

ORIGINAL ARTICLE

# Structured Treatment Interruption in Patients with Multidrug-Resistant Human Immunodeficiency Virus

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## ABSTRACT

### BACKGROUND

We compared two strategies for treating patients infected with multidrug-resistant human immunodeficiency virus (HIV).

### METHODS

Patients with multidrug-resistant HIV and HIV RNA levels of more than 5000 copies per milliliter were randomly assigned to a four-month structured interruption of treatment followed by a change in antiretroviral regimen (treatment-interruption group) or to an immediate change in regimen (control group). Genotypic and phenotypic resistance testing was performed. Disease progression, death, and changes in genotypic resistance, CD4 cell counts, HIV RNA levels, and quality of life were assessed.

### RESULTS

After a median follow-up of 11.6 months, disease progression or death occurred in 22 of the 138 patients in the treatment-interruption group and in 12 of the 132 patients in the control group ( $P=0.01$ ), with a hazard ratio of 2.57 (95 percent confidence interval, 1.2 to 5.5) for the treatment-interruption group. There were eight deaths in each group. In the treatment-interruption group, the mutant HIV populations completely or partially reverted to wild type by four months in 64.0 percent of patients. As compared with the control group, the treatment-interruption group had a mean CD4 cell count that was 85 cells per cubic millimeter lower from months 0 through 4 ( $P<0.001$ ), 47 cells per cubic millimeter lower from months 5 through 8 ( $P<0.001$ ), and 31 cells per cubic millimeter lower after eight months ( $P=0.11$ ). The mean HIV RNA levels were 1.2 log copies per milliliter higher (on a base-10 scale) in the treatment-interruption group during months 0 through 4 ( $P<0.001$ ), but they were not significantly different from those in the control group after month 4. The overall quality of life was similar in the two groups.

### CONCLUSIONS

In patients infected with multidrug-resistant HIV, structured interruption of treatment was associated with greater progression of disease and did not confer immunologic or virologic benefits or improve the overall quality of life.

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**T**HE BEST THERAPEUTIC APPROACH TO patients infected with multidrug-resistant human immunodeficiency virus (HIV) that does not respond to treatment is uncertain. Continuing partially effective antiretroviral therapy may preserve the CD4 cell count in the short term<sup>1,2</sup> but may jeopardize future treatment options by promoting further resistance over time.<sup>3,4</sup> Thus, alternative strategies are needed.

Interruptions of antiretroviral treatment are increasingly being used for treatment failure and to help manage the toxic effects of therapy. Although treatment interruption may lead to a decline in the CD4 cell count and an increase in the viral load, it has also been associated with the reemergence and predominance of a more sensitive (wild-type) viral population in patients with multidrug-resistant HIV.<sup>5-11</sup> Some studies have suggested that this change in the pattern of resistance may be associated with a better virologic response when treatment is reinitiated.<sup>9,12,13</sup> However, more recent randomized studies<sup>14,15</sup> have reported conflicting results, raising questions about the effect of this strategy. The Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) initiated a randomized clinical trial of structured interruption of treatment (CPCRA 064) to address this issue.

## METHODS

### STUDY POPULATION

Patients were enrolled at 16 units of the CPCRA, a consortium sponsored by the Division of AIDS of the National Institute of Allergy and Infectious Diseases. The CPCRA conducts clinical research on HIV infection and the acquired immunodeficiency syndrome (AIDS) in U.S. primary care settings. The institutional review board of each unit approved the protocol, and all patients or their parents or guardians gave written informed consent. HIV-infected patients 13 years of age or older were eligible if they had an HIV RNA level of more than 5000 copies per milliliter at the time of screening and genotypic evidence of multidrug-resistant virus (defined in Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>). The antiretroviral regimen had to remain stable from 14 days before screening through randomization. Patients were excluded from enrollment if they had an active opportunistic infection requiring treatment, had recently taken interleukin-2, had been vaccinated or had an illness judged to influence the HIV RNA level, or were pregnant or breast-feeding.

### STUDY DESIGN

CPCRA 064 was a randomized, nonblinded, multicenter trial in which eligible patients were randomly assigned to either a four-month structured interruption of treatment followed by the initiation of an optimized antiretroviral regimen (the treatment-interruption group) or the immediate initiation of an optimized antiretroviral regimen (the control group). Random assignments were made with the use of a permuted-block design in a 1:1 ratio and stratification according to the CPCRA unit. To assist with the selection of an optimized regimen, clinicians were given the results of both the genotypic and phenotypic antiretroviral-resistance tests performed at screening.

The primary outcome of the study was disease progression or death. Disease progression was defined as the first confirmed or probable<sup>16</sup> occurrence of an AIDS-defining condition on the basis of the classification of the Centers for Disease Control and Prevention.<sup>17</sup> An end-points committee whose members were unaware of the patients' treatment assignments reviewed all disease-progression events. Secondary outcomes included changes from base line in HIV RNA levels, CD4 cell counts, and genotypic resistance; self-reported adherence to the assigned regimen; adverse events; targeted symptoms; and quality of life, measured with the use of the physical and mental health summary scales of the Medical Outcomes Study 12-item Short-Form General Health Survey (SF-12).<sup>18</sup> Scores on each scale range from 0 (worst) to 100 (best). It was recommended that treatment be resumed before the specified four-month period in the event of disease progression or a 50 percent decrease in the CD4 cell count. The importance of adherence to standard guidelines for prophylaxis against opportunistic infections was emphasized.<sup>19,20</sup>

Patients were assessed at base line, monthly for eight months, and every four months thereafter. The data collected included the medical history, CD4 cell count, and HIV RNA level (Amplicor HIV-1 Monitor assay, Roche). Changes in antiretroviral therapy, disease-progression events and deaths, and severe or life-threatening (grade 4) events were reported as they occurred. Plasma-derived viral RNA was used for antiretroviral-resistance testing at screening and during follow-up with the use of genotypic (TRUGENE HIV-1 Genotyping Kit and OpenGene DNA Sequencing System, Bayer Diagnostics) and phenotypic (Antivirogram, Virco)<sup>21</sup> assays. The sensitivity of each drug was reported on genotypic testing as sensitive, intermediate, or re-

sistant, according to the CPCRA genotypic interpretive algorithm.

#### MONITORING

Enrollment opened in June 2000. The data and safety monitoring board of the Division of AIDS of the National Institute of Allergy and Infectious Diseases reviewed interim findings every three to six months. Reversion to wild-type virus and declines in the CD4 cell count were monitored in the treatment-interruption group. In addition, the differences between the treatment groups in the rates of disease progression and CD4 cell count and HIV RNA levels were monitored. On June 26, 2002, the board recommended that the study be closed to further enrollment owing to an inferior response of the CD4 cell count and an increased risk of disease progression in the treatment-interruption group. The results presented herein represent data from the 270 patients analyzed in the review by the data safety and monitoring board.

#### STATISTICAL ANALYSIS

We designed the study with a statistical power of 80 percent to detect a 33 percent reduction in the incidence of progression of disease or death in the treatment-interruption group, assuming that 60 percent of patients in the control group would have such events within 24 months and that there would be 200 primary events. A total of 480 patients were to be enrolled and followed for a minimum of two years. Proportional-hazards models, Kaplan–Meier curves, and log-rank tests were used to compare the treatment groups with respect to disease progression or death, adverse events, and the time to recovery of the CD4 cell count. The censoring date for the analyses of the time to a clinical event was May 9, 2002. Longitudinal regression models, with adjustment for base-line values and the CPCRA unit, were used to compare changes in CD4 cell counts and HIV RNA levels. Analysis of variance was used to compare changes in symptoms and quality-of-life scores.<sup>18</sup> All analyses were conducted according to the intention-to-treat principle, stratified according to the CPCRA unit, and based on a two-sided type I error with an alpha value of 0.05.

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## RESULTS

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#### PATIENTS AND FOLLOW-UP

Of the 270 patients, 138 were assigned to the treatment-interruption group and 132 to the control

group. Base-line characteristics were similar in the two groups (Table 1). The most common prior opportunistic infections were *Pneumocystis carinii* pneumonia (in 32.6 percent), esophageal candidiasis (in 15.9 percent), and *Mycobacterium avium* complex infection (in 6.3 percent). According to the treatment history, 96.7 percent of the patients had prior exposure to all three classes of drugs used for HIV infection, including protease inhibitors, nucleoside reverse-transcriptase inhibitors, and nonnucleoside reverse-transcriptase inhibitors. According to the viral genotype, 76.7 percent of patients were infected with HIV that had at least one major resistance mutation for each of these three classes of drugs, and 48.1 percent were infected with HIV that had broad resistance to all three classes (defined in Supplementary Appendix 1). The mean number of drugs (of 16 tested) to which the viruses were sensitive was 2.2 according to genotype and 5.1 according to phenotype. The median follow-up was 11.6 months. Fewer than 2 percent of patients were lost to follow-up.

#### SUMMARY OF STRUCTURED TREATMENT INTERRUPTION

Of the 138 patients in the treatment-interruption group, 36 (26.1 percent) had early termination of treatment interruption (mean, 2.3 months). Reasons for early termination (which are not mutually exclusive) included a decline in CD4 cell counts (in 80.6 percent of patients), an increase in plasma HIV RNA levels (in 38.9 percent), and disease progression (in 5.6 percent). Drug-resistance patterns had shifted partially (changes in all major reverse-transcriptase or protease mutations, but not both) or completely (changes in all major reverse-transcriptase and protease mutations) to wild type in 34.7 percent of patients at two months (43 of the 124 patients who underwent testing) and in 64.0 percent of patients at four months (73 of 114). Of the patients whose drug-resistance patterns showed a complete shift by the four-month visit, 45.0 percent (18 of 40) had had a complete shift by the two-month visit.

#### TREATMENTS PRESCRIBED

The first regimen prescribed after randomization included a mean of 3.6 drugs (2.2 nucleoside reverse-transcriptase inhibitors, 0.2 nonnucleoside reverse-transcriptase inhibitor, and 1.2 protease inhibitors) in the treatment-interruption group and 3.8 drugs (2.2 nucleoside reverse-transcriptase in-

<b>Table 1. Base-Line Characteristics of the Patients.*</b>			
<b>Characteristic</b>	<b>Treatment- Interruption Group (N=138)</b>	<b>Control Group (N=132)</b>	<b>All Patients (N=270)</b>
Mean age (yr)	45.0	43.9	44.4
Nonwhite race (%)	58.0	53.0	55.6
Female sex (%)	8.7	9.8	9.3
Prior injection-drug use (%)	12.3	9.2	10.8
Prior opportunistic infection or cancer (%)	53.6	59.1	56.3
CD4 cell count (cells/mm <sup>3</sup> )			
Median	153.0	124.8	144.5
Interquartile range	52–281	41–265	42–269
Lowest recorded CD4 cell count (cells/mm <sup>3</sup> )			
Median	34.0	31.0	32.0
Interquartile range	10–100	9–104	10–100
HIV RNA (log copies/ml)			
Median	5.0	5.0	5.0
Interquartile range	4.5–5.5	4.7–5.4	4.6–5.5
Highest recorded HIV RNA level (log copies/ml)			
Median	5.6	5.6	5.6
Interquartile range	5.3–5.9	5.3–5.9	5.3–5.9
Mean no. of NRTIs ever prescribed	5.0	4.9	5.0
Prior use of NRTIs (%)			
Lamivudine	99.3	98.5	98.9
Stavudine	98.6	96.2	97.4
Zidovudine	98.6	91.7	95.2
Didanosine	87.7	85.6	86.7
Abacavir	60.9	56.8	58.9
Zalcitabine	39.1	43.2	41.1
Tenofovir	2.9	3.8	3.3
Mean no. of PIs ever prescribed	4.2	4.1	4.2
Prior use of PIs (%)			
Indinavir	87.7	81.1	84.4
Ritonavir	84.1	84.1	84.1
Saquinavir	84.8	81.1	83.0
Nelfinavir	81.9	82.6	82.2
Amprenavir	58.0	56.8	57.4
Lopinavir	24.6	25.0	24.8
Mean no. of NNRTIs ever prescribed	1.5	1.5	1.5
Prior use of NNRTIs (%)			
Efavirenz	68.1	68.2	68.1
Nevirapine	64.5	62.9	63.7
Delavirdine	18.8	17.4	18.1
Mean no. of NRTIs, PIs, and NNRTIs ever prescribed	10.8	10.5	10.6
Mean no. of major HIV resistance mutations	5.7	5.5	5.6
NRTIs	2.2	2.1	2.1
PIs	2.5	2.5	2.5
NNRTIs	1.0	0.9	1.0

\* HIV denotes human immunodeficiency virus, NRTIs nucleoside reverse-transcriptase inhibitors, PIs protease inhibitors, and NNRTIs nonnucleoside reverse-transcriptase inhibitors.

hibitors, 0.2 nonnucleoside reverse-transcriptase inhibitor, and 1.4 protease inhibitors) in the control group. Lopinavir was significantly more likely to be included in the regimen for patients in the treatment-interruption group than in the regimen for those in the control group (68.8 percent vs. 50.8 percent,  $P=0.007$ ), whereas amprenavir was less likely to be included (17.4 percent vs. 31.8 percent,  $P=0.009$ ), as were ritonavir (12.8 percent vs. 29.5 percent,  $P=0.001$ ) and stavudine (36.7 percent vs. 52.3 percent,  $P=0.02$ ). The mean number of sensitive drugs included in the first regimen in the treatment-interruption group was 0.9 according to viral genotype and 1.5 according to viral phenotype. In the control group, the respective values were 0.8 and 1.8.

#### ADHERENCE

Self-reported adherence to antiretroviral therapy was similar in the two groups and was reported to be 100 percent by the majority of patients at each visit (data not shown). Adherence to the assigned treatment was measured on the basis of the mean percentage of follow-up time in which antiretroviral therapy was prescribed. During the first four months (the defined period of treatment interruption), antiretroviral therapy was prescribed for 16.5 percent of the follow-up time in the treatment-interruption group (reflecting early reinitiation of therapy in some patients) and 96.0 percent of the follow-up time in the control group. After month 4, the percentage of follow-up time in which therapy was prescribed was 92.1 percent in the treatment-

interruption group and 88.8 percent in the control group.

The CD4 cell count from the previous month was used in determining adherence to standard guidelines for prophylaxis against opportunistic infections during months 0 through 4. Adherence to *P. carinii* pneumonia prophylaxis was at least 89.0 percent in the treatment-interruption group and 83.6 percent in the control group. Adherence to *M. avium* complex prophylaxis was at least 72.5 percent in the treatment-interruption group and 63.6 percent in the control group. The percentage of patients receiving prophylaxis against *P. carinii* pneumonia and *M. avium* complex infection did not differ significantly between the two groups at any visit.

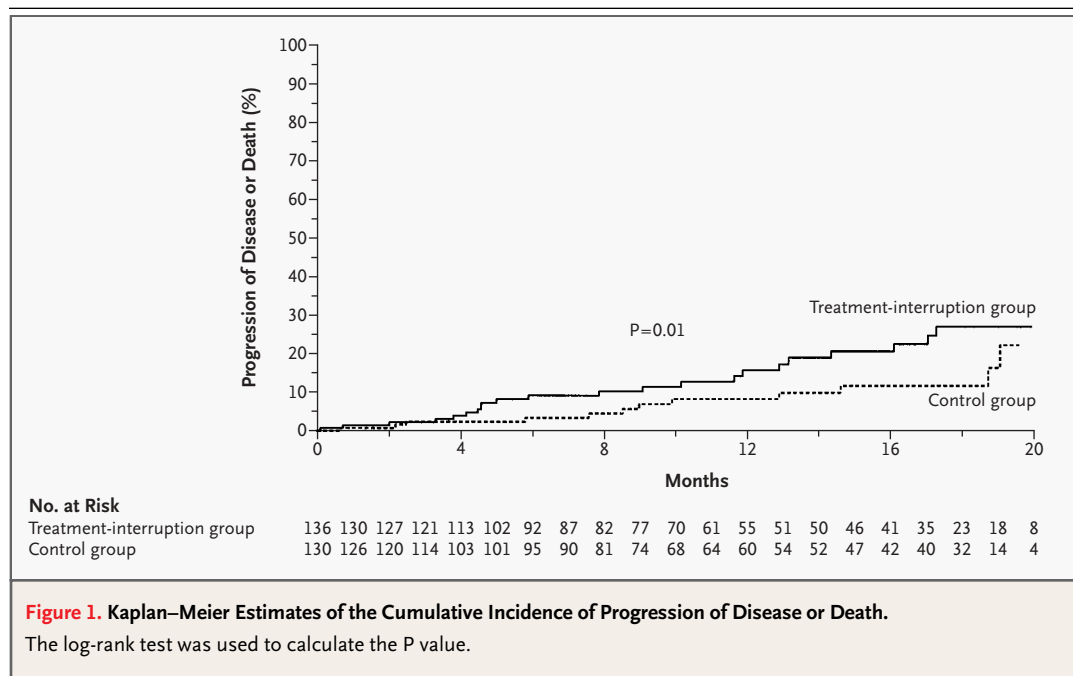
#### DISEASE PROGRESSION AND DEATH

A total of 22 patients in the treatment-interruption group and 12 in the control group reached the primary end point of disease progression or death (hazard ratio for the treatment-interruption group, 2.57; 95 percent confidence interval, 1.2 to 5.5;  $P=0.01$ ) (Table 2 and Fig. 1). There were eight deaths in each group. Death was a primary (first) event for five patients in the treatment-interruption group and seven in the control group. Of the 17 patients in the treatment-interruption group who had disease progression, 7 (41.2 percent) had esophageal candidiasis, 4 (23.5 percent) had *P. carinii* pneumonia, 3 (17.6 percent) had cryptosporidiosis, 2 (11.8 percent) had lymphoma, and 1 (5.9 percent) had cytomegalovirus infection. Of the five patients in the

**Table 2. Incidence of Progression of Disease or Death.**

Event	Treatment-Interruption Group		Control Group		Hazard Ratio (95% CI)*	P Value
	No. of Patients	Rate/100 Person-Yr	No. of Patients	Rate/100 Person-Yr		
Progression of disease or death	22	18.1	12	10.0	2.57 (1.2–5.5)	0.01
0–4 Mo	5	11.1	3	6.9		
5–8 Mo	7	8.0	2	2.3		
9–12 Mo	4	3.2	3	2.4		
13–20 Mo	6	5.3	4	3.4		
Death	8	6.1	8	6.5	1.44 (0.5–4.1)	0.50
Progression of disease	17	14.0	5	4.2	6.04 (1.8–20.8)	0.004

\* Hazard ratios are for the treatment-interruption group as compared with the control group. CI denotes confidence interval.



**Figure 1. Kaplan–Meier Estimates of the Cumulative Incidence of Progression of Disease or Death.**

The log-rank test was used to calculate the P value.

control group who had disease progression, one each had esophageal candidiasis, cryptosporidiosis, cytomegalovirus infection, *M. avium* complex infection, and herpes simplex infection. Of the eight cases of esophageal candidiasis, one occurred at each of months 1, 2, 3, and 12 in the treatment-interruption group; two cases, one in each treatment group occurred at month 8; and two cases in the treatment-interruption group occurred at month 16. The percentage of patients receiving imidazoles (antifungal agents) during follow-up ranged from 15 to 36 percent and did not differ significantly between the groups except at months 6 and 8, when it was lower in the treatment-interruption group. The incidence of oral candidiasis (not considered a primary end point) was 21 percent in the treatment-interruption group and 20 percent in the control group.

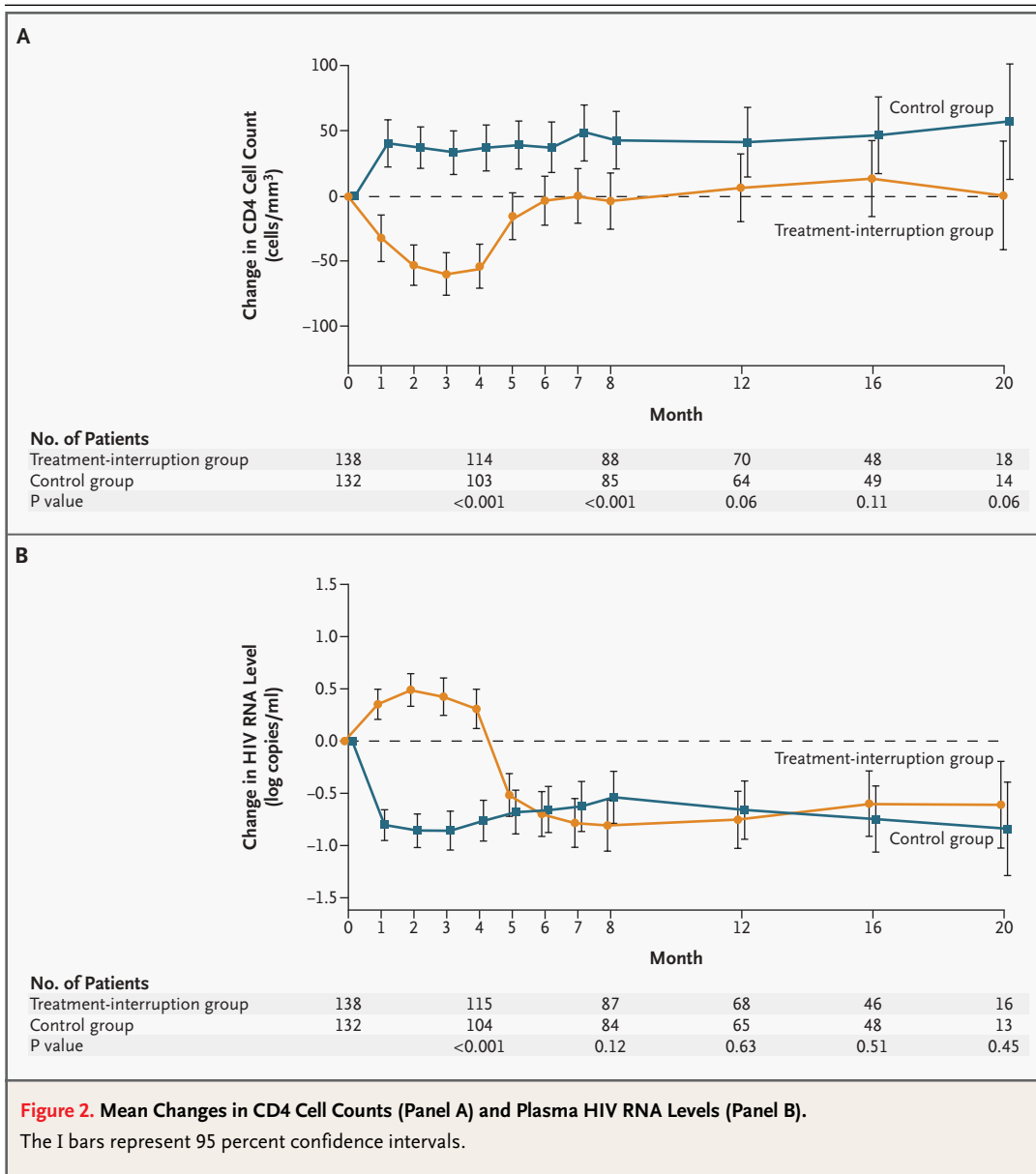
Most primary end points occurred after month 4 (hazard ratio for the treatment-interruption group, 2.97; 95 percent confidence interval, 1.21 to 7.32;  $P=0.02$ ), not during the treatment-interruption period of months 0 through 4 (hazard ratio, 1.64;  $P=0.50$ ) (Table 2). A multivariate model that included the treatment group, base-line CD4 cell count, base-line HIV RNA level, and presence or absence of a history of progression of disease was used to predict the likelihood of disease progression or death. Significant predictors were the treatment group (hazard ratio, 2.74 [95 percent confidence interval, 1.25

to 5.98] for the treatment-interruption group as compared with the control group;  $P=0.01$ ) and the base-line CD4 cell count (hazard ratio, 1.38 [95 percent confidence interval, 1.11 to 1.72] for each decrement of 50 cells per cubic millimeter;  $P=0.004$ ). Base-line HIV RNA levels and a history of disease progression were not significant predictors.

#### CD4 CELL COUNTS AND PLASMA HIV RNA LEVELS

Figure 2A shows the mean changes in CD4 cell counts in the two treatment groups. For months 0 through 4, the mean CD4 cell count was higher by 85 cells per cubic millimeter in the control group than in the treatment-interruption group ( $P<0.001$ ). The estimated median time for the CD4 cell count to exceed base-line values was 4.9 months in the treatment-interruption group. In this group, however, the CD4 cell count remained consistently lower than in the control group; the mean differences for months 5 through 8 and months 9 through 20 were 47 cells per cubic millimeter ( $P<0.001$ ) and 31 cells per cubic millimeter ( $P=0.11$ ), respectively.

HIV RNA levels increased during the treatment-interruption period (Fig. 2B). The mean HIV RNA levels were higher by 1.2 log (on a base-10 scale) copies per milliliter in the treatment-interruption group than in the control group for months 0 through 4 ( $P<0.001$ ). However, after the defined treatment-interruption period, the HIV RNA levels



in both groups remained suppressed below the base-line value by approximately 0.8 log copies per milliliter. Table 3 shows the percentage of patients with fewer than 400 copies of HIV RNA per milliliter in each treatment group at each visit. The percentage with such viral suppression peaked in each group approximately four months after the initiation of the optimized regimen.

In the treatment-interruption group, the mean HIV RNA level at eight months was 1.2 log copies per milliliter lower than the base-line value in those

who had a partial or complete shift in drug-resistance patterns by the four-month visit and 0.5 log copies per milliliter lower in those who did not have such a shift ( $P=0.01$ ). At the eight-month visit the respective mean change in CD4 cell counts from base line was an increase of 16 cells per cubic millimeter and a loss of 34 cells per cubic millimeter ( $P=0.01$ ). The risk of disease progression was not significantly different between those with a shift in the pattern of drug resistance and those without a shift (hazard ratio, 1.14;  $P=0.82$ ).

**Table 3. Patients with a Plasma Viral Load of Less Than 400 Copies per Milliliter.**

Time of Visit	Treatment- Interruption Group		Control Group	
	Total No. of Patients	Viral Load <400 Copies/ml	Total No. of Patients	Viral Load <400 Copies/ml
		no. (%)		no. (%)
Month 1	129	0	123	10 (8.1)
Month 2	128	0	116	13 (11.2)
Month 3	119	0	113	21 (18.6)
Month 4	115	0	104	19 (18.3)
Month 5	108	5 (4.6)	96	13 (13.5)
Month 6	98	12 (12.2)	94	11 (11.7)
Month 7	88	17 (19.3)	86	11 (12.8)
Month 8	87	19 (21.8)	84	7 (8.3)
Month 12	68	13 (19.1)	65	7 (10.8)
Month 16	46	7 (15.2)	48	6 (12.5)
Month 20	16	1 (6.3)	13	0

#### ADVERSE EVENTS, SYMPTOMS, AND QUALITY OF LIFE

There were no significant differences between the two groups in adverse events, symptoms, or overall quality of life. Thirty-one patients in the treatment-interruption group and 30 patients in the control group had a grade 4 adverse event (hazard ratio for the treatment-interruption group, 1.03;  $P=0.92$ ). Through month 12, no serious (grade 4) symptoms were reported in either group. As compared with the control group, the treatment-interruption group had a transient improvement in the SF-12 physical component score for quality of life. The change from base line to two months was +1.7 in the treatment-interruption group and -0.4 in the control group (difference, 2.1;  $P=0.04$ ). The physical and mental component scores did not differ significantly between the two groups at any other visit.

#### DISCUSSION

This randomized trial compared the effect of a structured interruption of treatment with continued antiretroviral therapy on clinical outcomes in patients with multidrug-resistant HIV infection. In this population, a structured interruption of treatment was associated with a greater number of clinical events.

In addition, patients assigned to treatment interruption did not have a greater immunologic or virologic benefit than the patients in the control group. Adverse events, adherence to treatment, and the quality of life were similar in the two groups.

We hypothesized that a four-month structured interruption of treatment would improve the subsequent treatment response owing to a switch in the predominant HIV population from highly resistant virus to wild-type virus during the interruption. A previous study reported that reversion to wild-type virus occurred 2 to 15 weeks after therapy was discontinued.<sup>13</sup> A 16-week interruption was chosen to allow adequate time to maximize the reversion to wild-type virus while minimizing the risk of a decline in the CD4 cell count. We found that the treatment-interruption group had poorer overall outcomes than the control group, despite partial or complete reversion of the HIV mutant population to the wild type in 64.0 percent of the patients in the treatment-interruption group.

Prior studies of the use of a structured interruption of treatment in the setting of salvage therapy differ from our study in terms of their design, eligibility criteria, and study outcomes.<sup>7-9,11,12,14,15,22</sup> Earlier studies were primarily nonrandomized; used virologic, rather than clinical, end points; and required only a history of prior exposure to multiple antiretroviral agents and drug classes rather than documented genotypic multidrug resistance before entry.

Two recently reported studies used a randomized clinical trial design.<sup>14,15</sup> The GIGHAART study<sup>15</sup> used a shorter (eight-week) period of treatment interruption and prescribed a combination of eight or more drugs in the new salvage regimen. Base-line CD4 cell counts were lower in that study (median, 27 cells per cubic millimeter) than in ours. In contrast to our results, the GIGHAART study found that the treatment-interruption group had better virologic and immunologic responses than the control group. The reasons for the discordant findings are not clear. Despite the use of a more intense salvage regimen, the control group in the GIGHAART study had a poorer virologic response than did the control group in our study. Only 22 percent of patients in the control group in the GIGHAART study were still receiving more than six drugs at 48 weeks. In our study, the overall virologic response after the reinitiation of treatment in the treatment-interruption group was similar to that in the control group. Both groups had a rela-

tively good response, with a reduction from base line of approximately 0.8 log copies of HIV RNA per milliliter.

The results of the Retrogene study,<sup>14</sup> which used a 12-week structured interruption of treatment, were consistent with those of our study. The investigators found no significant virologic advantage of treatment interruption, despite the reversion to wild-type virus in approximately two thirds of patients in the treatment-interruption group.

Preliminary subgroup analyses of the treatment-interruption group in our study suggest that patients whose virus reverted to wild type during treatment interruption had better virologic and CD4 cell responses after the reinitiation of therapy than did patients whose virus did not revert to wild type. However, the former group also had higher CD4 cell counts and lower HIV RNA levels at study entry (data not shown). Despite these differences, the rates of clinical events were similar in these two subgroups. More important, the CD4 cell response among the patients in the treatment-interruption group whose virus reverted to wild type was not superior to the CD4 cell response in the control group.

A decline in the CD4 cell count during treatment interruption has been reported in previous studies.<sup>5,8-10</sup> In our study, although the CD4 cell count recovered after the reinitiation of treatment, it remained consistently lower in the treatment-interruption group than in the control group throughout a period of 20 months. To our knowledge, the question of whether the decline in the CD4 cell count associated with a structured interruption of treatment leads to an increase in clinical events relative to those in the control group has not been examined previously in a large, randomized trial with statistical power to address this question. The results of one observational data-base study<sup>22</sup> suggested an increased risk of AIDS and death when therapy was stopped for at least three months, but it was not a study of a structured treatment interruption. In the recent randomized studies of a structured treatment interruption,<sup>14,15</sup> there was no increase in clinical events in the treatment-interruption

group, but the sample in these studies were not large enough to assess the issue accurately.

In our study, nearly half of all disease-progression events occurred in patients with a base-line CD4 cell count of less than 50 per cubic millimeter. The two most common primary disease-progression events were esophageal candidiasis and *P. carinii* pneumonia. The greater frequency of these events in the treatment-interruption group was not attributed to the rates of use of imidazoles or *P. carinii* prophylaxis. These results demonstrate the risks of treatment interruption and emphasize the importance of prophylaxis against opportunistic infections in patients with HIV infection in whom treatment is interrupted for any reason.

This randomized study was designed specifically to assess the clinical outcome of a structured interruption of treatment. Although there were equal numbers of deaths in each group, significantly more primary disease-progression events occurred in the treatment-interruption group. Our results indicate that in patients with multidrug-resistant HIV infection, it is best to continue treatment with an optimized antiretroviral regimen and avoid the use of treatment interruption.

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#### APPENDIX

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