

# Final Results of CPCRA 064: A Randomized Trial Examining Structured Treatment Interruption for Patients Failing Therapy with Multi-Drug Resistant HIV

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## Abstract\*

**Background:** CPCRA 064 examines the effect of structured treatment interruption (STI) on progression of disease or death, CD4, and HIV RNA in treatment-experienced patients with multi-drug resistant HIV. The study closed in June 2004 with median follow-up of 36 months.

**Methods:** HIV-infected patients on stable antiretroviral regimens with virologic failure and multi-drug resistant virus were randomized 1:1 to a 4-month STI followed by a new regimen, or to immediate change to a new regimen. Baseline genotypic (TRUGENE) and phenotypic (Antivirogram) resistance tests were provided to help optimize new regimens. The primary endpoint is progression of disease or death. Secondary endpoints include changes in CD4, HIV RNA, and quality of life. All analyses are intent-to-treat, using proportional hazard and longitudinal regression models adjusted for baseline CD4 and HIV RNA.

**Results:** Baseline measurements for 274 patients were: mean CD4 = 181, log HIV RNA = 5.0, nadir CD4 = 69, prior progression of disease = 58%, prior number of antiretrovirals = 10.6, number of drug-resistance mutations = 9.7, 3-class drug exposure = 97%, mean number of drugs in initial new regimen after randomization = 3.9. Minimum follow-up is 24 months (maximum 48). During the STI, 53% of the STI arm lost at least half of the mutations present at randomization; 27% lost all mutations. The treatment arm differences in log HIV RNA favor the control arm by 1.2 log ( $p < 0.0001$ ) for the follow-up period of 0 to 4 months; there are no differences for follow-up periods 5 to 24 and after 24 months. The treatment arm differences in CD4 for the follow-up periods 0 to 4, 5 to 24, and after 24 months are 84.3 ( $p < 0.0001$ ), 47.0 ( $p = 0.0001$ ), and 42.8 ( $p = 0.07$ ), favoring the control arm. In the STI arm 57 patients experienced 94 progression of disease or death events; in the control arm 48 patients had 74 events (adjusted hazard ratio for the time to first event = 1.28,  $p = 0.22$ ). There were 30 deaths in the STI arm and 33 in the control arm, of which 13 and 19 were first events. Considering only progression of disease, 44 patients in the STI arm and 29 patients in the control arm experienced at least 1 event (adjusted hazard ratio = 1.66,  $p = 0.04$ ). There are no significant differences between the treatment arms in adherence, symptoms or quality of life.

**Conclusions:** Results of CPCRA 064, with median follow-up of 36 months, show that STI prior to changing treatment in patients failing therapy with multi-drug resistant virus does not confer clinical, immunologic, virologic, or quality of life benefits. STI is associated with a significantly unfavorable CD4 response and increased progression of disease that persists well after treatment reinitiation.

\*Updated version of abstract based on currently available data.

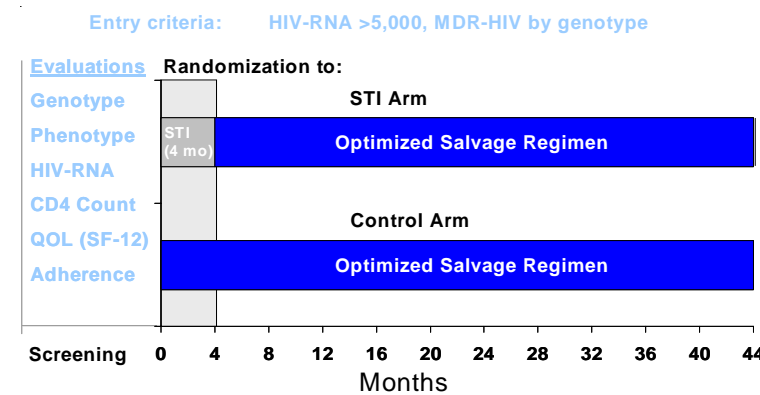
## Background

- Structured treatment interruption (STI) is being examined in various settings in HIV disease and is likely to have different utility and impact depending on the stage of disease, level of viral control prior to STI, drug regimens used, and number and duration of STI.
- The CPCRA 064 (MDR-HIV) study examined STI in the setting of treatment failure in patients with multi-drug resistant HIV who had persistent viremia despite combination antiretroviral therapy. The primary objective was to determine the clinical impact of STI on progression of disease or death in this setting.
- This study closed to enrollment early (June 2002) due to safety concerns in the STI arm (preliminary data reported previously). Patients continued to be followed on study for a minimum of 24 months (median follow-up 36 months). The study was closed to follow-up June 30, 2004.
- We present the final results of the impact of STI on progression of disease or death, CD4+ T-cell counts, and HIV-RNA in this patient population.

## Methods

- Design: randomized controlled trial; clinical primary endpoint.
- Patient population: N = 274. HIV-infected persons on current combination antiretroviral therapy with virologic failure (HIV-RNA > 5,000) and multi-drug resistant (MDR) defined by genotype.
- Treatment (1:1 randomization):
  - STI arm: a 4-month STI followed by a change in regimen (N=140)
  - Control arm: an immediate change in regimen (N=134)
- Early termination of the STI was recommended if a progression of disease event or a greater than 50% drop in CD4 cell count occurred before the 4-month visit.
- Baseline genotypic (TRUGENE) and phenotypic (Antivirogram) resistance tests were provided to help optimize new regimens.
- The primary endpoint is progression of disease or death. Secondary endpoints include changes in CD4, HIV RNA, and quality of life. All analyses are intent-to-treat, using proportional hazard and longitudinal regression models adjusted for baseline CD4 and HIV RNA.

## Study Design



## Baseline Characteristics

Characteristic	STI	Control	Total
Number of patients	140	134	274
Mean age (years)	44.8	43.9	44.3
Female (%)	8.6	9.7	9.1
Race - White (%)	42.9	47.0	44.9
Prior progression of disease (%)	56.4	59.7	58.0
CD4 count (mean, cells/mm <sup>3</sup> ), [S.D.]	183.3 [145.8]	177.5 [171.9]	180.5 [158.8]
Nadir CD4 count (mean, cells/mm <sup>3</sup> )	66.7	71.8	69.2
HIV RNA (mean, log <sub>10</sub> copies/mL), [S.D.]	5.0 [0.6]	5.0 [0.5]	5.0 [0.6]
Prior number of ARVs (median)	11.0	11.0	11.0
Three-class drug exposure (%)	96.4	97.0	96.7
Number of drug resistance mutations* (mean)	10.0	9.3	9.7

\*Maximum of 54 mutations; Reference: IAS Oct. 2004

## Treatment prescribed after randomization

1 <sup>st</sup> Regimen after Randomization*	STI	Control	p-value
Total # Drugs	3.8	3.9	NS
Lopinavir included	70%	56%	0.02
Amprenavir included	19%	33%	0.01
d4T included	40%	54%	0.02
Tenofovir included	46%	35%	0.06

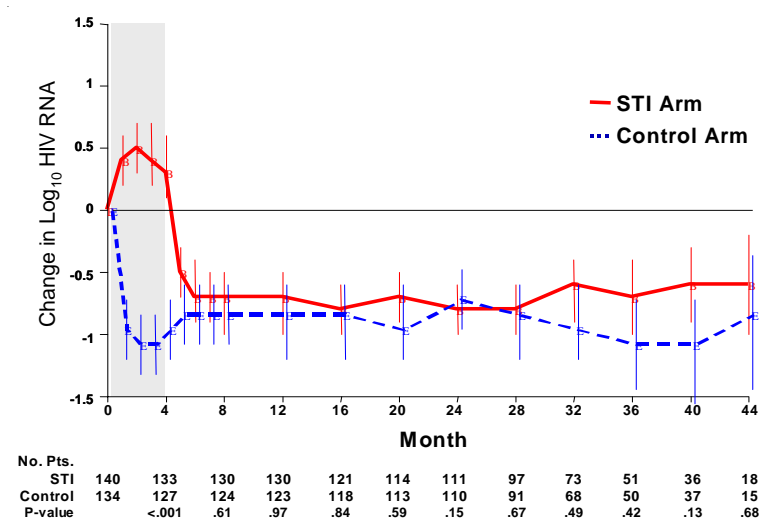
\*The new optimized regimen began immediately after randomization for the Control arm and was delayed until after the treatment interruption period in the STI arm.

## Shift in resistance levels during STI

- During the STI, the predominant virus population shifted to a more sensitive resistance pattern (wild-type) in the majority of subjects in the STI arm.
- Fifty-three percent of the STI arm lost at least half of the mutations\* present at randomization; 27% lost all mutations\*.
- For the STI arm, the mean number of mutations\* (Mutation Score) present at randomization was 10.0 and dropped to 5.1 at the end of the STI.

\*Based on a total of 54 possible mutations (including different alleles at a single codon) from the IAS October 2004 list.

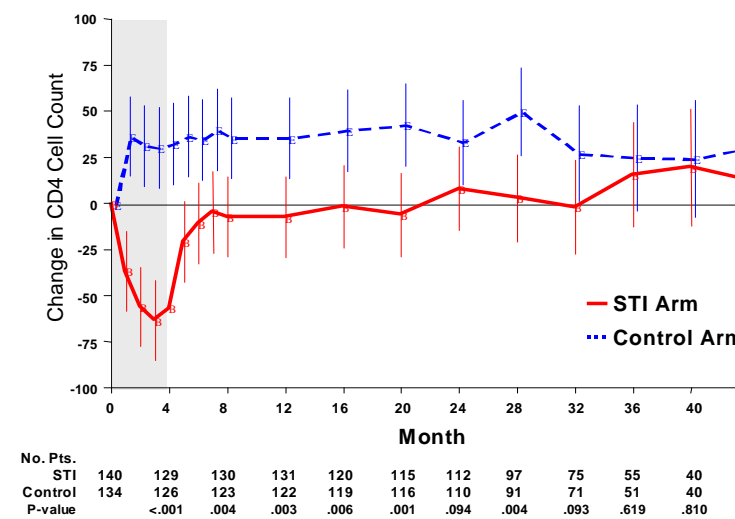
## Mean Change from Baseline in HIV RNA



## HIV RNA Response

Time Interval	STI	Control	Difference	SE	P-value
Months 0-4	+ 0.4	- 0.8	1.2	0.1	<0.0001
Months 5-24	- 0.7	- 0.7	0.0	0.1	0.85
After month 24	- 0.8	- 0.8	0.0	0.2	0.92

## Mean Change from Baseline in CD4 Cell Count



## CD4 Response

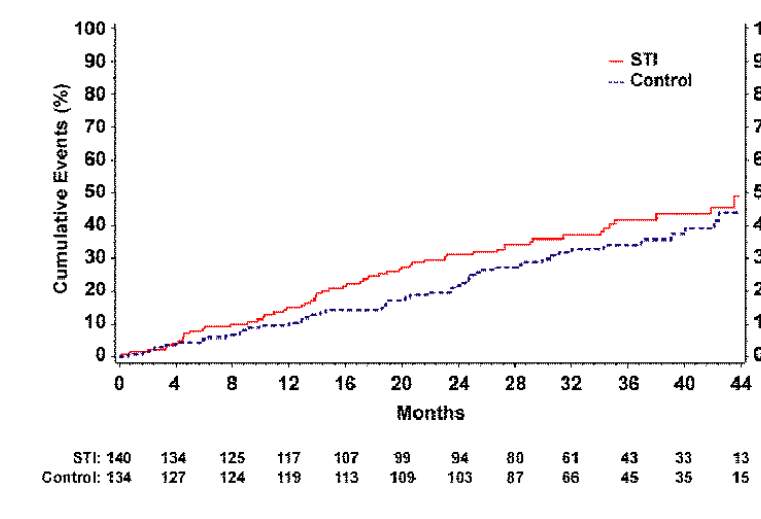
Time Interval	STI	Control	Difference	SE	P-value
Months 0-4	- 48.8	+ 35.6	84.3	8.2	<0.0001
Months 5-24	- 7.9	+ 39.1	47.0	12.0	0.0001
After month 24	- 3.2	+ 39.6	42.8	23.4	0.07

## Incidence of First Clinical Event

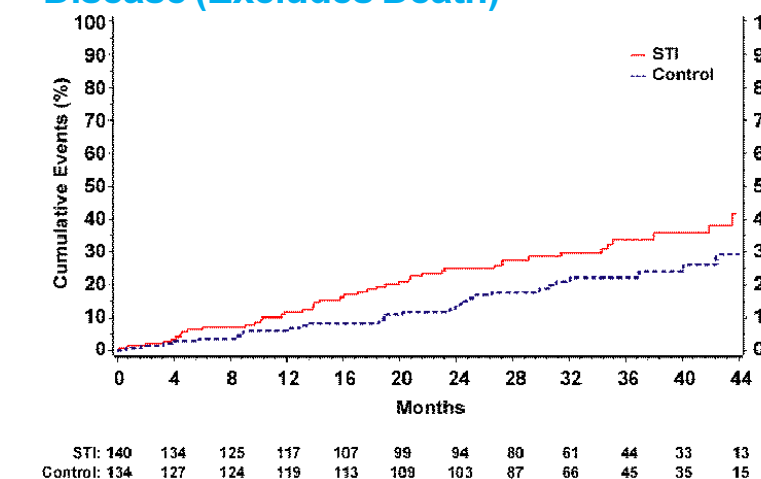
Event	STI*	Control*
Esophageal Candidiasis	15 (26.3%)	5 (10.4%)
PCP	7 (12.3%)	3 (6.3%)
CMV	4 (7.0%)	6 (12.5%)
Cryptosporidiosis, chronic intestinal	5 (8.8%)	3 (6.3%)
HIV wasting syndrome	1 (1.8%)	1 (2.1%)
Cryptococcosis	4 (7.0%)	1 (2.1%)
Lymphoma	3 (5.3%)	1 (2.1%)
MAC	0 (0.0%)	3 (6.3%)
Toxoplasmosis (CNS)	2 (3.5%)	0 (0.0%)
KS, mucocutaneous or visceral	1 (1.8%)	1 (2.1%)
Herpes simplex, >1month or >2cm	0 (0.0%)	2 (4.2%)
Herpes zoster, disseminated	1 (1.8%)	0 (0.0%)
Histoplasmosis	0 (0.0%)	1 (2.1%)
Aspergillosis	1 (1.8%)	0 (0.0%)
Recurrent bacterial pneumonia	0 (0.0%)	1 (2.1%)
AIDS Dementia Complex	0 (0.0%)	2 (4.2%)
Neurologic event, unspecified	1 (1.8%)	0 (0.0%)
Death	13 (22.8%)	19 (39.6%)

\* Two people, one in each treatment arm, presented with two clinical events simultaneously as their first event. Both events for each person are listed above.

## Cumulative Incidence of Progression of Disease or Death



## Cumulative Incidence of Progression of Disease (Excludes Death)



## Incidence of Progression of Disease or Death

Event	Number of First Events*	Hazard Ratio**	P-value
POD or Death	57	1.28	0.22
Death	30	0.97	0.91
POD	44	1.66	0.04

\*Total POD or death events: 94 in the STI arm and 74 in the control arm  
 \*\*HR adjusted for baseline CD4, HIV-RNA, prior POD, and clinical site

## Results: Major Points

- These results represent a minimum follow-up of 24 months (median 36 months, maximum 48 months).
- During the STI, the predominant virus population shifted to a more sensitive virus in the majority of subjects in the STI arm.
- During months 0 to 4 (i.e. the period in which treatment interruption was prescribed for the STI arm) the treatment arm differences favored the control arm in HIV RNA by 1.2 log<sub>10</sub> copies/mL ( $p < 0.0001$ ) and in CD4 count by 84.3 cells/mm<sup>3</sup> ( $p < 0.0001$ ).
- There were no differences between the treatment arms in HIV RNA for follow-up periods 5 to 24 months and after 24 months. However there were persistent differences in CD4 count favoring the control arm. For the follow-up periods 5 to 24 months and after 24 months, the CD4 count differences were 47.0 ( $p = 0.0001$ ), and 42.8 ( $p = 0.07$ ).
- The total number of deaths were similar in the two treatment arms (STI: 30, Control: 33,  $p=NS$ ). However, there were significantly more progression of disease events (excluding deaths) in the STI arm compared with the control arm. Forty-four patients in the STI arm and 29 in the control arm had at least one POD event (adjusted hazard ratio = 1.66,  $p = 0.04$ ). The most common POD events in the STI arm were esophageal candidiasis and pneumocystis pneumonia.
- There were no significant differences between the treatment arms in adherence, symptoms or quality of life (data not shown).

## Conclusions

- CPCRA 064 shows that when compared with the control arm, the strategy of using a 4 month STI in salvage was associated with the following:
  - Increase in clinical events
  - Poorer CD4 response that persists well after reinitiation of therapy
  - No significant benefit in HIV RNA response
- These results confirm our preliminary findings and indicate that patients with MDR-HIV should be maintained on continuous optimized HAART and avoid the use of treatment interruption.

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