

Disadvantages of Structured Treatment Interruption Persist in Patients With Multidrug-Resistant HIV-1

Final Results of the CPCRA 064 Study

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Background: We report the final results of Community Programs for Clinical Research on AIDS (CPCRA-064) study, a multicenter, prospective, randomized, controlled trial that determines the long-term clinical impact of structured treatment interruption (STI) in patients with multidrug-resistant (MDR) HIV-1.

Methods and Results: Two hundred seventy-four patients on stable antiretroviral therapy with MDR HIV-1 treatment failure were randomized to a 4-month STI, followed by an optimized antiretroviral regimen (STI arm, n = 140) or an immediate change to an optimized antiretroviral regimen (control arm, n = 134). Main outcome measures were progression of disease or death and changes from baseline in HIV RNA levels (log copies/mL) and CD4 cell counts (cells/mm³). The median baseline HIV RNA level was 5.0 log copies/mL, the median CD4 count was 147 cells/mm³, and the nadir CD4 count was 32 cells/mm³. The median follow-up was 37 months. After the STI period, there were no differences in HIV RNA level responses between treatment arms. Differences in CD4 count responses always favored the control arm, with an advantage of 84 cells from 0 to 4 months ($P < 0.0001$), 50 cells from 4 to 12 months ($P < 0.0001$), 45 cells from 12 to 24 months ($P = 0.006$), and 43 cells after

24 months ($P = 0.07$). Rates in the STI and control arms for first progression-of-disease event or death were 17.5 and 14.3, respectively (hazard ratio = 1.28; $P = 0.22$).

Conclusion: STI before changing regimens in patients with MDR HIV-1 treatment failure has a prolonged negative impact on CD4 cell count recovery and does not confer progression of disease or virologic benefits.

Key Words: HIV infection, salvage therapy, treatment failure, treatment interruption

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Many people with HIV-1 disease experience incomplete suppression of their HIV-1 despite highly active antiretroviral therapy (HAART).^{1–3} This can occur for various reasons, including difficulties with treatment adherence, exposure to suboptimal regimens, altered drug metabolism, and acquisition of drug-resistant virus during primary infection. Unfortunately, these conditions frequently lead to multidrug-resistant (MDR) HIV-1 and an absence of effective treatment options.^{4,5}

The optimal therapeutic options for patients with MDR HIV-1 remain unclear. Continuing current therapy in the setting of persistent viremia carries the risk of accumulating additional HIV-1 drug-related mutations that may further compromise the efficacy of future treatments.^{6–9} Maintaining a failing regimen may also expose patients to unnecessary drug-related toxicities. Stopping all antiretroviral therapy can eliminate drug toxicities and permit the re-emergence of drug-sensitive virus but is frequently associated with an abrupt decline in CD4 cell counts.^{10–16} Determining which strategy is best for these patients is important to maximize their health and quality of life while awaiting new drugs that are effective against MDR HIV-1.

To address these issues, we developed a randomized clinical trial within the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA 064) for patients with MDR HIV-1. The primary goal was to determine whether a prescribed 4-month structured treatment interruption (STI) before switching therapy results in an improved response that

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delays clinical disease progression or death compared with a strategy of immediately initiating a new antiretroviral regimen.

The study was closed to enrollment early (in 2002) based on preliminary findings after a median follow-up of 12 months that showed STI was associated with greater progression of disease or death and did not lead to an improved HIV RNA level or CD4 cell count response.¹⁷ Study visits continued through June 30, 2004 for all randomized patients to assess the long-term impact of STI in this cohort. We report here the final study results, with a median of 37 (minimum of 24) months of patient follow-up.

METHODS

The CPCRA 064 is a prospective randomized clinical end-point trial. Complete details of the study design, including the genotypic definition of MDR HIV-1, have been described in depth elsewhere.¹⁷ The institutional review board of each clinical site approved the protocol, and all patients or their parents or guardians gave written informed consent. The study was originally designed to enroll and follow 480 patients but was closed to enrollment early based on the recommendations of the Data and Safety Monitoring Board. When the study closed to enrollment, there were 274 patients randomized (from August 11, 2000 to June 27, 2002) from 16 clinical sites. Study visits continued until a common closing date (June 30, 2004) to obtain a minimum follow-up of 24 months. All patients were followed for death, progression of disease, and other events as well as for laboratory markers (CD4 cell counts and HIV RNA levels) through that common closing date.

HIV-1-infected patients on stable antiretroviral regimens with virologic failure (viral load >5000 copies/mL) and MDR HIV-1 virus were randomized to a 4-month STI, followed by the initiation of an optimized antiretroviral regimen (STI arm) or immediate initiation of an optimized antiretroviral regimen (control arm). Baseline genotypic (TRUGENE HIV-1 Genotyping Kit and OpenGene DNA Sequencing System; Bayer Diagnostics, Tarrytown, NY) and phenotypic (Antivirogram; Virco Lab, Raritan, NJ) drug resistance tests were provided to assist the patient's primary care provider in selecting an optimized regimen. Sixteen drugs were included in the genotypic and phenotypic panels.

The primary outcome for the study was new or recurrent clinical disease progression events or death. HIV-1 disease progression clinical events included those in the 1993 US Centers for Disease Control and Prevention revised AIDS case definition¹⁸ and a number of other serious opportunistic infections or cancers associated with HIV-1 immunodeficiency. A clinical events committee blinded to treatment assignment reviewed all primary events. Events classified as confirmed or probable using pre-established criteria by the Centers for Disease Control and Prevention were considered to be an end point. Secondary outcomes included changes from baseline in HIV-1 RNA levels, CD4 cell counts, and antiretroviral resistance; adverse events; targeted symptoms; self-reported adherence to antiretroviral treatment; and quality of life. Patients in the STI arm who experienced a progression-of-disease event or a greater than 50% decline in CD4 cell count during the 4-month STI period were encouraged to terminate the STI early.

Proportional hazards models, Kaplan-Meier curves, and log-rank tests were used to compare the treatment arms with respect to disease progression or death, time to CD4 cell count recovery, and adverse events. Hazard ratios are for the time to the first event and compare the STI arm with the control arm. Proportional hazards models for progression of disease adjust for prior progression of disease as well as baseline CD4 cell counts and HIV-1 RNA levels. Rates are given for 100 person-years of follow-up. Longitudinal regression models, with adjustment for baseline value, were used to compare the treatment arms for changes in CD4 cell counts and HIV-1 RNA levels. All HIV-1 RNA levels are reported as log₁₀ copies/mL.

HIV-1 drug resistance mutations considered are from the October 2004 International AIDS Society definition¹⁹ and include 54 possible allelic mutations at 36 different codons. The mutations include 22 nucleoside reverse transcriptase inhibitor (NRTI) mutations, 15 nonnucleoside reverse transcriptase inhibitor (NNRTI) mutations, and 17 major protease inhibitor (PI) mutations. Quality of life was measured using the Medical Outcomes Study 12-item Short-Form General Health Survey (SF-12). Scores for each of 8 domains ranged from 0 (worst) to 100 (best). An overall quality-of-life score was calculated at each measurement time as the average score over all domains. Targeted symptoms were reported by grade (1 = mild to 4 = severe) at each visit using a toxicity manual developed by the National Institutes of Health, Division of AIDS. All participants underwent a second randomization to complete 1 of 2 instruments designed to capture self-reported adherence to antiretroviral medications during follow-up: a 7-day recall or a 3-day recall. For each instrument, an overall adherence score was calculated at each visit based on the percentage of antiretrovirals taken for that visit.

General linear models were used to compare changes in the number of drug resistance mutations, symptoms, and quality-of-life scores. Generalized estimating equations for correlated repeated binary measurements were used to compare the occurrence of viral load measurements less than 400 copies/mL and the use of prophylactic agents for opportunistic infections by treatment arm. Subgroups prespecified in the protocol were formed according to age, gender, race, baseline, and lowest CD4 cell count ever recorded, baseline HIV-1 RNA level, and antiretroviral treatment history. Analyses were conducted to determine whether differences between treatment arms varied by subgroups in clinical disease progression, survival, and changes in CD4 cell count and HIV-1 RNA level. All analyses were conducted according to the intention-to-treat principle, stratified according to randomization location, and based on a 2-sided type I error with an α -value of 0.05.

RESULTS

Baseline Characteristics

Baseline characteristics of the 2 treatment arms were similar (Table 1). The median baseline CD4 cell count (cells/mm³) was 155 in the STI arm and 133 in the control arm ($P = 0.33$). A total of 56% of the STI arm and 60% of the control arm had a progression-of-disease event recorded before randomization. The most common progression-of-disease

TABLE 1. Baseline Characteristics of the Patients

Characteristic	STI Arm (n = 140)	Control Arm (n = 134)	All Patients (n = 274)
Mean age, years	44.8	43.9	44.3
Nonwhite race (%)	57.1	53.0	55.1
Female gender (%)	8.6	9.7	9.1
Prior injection drug use (%)	12.1	9.0	10.6
Prior progression of disease (%)	56.4	59.7	58.0
CD4 cell count (cells/mm ³)			
Median	154.8	133.0	146.8
Interquartile range	53–292	41–264	47–269
Less than 100 cells (%)	36.4	42.5	39.4
Lowest recorded CD4 cell count (cells/mm ³)			
Median	35.5	31.0	32.0
Interquartile range	10–101	9–112	10–102
HIV RNA level (log copies/mL)			
Median	5.0	5.0	5.0
Interquartile range	4.5–5.5	4.7–5.4	4.6–5.4
Highest reported HIV RNA level (log copies/mL)			
Median	5.7	5.6	5.7
Interquartile range	5.3–5.9	5.3–5.9	5.3–5.9
Mean number of NRTIs ever prescribed	5.0	4.9	5.0
Prior use of NRTIs (%)			
Lamivudine	99.3	98.5	98.9
Stavudine	97.9	96.3	97.1
Zidovudine	98.6	91.8	95.3
Didanosine	87.9	85.8	86.9
Abacavir	61.4	56.7	59.1
Zalcitabine	39.3	43.3	41.2
Tenofovir	2.9	3.7	3.3
Mean number of PIs ever prescribed	4.2	4.1	4.2
Prior use of PIs (%)			
Indinavir	87.1	80.6	83.9
Ritonavir	84.3	84.3	84.3
Saquinavir	85.0	81.3	83.2
Nelfinavir	81.4	82.8	82.1
Amprenavir	57.9	56.7	57.3
Lopinavir (Kaletra)	25.0	26.1	25.5
Mean number of NNRTIs ever prescribed	1.5	1.5	1.5
Prior use of NNRTIs (%)			
Efavirenz	68.6	68.7	68.6
Nevirapine	64.3	63.4	63.9
Delavirdine	18.6	18.7	18.6
Mean number of NRTIs, PIs, and NNRTIs ever prescribed	10.8	10.5	10.6
Mean number of HIV resistance mutations			
NRTIs	5.6	5.1	5.3
PIs	2.9	2.8	2.8
NNRTIs	1.6	1.6	1.6
Overall	10.0	9.3	9.7

events experienced before randomization were *Pneumocystis jirovecii* (previously *carinii*) pneumonia (PCP) in 33%, esophageal candidiasis in 16%, and *Mycobacterium avium* complex (MAC) in 7%.

The mean number of antiretroviral drugs ever prescribed was 10.8 in the STI arm and 10.5 in the control arm. The mean number of antiretroviral drugs in the failing regimen at the

time of study entry was 3.6 for the STI arm and 3.7 for the control arm. For the STI and control arms, respectively, the mean numbers of active drugs in the failing regimen were 0.2 and 0.3 by genotype and 0.6 and 0.7 by phenotype. The mean number of drug resistance mutations present at randomization was 10.0 in the STI arm and 9.3 in the control arm. Among all 16 drugs considered in the genotypic panel, the mean numbers

of drugs to which the virus was sensitive at randomization were 2.3 and 2.6 for the STI and control arms, respectively. In the phenotypic panel, the mean number was 4.7 for the 2 treatment arms.

Study Compliance With Randomization Assignment and Follow-Up

Two patients randomized to the STI arm (1.4%) did not start an STI, and 4 patients randomized to the control arm (3.0%) initiated an STI immediately after randomization. In the STI arm, the overall median duration of time off antiretroviral therapy during the STI period was 3.9 months. Twenty-eight percent ($n = 39$) of the STI arm terminated the STI early (median = 2.5 months, range: 0–3.5 months). The main reasons given for early STI termination included a decline in CD4 cell count ($n = 29$), a rise in HIV RNA level ($n = 16$), progression of disease ($n = 3$), and other causes (eg, weakness, hospitalization, worsened neuropathy, patient or clinician choice; $n = 9$). Twenty-six (66.7%) of those who terminated the STI early experienced at least a 50% decline in CD4 cell count during the STI. Median study follow-up was 37 months in the STI arm (with 1.4% lost to follow-up) and 38 months in the control arm (with 0% lost to follow-up).

Treatments Prescribed After Randomization

The first regimen prescribed after randomization included a mean of 3.8 drugs (2.3 NRTIs, 1.3 PIs, and 0.2 NNRTI) in the STI arm and 3.9 drugs (2.3 NRTIs, 1.4 PIs, and 0.2 NNRTI) in the control arm. The mean number of drugs in the first regimen to which the patient had not been previously exposed was 1.5 for the STI arm and 1.3 for the control arm. Using baseline resistance testing, the mean number of drugs in the first regimen to which the virus was sensitive by genotype was 0.9 for both treatment arms; by phenotype, the mean numbers were 1.3 for the STI arm and 1.6 for the control arm. Coformulated lopinavir/ritonavir (Kaletra) was included in the first regimen for a significantly higher percentage of patients in the STI arm than in the control arm (70% vs. 56%; $P = 0.02$). Other drugs whose inclusion in the first regimen was significantly different in the STI arm compared with the control arm were stavudine (d4T; 40% vs. 54%; $P = 0.02$), amprenavir (19% vs. 33%; $P = 0.01$), and ritonavir (14% vs. 29%; $P < 0.001$). Ritonavir was primarily used for boosting; only 3 patients were known to be on full-dose ritonavir.

The mean number of months on the first antiretroviral regimen prescribed after randomization was 12.1 for the STI arm and 11.6 for the control arm ($P = 0.71$). The mean number of antiretroviral regimen changes during follow-up was 3.9 for each treatment arm.

Genotypic Resistance Patterns After Randomization

The virus from patients in the STI arm shifted to a less drug-resistant genotype during treatment interruption. At the earlier of STI termination or the 4-month visit, the mean change in the number of mutations present was a decrease of 4.9 mutations in the STI arm (2.4 NRTI mutations, 0.8 NNRTI mutation, and 1.7 PI mutations) and no change in the control arm ($P < 0.0001$). Fifty-one percent of the STI arm lost at

least half of the mutations present at randomization, and 26% lost all mutations. For the STI arm, the mean increases from baseline in the number of sensitive drugs according to genotype and phenotype at the earlier of STI termination or the 4-month visit were 6.3 and 6.4, respectively. At the 4-month visit, the control arm had no increase in the number of sensitive drugs according to genotype and a mean increase of 0.5 drug according to phenotype. For 19 patients in the control arm, resistance testing was not possible at the 4-month visit because of low viral load.

Disease Progression and Death

For progression of disease or death (the primary end point), 57 patients in the STI arm experienced a total of 102 events, whereas 48 patients in the control arm experienced a total of 81 events (Table 2; Fig. 1, top panel). The rates per 100 person-years for experiencing the first of progression-of-disease event or death in the STI and control arms were 17.5 and 14.3, respectively (hazard ratio = 1.28; $P = 0.22$). The most recent CD4 cell count before the first event was less than 100 cells/mm³ for 83% of events in the STI arm and for 67% of events in the control arm ($P = 0.11$). The mean proximal CD4 cell count before a progression-of-disease event or death was 70 cells/mm³ in the STI arm and 89 cells/mm³ in the control arm ($P = 0.45$).

In the STI arm, 50 events (88%) occurred after the study-defined STI period. Hazard ratios for progression of disease or death by time intervals are given in Figure 1 (bottom panel). In all intervals, the hazard ratio (STI arm compared with control arm) was ≥ 1 ; for the period of months 4 through 12, the hazard ratio was 2.20 (95% confidence interval: 0.99 to 4.88; $P = 0.05$).

The number of deaths was similar in each treatment arm (see Table 2). Considering progression-of-disease events, 44 patients in the STI arm experienced a total of 72 events, whereas 29 patients in the control arm experienced a total of 48 events. The most common progression-of-disease events were esophageal candidiasis, PCP, and cytomegalovirus (see Table 2). Of the 22 esophageal candidiasis events, 17 were classified as probable and 5 were classified as confirmed.

The odds of being on prophylaxis for PCP or MAC did not differ significantly by treatment arm for any time period (months 0–4, months 4–12, months 12–24, after month 24, or overall). The odds of being on an antifungal agent for any reason were significantly higher in the control arm than in the STI arm only for the period of months 4 through 12 (odds ratio = 1.71; $P = 0.04$). Among the patients who experienced an esophageal candidiasis event, this occurred in the period of months 4 through 12 in only 3 patients (18%) in the STI arm and 1 patient (20%) in the control arm. Most esophageal candidiasis events occurred after month 12: 11 (65%) in the STI arm and 3 (60%) in the control arm.

The hazard ratios for a progression-of-disease event or death did not vary by the study-defined subgroups listed earlier (data not shown).

CD4 Cell Counts and Plasma HIV-1 RNA Levels

The mean treatment arm differences in CD4 cell count change from baseline favored the control arm throughout

TABLE 2. Progression-of-Disease Event or Death

Event/Death	STI Arm		Control Arm		Hazard Ratio (95% CI)†	P value
	No. Patients	Rate*	No. Patients	Rate*		
Progression of disease or death	57	17.5	48	14.3	1.28 (0.86 to 1.91)	0.22
All-cause mortality	30	7.7	33	9.0	0.97 (0.58 to 1.62)	0.91

Specific Event Type	No. Patients With Event (Total Number of Events/Deaths‡)	
	STI Arm	Control Arm
Cryptosporidiosis	5 (6)	3
PCP	10 (11)	6 (7)
Toxoplasmosis	2	0
Microsporidiosis	2	0
MAC	3	4
Other mycobacterial	1	0
Bacterial pneumonia	1	2 (3)
Esophageal candidiasis	17 (21)	5 (8)
Cryptococcosis	5	2
Histoplasmosis	0	1
Aspergillosis	3	0
Cytomegalovirus	8 (9)	7 (9)
Herpes simplex	0	2
Herpes zoster	1 (2)	0
Kaposi sarcoma	1	2
Lymphoma	3	2
AIDS dementia complex	0	3
HIV wasting	2	2
Progression of disease	44 (72)	29 (48)
Progression of disease or death	57 (102)	48 (81)

*Per 100 person-years.

†Hazard ratios for the STI arm compared with the control arm; adjusted for prior progression of disease, baseline CD4 cell count, and baseline HIV RNA level.

‡If different from the number of patients with an event or death.

CI indicates confidence interval.

follow-up (Fig. 2, top panel). For the period from randomization through 4 months (the study-defined STI period), the mean CD4 cell count was higher by 84 cells/mm³ in the control arm than in the STI arm ($P < 0.0001$; Table 3). The mean differences for months 4 through 12, months 12 through 24, and after month 24 were 50 cells/mm³ ($P < 0.0001$), 45 cells/mm³ ($P = 0.006$), and 43 cells/mm³ ($P = 0.07$), respectively.

The median time to the CD4 cell count being greater than the baseline CD4 cell count at a follow-up visit was 5.0 months for the STI arm and 1.2 months for the control arm ($P < 0.001$). The median time to the CD4 cell count being 50 cells greater than the baseline CD4 cell count was 13.0 months in the STI arm and 3.6 months in the control arm ($P < 0.001$). At the most recent follow-up visit before the end of the study, 50% of the STI arm and 40.3% of the control arm had a CD4 cell count less than 100 cells/mm³ ($P = 0.11$).

During the study-defined STI period, the mean treatment arm differences in HIV-1 RNA level change from baseline were significantly different and favored the control arm (see Fig. 2, bottom panel). For the follow-up period from randomization to month 4, the mean change from baseline HIV-1 RNA level was an increase of 0.4 log copies/mL in the STI arm and a decrease of 0.8 log copies/mL in the control arm

(see Table 3; treatment arm difference of 1.2 log copies/mL; $P < 0.0001$). For the time after the study-defined STI period of months 4 through 12, months 12 through 24, and after month 24, the HIV-1 RNA level changes from baseline and the odds of having a viral load measurement less than 400 copies/mL were not significantly different between the treatment arms. At any follow-up visit, the percentage of patients with viral suppression < 400 copies/mL did not exceed 25% for either treatment arm. Changes in CD4 cell count and HIV-1 RNA level did not vary by protocol-defined subgroups (data not shown).

Adverse Events, Antiretroviral Adherence, Quality of Life, and Symptoms

The rates for any grade 4 (serious) adverse event were not significantly different between the treatment arms for the first 4 months of follow-up, after 4 months of follow-up, or overall. Sixty-one patients in the STI arm and 55 patients in the control arm had at least 1 grade 4 adverse event (hazard ratio = 1.09; $P = 0.66$). The mean quality-of-life scores at baseline, month 4 (the end of the STI period), month 12, and month 24 were not significantly different for the treatment arms. The respective scores were 65.4, 63.5, 64.8, and 64.3 for the STI arm and 65.0, 66.5, 63.1, and 60.6 for the control arm. There

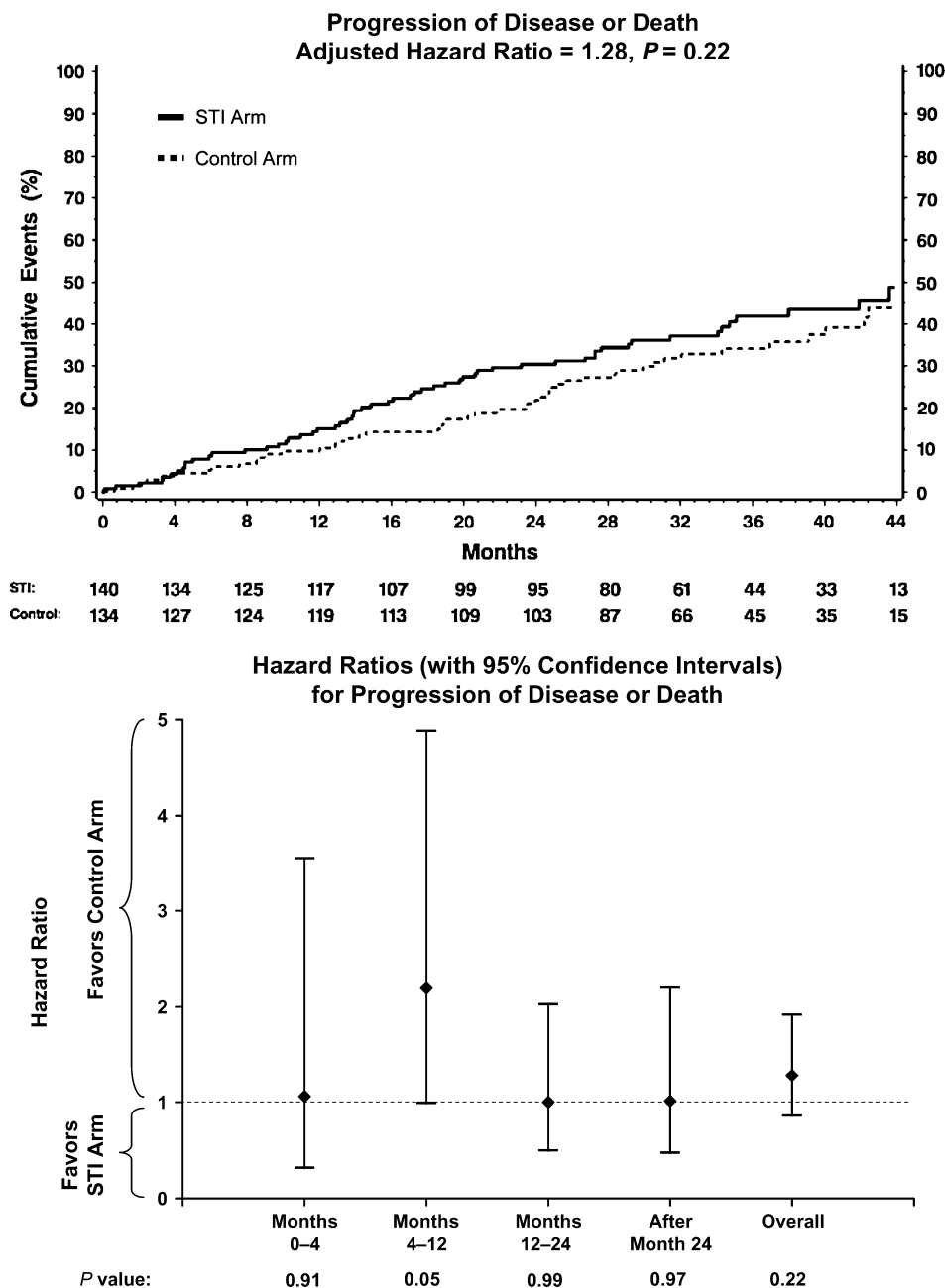


FIGURE 1. Kaplan-Meier estimate of the cumulative incidence of progression of disease or death (top panel) and hazard ratios for progression of disease or death for the intervals of randomization through month 4, months 4 through 12, months 12 through 24, after month 24, and overall (bottom panel).

were no significant differences between the treatment arms in the mean change from baseline for the proportions reporting symptoms by grade or self-reported adherence to antiretroviral treatment as measured with 7-day recall and 3-day recall (data not shown).

DISCUSSION

The participants in CPCRA 064 are representative of an expanding population of HIV-infected individuals in need of more effective treatment strategies. These patients were highly experienced with regard to antiretroviral treatment (97% had 3-class drug exposure), with elevated viral loads, MDR HIV-1,

and advanced immunodeficiency. This randomized, prospective, clinical end-point study was designed based on findings from observational and small pilot studies of patients who interrupted HIV treatment for various lengths of time.^{10,11,20-22} We hypothesized that for patients with MDR HIV-1 and antiretroviral treatment failure, an STI would induce a shift toward a drug-sensitive viral population and result in an improved HIV-1 RNA response on treatment reinitiation with a new (optimized) regimen. We further hypothesized that this strategy would lead to a concomitant improvement in CD4 cell count on the new regimen and, ultimately, a reduction of at least 33% in progression-of-disease events or death in the STI arm compared with the control arm. A 16-week

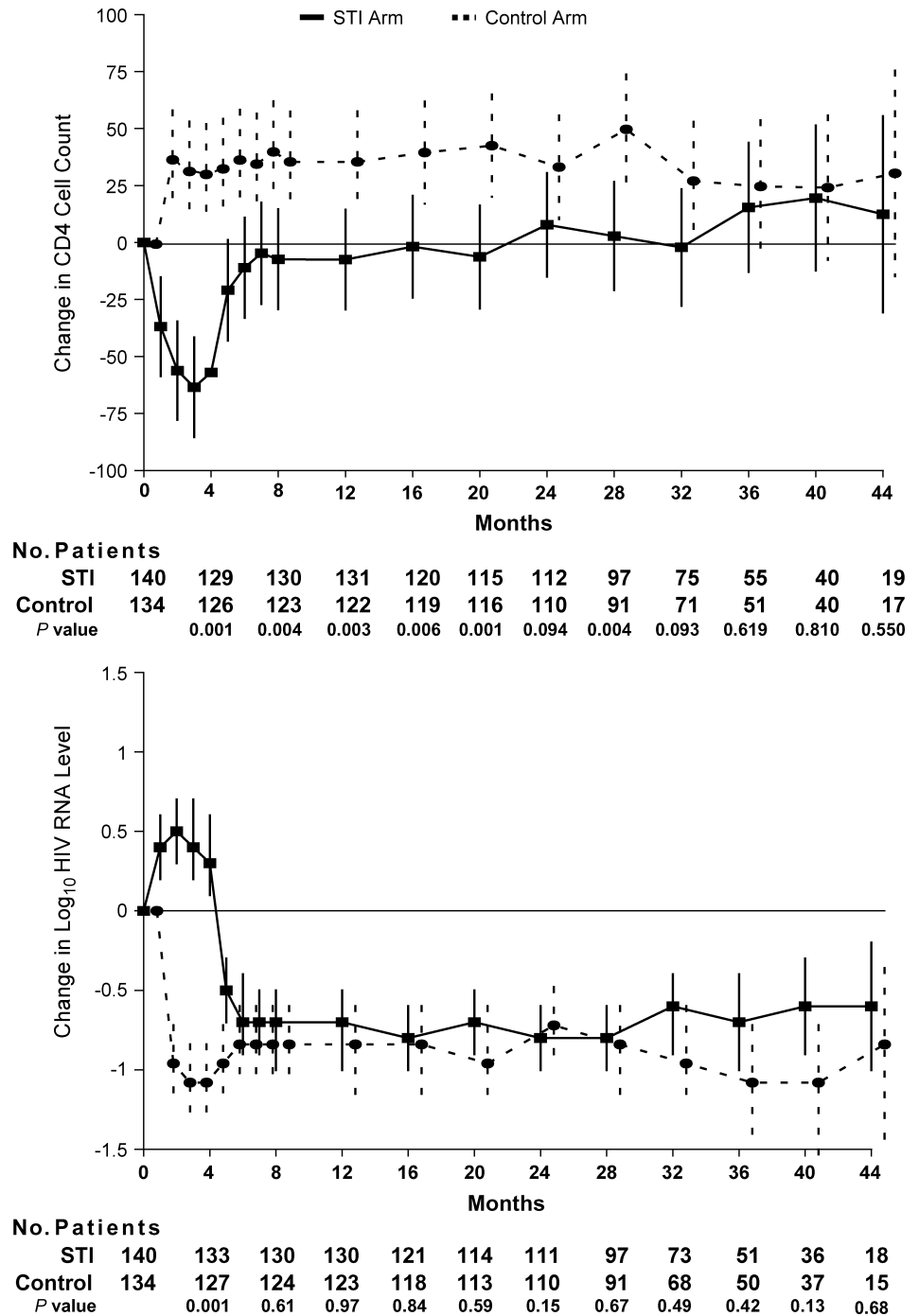


FIGURE 2. Mean changes from baseline in CD4 cell counts (top panel) and plasma HIV RNA levels (bottom panel). The bars represent 95% confidence intervals.

treatment interruption was chosen to allow adequate time to maximize reversion to wild-type virus while attempting to minimize the immediate risk of CD4 decline.

As reported previously, the CPCRA 064 study was closed to enrollment early when the STI arm showed an increase in progression-of-disease events or death and an unfavorable CD4 cell count response compared with the control arm.¹⁷ When the study closed to enrollment (June 2002), the median follow-up was 12 months, and it was not certain how long the negative impact of the 4-month STI

would be sustained. These final results, based on a median follow-up of 37 months, confirm our preliminary findings on CD4 cell count response and provide additional information on the long-term impact of STI in this setting. With the current results, after an additional 24 months of study follow-up, there is not a persisting significant difference between treatment arms for progression of disease or death.

In our study, similar to others,^{10,11,16,20-25} the HIV-1 isolated from plasma shifted from a highly drug-resistant pattern toward a more drug-sensitive pattern during the STI in

TABLE 3. Changes in CD4 Cell Count and HIV RNA Level by Follow-Up Period

	STI Arm		Control Arm		(STI Arm) – (Control Arm)		
	Mean	SE	Mean	SE	Difference	95% CI	P value
CD4 cell count (cells/mm ³)							
Months 0–4	–48.8	6.5	35.6	6.5	–84.3	(–100.4 to –68.3)	<0.0001
Months 4–12	–9.5	9.0	40.6	9.0	–50.0	(–72.3 to –27.7)	<0.0001
Months 12–24	–3.0	13.3	42.2	13.2	–45.2	(–77.2 to –13.1)	0.006
After month 24	–3.2	18.6	39.3	19.7	–42.5	(–88.6 to 3.6)	0.07
HIV RNA level (log copies/mL)							
Months 0–4	0.41	0.08	–0.82	0.08	1.24	(1.05 to 1.43)	<0.0001
Months 4–12	–0.68	0.10	–0.72	0.10	0.04	(–0.22 to 0.29)	0.78
Months 12–24	–0.80	0.13	–0.81	0.13	0.01	(–0.30 to 0.31)	0.96
After month 24	–0.76	0.15	–0.78	0.15	0.02	(–0.34 to 0.38)	0.90

CI indicates confidence interval for the difference between the treatment arms.

most patients based on standard HIV-1 population genotyping. This strategy failed to produce a superior overall HIV-1 RNA response in the STI arm compared with the control arm, however. After patients in the STI arm reinitiated therapy, the HIV-1 RNA response between the 2 randomized treatment arms was indistinguishable. Notably, both arms had a mean overall decrease in HIV-1 RNA level of approximately 0.7 log copies/mL less than baseline, which was maintained during follow-up. This response was achieved with a mean of only 3.9 drugs in the initially prescribed salvage regimen. Factors that likely contributed to this favorable virologic response in patients with MDR-resistant HIV-1 include the availability of genotypic and phenotypic drug resistance testing to help optimize the new salvage regimen and US Food and Drug Administration (FDA) approval of lopinavir/ritonavir (Kaletra) and tenofovir early on in this study. Although a significantly higher proportion of patients in the STI arm received coformulated lopinavir/ritonavir in their first regimen after randomization, more patients in the control arm were administered amprenavir and ritonavir. Of note, no patients in either treatment arm were prescribed atazanavir, tipranavir, or enfuvirtide in the first regimen. Because both randomization arms had similar HIV-1 RNA responses on treatment, it is unlikely that regimen differences contributed to the long-term CD4 count responses.

An important finding in the CPCRA 064 study is that even though the mean CD4 cell counts in the STI arm returned to baseline levels soon after treatment reinitiation, CD4 cell counts in the STI arm remained significantly lower than in the control arm for 24 months despite similar virologic responses. Impairment of immune recovery in the STI arm is also evident by the fact that the median time to reaching a CD4 cell count of 50 cells/mm³ greater than baseline was significantly longer (by 9 months) in the STI arm than in the control arm. At the beginning of the study, the proportion of patients with a CD4 cell count less than 100 cells/mm³ was similar in the 2 randomized treatment arms. Although this proportion remained fairly constant in the control arm during follow-up, in the STI arm, the proportion of patients with CD4 cell counts less than 100 cells/mm³ increased from 36% at the beginning of the study to 50% at the end. Because most clinical events occurred

in patients who had CD4 cell counts less than 100 cells/mm³, these results further demonstrate that in this patient population, treatment interruption imposes an increased risk of immunosuppression that is clinically relevant and lasts well beyond the time the patient is off antiretroviral therapy.

Consistent with the observed CD4 count response and contrary to what we hypothesized, the STI did not result in a significant reduction in the primary end point of progression of disease or death for the STI arm. Because this study was closed to enrollment before complete accrual was obtained, power for progression of disease or death is lower than planned. The confidence interval for the overall hazard ratio excludes the hypothesized 33% reduction in events for the STI arm, however, and it seems that the STI arm was at increased risk for a progression-of-disease event or death during the period immediately after the STI (months 4–12). During that period, the difference between the treatment arms in concomitant use of antifungal medication may have contributed to the increased risk in the STI arm. The purpose for the antifungal agents (eg, systemic vs. topical, treatment vs. prophylaxis) was not recorded for this study, however. Importantly, only a few esophageal candidiasis events occurred during this period, and most occurred after month 12.

Despite differences in patient populations (eg, baseline CD4 counts) and treatment regimens used, 4 other smaller randomized trials have results that are consistent with our study, finding no immunologic or virologic benefit to prescribing an STI before switching salvage therapy in patients with MDR HIV-1 treatment failure.^{24,26–28} In contrast, a single smaller randomized study²³ reported improved HIV-1 RNA level and CD4 cell count responses after STI in patients with extremely advanced HIV-1 disease treated with at least 7 antiretroviral agents. Final results from an ongoing randomized factorial trial of STI versus continuous therapy and standard HAART versus mega-HAART (5 or more drugs) for patients with MDR HIV-1²⁹ are not yet available.

The CPCRA 064 study is unique in that it is the first randomized trial of STI for patients with MDR HIV-1 and treatment failure that has a clinical end point in addition to virologic and immunologic outcomes, allowing us to determine the long-term impact of STI in this setting. These

final results show no clinical, virologic, immunologic, or quality-of-life benefit to prescribing a 4-month treatment interruption before changing salvage regimens compared with immediately changing regimens in patients with MDR HIV-1 treatment failure. In these patients, we further demonstrate that STI is associated with a significant and prolonged impairment of CD4 cell count recovery that lasts well after treatment is reinitiated. Based on these results, antiretroviral treatment interruption in this patient population should be avoided.

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APPENDIX

Participating Sites and Investigators

The following centers and investigators participated in the study: AIDS Research Alliance of Chicago: R. Luskin-Hawk, R. Verheggen, and M. Schultz; Bronx AIDS Research Consortium: E. Telzak, J. McGowan, and J. Shuter;

Community Consortium of San Francisco: the Care Providers of the Castro Mission Health Center, P. A. Pell, and C. C. Child; Denver Community Program for Clinical Research on AIDS: D. Cohn, R. Fernandez, and F. Moran; Harlem Aids Treatment Group: E. Monde and L. Fuentes; Henry Ford Hospital: N. Markowitz, L. Faber, and L. Makohon; Houston AIDS Research Team: H. Cuervo, R. Manning, and R. Arduino; Louisiana Community AIDS Program: S. Pablovich and J. Walker; Philadelphia FIGHT: E. Tedaldi and FIGHT

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