, **334**:426–431.
30. Craib KJP, Strathdee SA, Hogg RS, *et al.* **Serum levels of human immunodeficiency virus type 1 (HIV-1) RNA after seroconversion: a predictor of long-term mortality in HIV infection.** *J Infect Dis* 1997, **176**:798–800.
31. Hogg RS, Yip B, Chan K, *et al.* **Rates of disease progression by baseline CD4 cell count and viral load after initiating triple drug therapy.** *JAMA* 2001, **286**:2568–2577.
32. Chen R, Westfall A, Coud G, *et al.* **Long-term survival after initiation of antiretroviral therapy.** *Eighth Conference on Retroviruses and Opportunistic Infections.* Chicago, February 2000 [abstract 341].
33. Sterling TR, Chaisson RE, Moore RD. **HIV-1 RNA, CD4 T-lymphocytes, and clinical response to highly active antiretroviral therapy.** *AIDS* 2001, **15**:2251–2257.
34. Cozzi Lepri A, Phillips AN, d'Arminio Monforte A, *et al.* **When to start highly active antiretroviral therapy in chronically HIV-infected patients: evidence from the ICONA study.** *AIDS* 2001, **15**:983–990.