Rates of Disease Progression among Human Immunodeficiency Virus–Infected Persons Initiating Multiple-Drug Rescue Therapy

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To characterize survival and to compare rates of disease progression to death of human immunodeficiency virus (HIV)–infected patients, between those initiating multiple-drug rescue therapy (MDRT) and those antiretroviral-inexperienced initiating triple-drug antiretroviral therapy (ART), we conducted a population-based analysis of HIV-infected men and women aged ≥18 years in British Columbia, Canada. Cumulative mortality rates were estimated by use of Kaplan-Meier methods, and Cox-proportional hazard regression was used to model the simultaneous effect of prognostic variables on survival. Cumulative mortality at 36 months was 14.2% ± 2.0% and 10.9% ± 1.0% for the MDRT and triple-drug ART groups, respectively (P = .105, log-rank test). After adjustment for other baseline prognostic variables, MDRT was found not to be a predictor of increased all-cause mortality (relative risk, 1.17; 95% confidence interval, 0.82–1.66) in multivariate analysis. Over the short-term, patients receiving MDRT had relatively low mortality. After adjustment for baseline prognostic factors, rates of survival were comparable with those in patients initiating triple-drug ART.

Clinical trials and observational studies have conclusively shown that triple-drug combination regimens can dramatically decrease AIDS-related mortality and morbidity, as well as change the spectrum and natural history of human immunodeficiency virus (HIV) disease [1–4]. Yet, rates of virologic failure are substantial, varying from 20% to 50% during 1 year [5]. Furthermore, rates of virologic failure have been reported to increase with each successive round of therapy [6, 7]. Because of the limited number of antiretroviral (ARV) drugs available and the substantial levels of cross-resistance among them, many persons either have failed or have not achieved a durable virologic response with most standard highly active antiretroviral therapy (HAART) regimens.

Multiple-drug rescue therapy (MDRT) has been used in some centers to treat patients who have failed previous antiretroviral therapy (ART) regimens and were considered to be not likely to achieve a durable virologic response with most standard HAART regimens. In several studies, the use of MDRT has led to encouraging viral response rates, with 40%–50% of patients reaching complete virologic suppression [7–13]. The clinical use of such a strategy remains controversial, because the regimens can be quite complex and often are associated with toxicities. Furthermore, the impact of MDRT on clinical outcome is uncertain [14, 15]. In this study, we characterized the survival of a large cohort of MDRT-treated patients. Furthermore, we compared rates of disease progression to death among patients beginning MDRT in a population-based setting.

Methods. The distribution of ART in British Columbia, Canada, has been described in detail elsewhere [1, 16]. In brief, in this province, ARV drugs and plasma viral load monitoring are provided free of charge to eligible HIV-infected individuals. ARV drugs are delivered through a centralized Drug Treatment Program of the British Columbia Centre for Excellence in HIV/AIDS (designated “Centre”), which is the only free source of such therapy within the province.

Physicians enrolling an HIV-infected individual must complete a drug-request enrollment form. The form acts as a legal prescription and compiles baseline demographic information, previous HIV-specific drug history, CD4 cell counts, plasma HIV-1 RNA levels, current drug requests, and enrolling-physician data. Each request is reviewed by a qualified practitioner to ensure that it meets the Centre’s guidelines. Typically, persons receiving ART in the province are monitored by physicians at least once every 3 months, at which time prescriptions are renewed or modified. For all program participants, a complete prospective profile of ART is maintained, including the medication name, strength, dose, quantity dispensed, and dates dispensed.

The Centre distributes ARV drugs on the basis of specific guidelines generated by the therapeutic guidelines committee [17]. In 1997, the Centre adopted plasma viral load–driven
ART guidelines, which are consistent with those put forward by the International AIDS Society–USA [18]. Triple-drug ART was recommended for all ART-inexperienced individuals with plasma HIV-1 RNA levels >5000 copies/mL or CD4 cell counts <500 × 10⁶ cells/L. The program also conforms to the province’s Freedom of Information and Protection of Privacy Act and has been approved by the University of British Columbia/Providence Health Care Research Ethics Board.

A population-based analysis of ART-experienced and -inexperienced HIV-infected men and women aged ≥18 years in British Columbia, Canada, was performed. The ART-experienced group included patients for whom at least 2 separate courses of nonexperienced triple-drug ART had failed, as defined by virologic rebound (2 consecutive plasma HIV-1 RNA level measurements >400 copies/mL from an initially undetectable level) and who began an MDRT regimen between 1 August 1997 and 31 July 2000. These patients had a previous ARV drug–exposure median of 7 ARV drugs [8]. MDRT regimens included a median of 6 ARV drugs (interquartile range [IQR], 5–7 ARV drugs): up to 4 nucleoside reverse-transcriptase inhibitors (NRTIs; didanosine, lamivudine, stavudine, and abacavir), up to 2 protease inhibitors (PIs; indinavir, nelfinavir, saquinavir, lopinavir, and/or ritonavir), and up to 2 nonnucleoside reverse-transcriptase inhibitors (NNRTIs; nevirapine, delavirdine, and efavirenz) [8]. Hydroxyurea was used as an adjuvant. The ART-inexperienced group included HIV-infected men and women who never received ART and were first prescribed triple-drug ART during the same study period. Study subjects were initially prescribed triple-drug ART with regimens including a PI or an NNRTI.

The primary end point in this analysis was all-cause mortality. Deaths that occurred during the follow-up period were identified on a continuous basis from physician reports and through record linkages conducted with the British Columbia Division of Vital Statistics. In addition, causes of deaths were classified according to the International Classification of Diseases, 9th and 10th revision (ICD-9 and ICD-10) coding as HIV/AIDS-related or accidental.

Cumulative all-cause mortality rates were estimated by use of Kaplan-Meier methods. Event-free subjects were right censored as of 31 March 2002. Participants were not monitored 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 at the Centre. Cox proportional hazards regression was used to calculate univariate and adjusted relative risks (RRs) and 95% confidence intervals (CIs) [19]. For the purposes of these analyses, we followed the intent-to-treat principle; thus, all eligible subjects were included as they were first dispensed ARV drugs, regardless of whether they later discontinued or modified their therapeutic regimen.

A multivariate model including all significant variables in the univariate analysis was used to estimate adjusted RRs. A number of salient baseline prognostic variables were examined in this analysis. Plasma HIV-1 RNA levels (≥100,000 vs. <100,000 copies/mL), MDRT use (“yes” vs. “no”), sex (male vs. female), and a previous diagnosis of AIDS (“yes” vs. “no”) were treated as fixed binary variables. Age (in years) was treated as a continuous variable, and CD4 cell count was treated as a categorical variable (<50, 50–199, and ≥200 × 10⁶ cells/L). In addition to all-cause mortality, the analyses were repeated and restricted to HIV/AIDS-related deaths as the outcome of interest.

Analyses were performed by use of SAS software (version 6.0; SAS Institute). All tests of significance were 2-sided, and \( P < .05 \) was considered to be statistically significant.

**Results.** A total of 1388 patients were eligible. Of these 1388 patients, 341 ART-experienced patients initiated MDRT, and 1047 ART-inexperienced patients initiated triple-drug ART. The median follow-up period was 36 months for the MDRT group (IQR, 24–44 months) and 36 months for the triple-drug ART group (IQR, 26–46 months). Patients receiving MDRT had a history of exposure to a median of 7 ARV drugs (IQR, 5–8 ARV drugs), for a median of 41 months (IQR, 25–56 months) before the initiation of MDRT. Of the ART-experienced patients, 122 (36%) were exposed to all 3 classes (NRTIs, NNRTIs, and PIs) of ARV drugs before initiating MDRT.

As shown in table 1, patients in the MDRT were more likely to be older (median age, 41 vs. 37 years; \( P < .001 \)), to be male (94% vs. 81%; \( P = .001 \)), and to have a previous AIDS diagnosis (40% vs. 11%; \( P = .001 \)) than did those in the triple-drug ART group, which was consistent with observations described elsewhere [8–12]. Although there was no difference in median baseline plasma HIV-1 RNA levels between the 2 groups, patients in the MDRT group did have a lower median CD4 cell count than did those in the triple-drug ART group (170 × 10⁶ cells/L vs. 280 × 10⁶ cells/L; \( P < .001 \)).

Immunologic and virologic responses in the 2 groups also were examined. On the basis of the latest test results during the study period, the MDRT group had lower median CD4 cell counts (230 × 10⁶ cells/L [IQR, 90–380 × 10⁶ cells/L] vs. 390 [IQR, 230–560 × 10⁶ cells/L] \( P < .001 \)), and higher median plasma HIV RNA levels (112 copies/mL [IQR, <50–66,900 copies/mL] vs. 104 copies/mL [IQR, <50–20,300 copies/mL]) \( P = .017 \) in the triple-drug ART group. The median increase of CD4 cell count was 40 versus 100 × 10⁶ cells/L \( P < .001 \), and the median reduction in plasma virus load was \(-1.74 \log_{10} \) versus \(-2.39 \log_{10} \) \( P = .012 \) in the MDRT and the triple-drug ART groups, respectively.

As of 31 March 2002, a total of 169 deaths were identified in the study population: 50 (29.6%) in the MDRT group and 119 (70.4%) in the triple-drug ART group. When classified, there were 48 (96%) of 50 and 90 (76%) of 119 nonaccidental deaths in the 2 groups, respectively. As highlighted in figure 1,
Table 1. Comparison of baseline characteristics between 341 treatment-experienced patients receiving multiple-drug rescue therapy (MDRT) and 1047 treatment–inexperienced patients receiving triple-drug antiretroviral therapy (ART), who initiated their respective therapies between 1 August 1997 and 31 July 2000

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>MDRT</th>
<th>Triple-drug ART</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (IQR)</td>
<td>41 (36–47)</td>
<td>37 (32–44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>322 (94.4)</td>
<td>852 (81.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Female</td>
<td>19 (5.6)</td>
<td>195 (18.6)</td>
<td></td>
</tr>
<tr>
<td>Previous AIDS diagnosis</td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Yes</td>
<td>136 (39.9)</td>
<td>111 (10.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>205 (60.1)</td>
<td>936 (89.4)</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, ×10⁶ cells/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>66 (19.4)</td>
<td>102 (9.7)</td>
<td>.001</td>
</tr>
<tr>
<td>50–199</td>
<td>131 (38.4)</td>
<td>267 (25.5)</td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>144 (42.2)</td>
<td>678 (64.8)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>170 (60–260)</td>
<td>280 (140–420)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plasma HIV RNA level, copies/mL, median (IQR)</td>
<td>71,000 (15,000–290,000)</td>
<td>86,000 (28,000–260,000)</td>
<td>.065</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated. HIV, human immunodeficiency virus; IQR, interquartile range.

The product limit estimates of the cumulative all-cause mortality rate at 36 months were 14.2% ± 2.0% and 10.9% ± 1.0% for the MDRT and triple-drug ART groups, respectively (P = .105, log-rank test).

The univariate and multivariate analyses of the baseline factors associated with the time to death are presented in table 2. Age, HIV-1 RNA levels, and CD4 cell count were found to be baseline predictors of survival in the univariate analysis. Use of MDRT and previous diagnosis of AIDS were marginally significant as predictors of all-cause mortality. Participants in the MDRT group were 1.31 (95% CI, 0.94–1.83; P = .106) times more likely to die than those in the triple-drug ART group. In the multivariate model, after controlling for baseline prognostic variables that were significant to marginally significant (P ≤ .100) in the univariate analysis, the use of MDRT therapy (RR, 1.17; 95% CI, 0.82–1.66; P = .385) was not found to be a prognostic factor associated with all-cause mortality. Only CD4 cell count and plasma HIV-1 RNA level were found to be prognostic factors associated with mortality in this analysis. These results remained consistent when accidental deaths were censored in the mortality analysis (data not shown; P = .086). Results also remained consistent when the outcome was either AIDS and/or death (all-cause mortality, P = .358; nonaccidental causes only, P = .083).

**Discussion.** The results of our study demonstrate a high survival rate among patients for whom previous courses of ART had failed and who began MDRT at 36 months. The cumulative all-cause mortality was 14.2% ± 2.0% at 36 months among the MDRT recipients. Interestingly, after adjustment for other well-characterized baseline prognostic factors, these survival rates were statistically not different than those seen among ART-inexperienced patients who initiated triple-drug ART during the same period in the province of British Columbia.

The survival rates observed in the MDRT cohort described in the present study are most likely attributed to the ability of the MDRT regimen to suppress viral replication, which, in turn, was responsible for the preservation of CD4 cell counts, often gained as a result of previous rounds of therapy [8, 10, 15]. Consistent with previous studies, our data suggest that even partial or transient virus suppression can be translated into substantial and often sustained immunologic [20–22] and clinical benefits [23–27]. Notably, CD4 cell count response in our study cohort was negatively associated with the initial use of hydroxyurea in pa-

Figure 1. Kaplan-Meier product limit estimates of cumulative all-cause mortality among 341 human immunodeficiency virus–infected subjects who initiated multiple-drug rescue therapy (MDRT group) and 1047 antiretroviral (ARV) therapy–inexperienced patients who began triple-drug antiretroviral therapy (3-ARV group) between 1 August 1997 and 31 July 2000.
Table 2. Univariate and multivariate Cox proportional hazard analyses of the baseline factors associated with all-cause mortality between 341 treatment-experienced patients receiving multiple-drug rescue therapy (MDRT) and 1047 treatment-inexperienced patients receiving triple-drug antiretroviral therapy, who initiated their respective therapies between 1 August 1997 and 31 July 2000.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.02 (1.00–1.04)</td>
<td>1.01 (0.99–1.03)</td>
</tr>
<tr>
<td>Male vs. female</td>
<td>0.75 (0.51–1.11)</td>
<td>—</td>
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<tr>
<td>CD4 cell count, ×10⁶ cells/L</td>
<td></td>
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</tr>
<tr>
<td>&gt;200</td>
<td>1.00 (—)</td>
<td>1.00 (—)</td>
</tr>
<tr>
<td>50–199</td>
<td>2.06 (1.46–2.91)</td>
<td>1.79 (1.25–2.58)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>3.43 (2.31–5.08)</td>
<td>2.76 (1.77–4.30)</td>
</tr>
<tr>
<td>MDRT use, “yes” vs. “no”</td>
<td>1.31 (0.94–1.83)</td>
<td>1.17 (0.82–1.66)</td>
</tr>
<tr>
<td>Previous AIDS diagnosis, “yes” vs. “no”</td>
<td>1.37 (0.96–1.97)</td>
<td>0.78 (0.52–1.17)</td>
</tr>
<tr>
<td>HIV-1 RNA level, &gt;100,000 vs. &lt;100,000 copies/mL</td>
<td>2.24 (1.64–3.07)</td>
<td>1.79 (1.28–2.50)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; HIV, human immunodeficiency virus; RR, relative risk.

Patients receiving MDRT (67%). Whether MDRT regimens containing no hydroxyurea could achieve a better CD4 count response remains to be determined [8, 9]. Nonetheless, complete viral suppression should remain the primary goal of MDRT, because this is the best method to achieve a truly sustained therapeutic benefit and to minimize the evolution of resistance.

Rescue strategies, such as those documented in the present study, are increasingly needed for HIV-infected patients who have repeatedly failed to respond to various ART regimens. However, the use of MDRT among patients for whom several successive regimens have failed to achieve complete virus suppression has been controversial [14, 15]. Virologic and immunologic response among patients initiating this type of therapy has been variable and heavily dependent on these patients’ previous ARV experience [7–13]. There also are additional concerns about the potential of these complex drug combinations to cause serious toxic effects, drug-drug interactions, and adherence problems. In our experience, we have observed no unexpected toxicity, and the overall discontinuation rate among MDRT-treated patients has remained low [8]. As Youle et al. has suggested elsewhere [9], careful toxicity monitoring, regimen/dosage adjustment, and adherence support are critically important to optimize the benefits that can be derived from the use of MDRT.

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 ART (including MDRT), and laboratory monitoring free of charge. Therefore, we are confident that our results are not influenced by access to therapy-related issues, which have often compromised the interpretation of cohort-based studies. Second, 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. Third, the intent-to-treat principle was used when allocating patients to the treatment groups. Finally, although we did not observe survival differences between the 2 groups, it is still undetermined whether this survival benefit can be maintained over the longer term among patients in MDRT group, especially since patients in this study who initiated MDRT had a lower increase in CD4 cell counts (although confounded by hydroxyurea use) and a lower decrease in viral load, compared with that in ART-inexperienced patients.

In summary, our study demonstrates that rates of short-term survival among those initiating MDRT were comparable with rates among ART-inexperienced patients who initiated triple-drug ART during the same period, after adjustment for other well-known prognostic factors. At 36 months, cumulative all-cause mortality was 14.2% ± 2.0% in the MDRT cohort. These results indicate that MDRT merits further consideration as a therapeutic option for patients who have failed to respond to most standard HAART regimens. Judicious use of this strategy may serve as the necessary bridging mechanism that will allow selected patients to eventually benefit from more attractive therapeutic options as they emerge [8, 15].

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References


