Structured interruption of treatment hastened disease progression in multidrug-resistant HIV

Lawrence J, Mayers DL, Huppler Hullsiek K, et al. **Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus.** N Engl J Med. 2003;349:837-46.

QUESTION

In patients with multidrug-resistant HIV infection, is structured treatment interruption (STI) more effective than an immediate change in drug regimen for delaying disease progression or death?

DESIGN

Randomized (allocation concealed*), blinded {outcome assessors and monitoring committee}†,* controlled trial with median 11.6-month follow-up (Terry Beirn Community Programs for Clinical Research on AIDS [CPCRA] 064 study).

SETTING

16 primary care units of the CPCRA in the United States.

PATIENTS

270 patients who were ≥ 13 years of age (mean age 44 y, 91% men), had an HIV RNA level > 5000 copies/mL, and genotypic evidence of multidrug-resistant virus. Exclusion criteria included an opportunistic infection needing treatment and pregnancy or breastfeeding. Follow-up was > 98%. All patients were included in the analysis.

INTERVENTION

Patients were allocated to STI (4-mo structured interruption of treatment followed by the initiation of an optimized antiretroviral regimen [selected according to the results of the genotypic and phenotypic antiretroviral-resistance tests done at screening]) (n = 138) or immediate initiation of an optimized antiretroviral regimen (control) (n = 132). Treatment could be resumed in the intervention group if disease progression or a 50% decrease in CD4 count occurred before 4 months.

MAIN OUTCOME MEASURES

Disease progression (confirmed or probable occurrence of an AIDS-defining condition on the basis of the classification of the Centers for Disease Control and Prevention) or death. Secondary outcomes included changes from baseline in CD4 cell counts, HIV RNA levels, and quality of life.

MAIN RESULTS

Analysis was by intention to treat. More patients in the STI group had disease progression or died than did patients in the control group (Table). The groups did not differ for death (P = 0.5). CD4 cell counts in the STI group were lower than those on the control group from 0 to 4 months (difference 85 cells/mm^3, P < 0.001) and 5 to 8 months (difference 47 cells/mm^3, P < 0.001). After 4 months, the groups did not differ for HIV RNA levels or for any other outcomes or adverse events.

CONCLUSION

In patients with multidrug-resistant HIV infection, structured interruption of treatment was associated with greater disease progression or death than immediate change in drug regimen.

Source of funding: National Institute of Allergy and Infectious Diseases.

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*See Glossary.

Structured treatment interruption (STI) vs immediate initiation of an optimized antiretroviral therapy (control) for multidrug-resistant HIV at median 11.6 months†

Outcomes	STI	Control	RRI (95% CI)	NNH (CI)
Progression of disease or death	16%	9%	139% (19 to 350)	8 (4 to 59)
Progression of disease	12%	4%	446% (77 to 1331)	6 (2 to 32)
Death	6%	6%	42% (–49 to 273)	Not significant

†Abbreviations defined in Glossary; RRI, NNH, and CI calculated from Cox proportional-hazards model in article.

COMMENTARY

STI is being evaluated as a strategy in many stages of HIV infection. A retrospective cohort study suggested that an STI before the initiation of salvage therapy could result in improved viral load and CD4 count responses (1). A series of controlled trials tested this hypothesis, but the conclusions of these trials conflict.

The GIGHAART study (2) found that the STI group had better immunologic and virologic responses than the control group with no difference in the incidence of clinical events. In contrast, the Retrogene study (3) and the current CPCRA study by Lawrence and colleagues (the largest study of the group), found no virologic or immunologic advantage. Although the CPCRA study closed early because of futility, it suggested harm because more patients in the STI group showed evidence of disease progression.

The reason for the differences in outcome of these studies remains unclear but could be related to the stage of disease, duration of the STI, potency of the salvage regimens, adherence and drug levels, use of secondary opportunistic infection prophylaxis, certainty of the diagnosis of the disease progression events, and available treatment options.

Nonetheless, when combined, these studies suggest that in patients with multidrug-resistant virus, a short STI before the initiation of salvage therapy is unlikely to be beneficial and could be harmful.

The results cannot be generalized to patients in earlier stages of illness with higher CD4 counts and better treatment options for salvage therapy in whom opportunistic infection prophylaxis is consistently applied.

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References

1. **Miller V, Sabin C, Hertogs K, et al.** Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. AIDS. 2000;14:2857-67.
2. **Katlama C, Dominguez S, Duvivier C, et al.** Long-term benefit of treatment interruption in salvage therapy (GIGHAART ANRS 097). 10th Conference on Retroviruses and Opportunistic Infections [Abstract]. Boston, February, 2003.
3. **Ruiz L, Ribera E, Bonjoch A, et al.** Role of structured treatment interruption before a 5-drug salvage antiretroviral regimen: the Retrogene Study. J Infect Dis. 2003;188:977-85.