

Beware of Drug Holidays before HIV Salvage Therapy

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Not unlike its human host, the human immunodeficiency virus (HIV) is often unfaithful while reproducing. Copies made are not completely true to the original; a mistake occurs about once every 10,000 nucleotides. This may not seem like much, until we remember the enormous production rate of the virus, which guarantees that every possible mutation will arise at each position of the genome every day. Errors in reproduction, as well as recombination between the two RNA genomes, drive the diversification of HIV into quasi-species and strains.

Antiretroviral treatment has diverse effects, including selection for mutants with decreased drug sensitivity that progressively outgrow the wild-type virus. HIV pays a price for becoming resistant to drugs, in that resistant mutants usually reproduce less well, or are less fit, than the wild type. This concept of reduced fitness is difficult to quantify, but it makes intuitive sense, because otherwise, the drug-resistance mutations would have been prevalent even before the drugs were introduced. Withdraw drugs in a patient with resistant virus, and the wild type will often reappear within 2 to 12 weeks.

In patients infected with a resistant strain of HIV, the virus remains detectable in plasma, and CD4 cell counts may continue to fall. Should such patients continue to take the medication? Why not stop, avoid the inconvenience, expense, and side effects of treatment, wait for a sensitive virus to replace the resistant one, and thus improve the chances of eventual salvage therapy? There is a rub: the fitter virus may also be more immunosuppressive. In 1998, Kaufmann et al.¹ found that the discontinuation of ineffective treatment in patients with drug-resistant HIV was followed by a decrease in CD4 cells, and in 2001, Deeks et al.² showed that the decrease in CD4 cells began precisely at the time of the reversion to wild type. In pilot studies, Miller et al. found that the CD4 cell count decreased by a

median of 89 cells per cubic millimeter during the interruption of treatment, thus increasing the risk of AIDS-defining opportunistic infections.³

The theoretical foundations of interrupting treatment before the initiation of salvage therapy have also come under attack. First, the idea that mutant HIV is replaced by wild-type virus may be an illusion; the process is more appropriately referred to as overgrowth. Genotypic resistance assays will not detect resistant viral populations that constitute less than 15 percent of the total. Thus, a hypothetical patient who has a drug-resistant virus concentration of 5000 RNA copies per milliliter before the drug holiday may have a drug-sensitive viral load of 100,000 RNA copies per milliliter after the drug holiday, but the drug-resistant copies may still be present. This possibility is reflected by the finding that virologic failure occurs in some patients despite genotypic tests showing that the virus is sensitive before salvage therapy is initiated. The use of more sensitive assays has revealed that such patients have minority populations harboring drug-resistance mutations, which subsequently become predominant and cause treatment failure.⁴

Second, resistant viruses presumably originate from proviral copies integrated into cellular DNA. Cells with such integrated DNA have a half-life of years. Thus, it is hard to see what could be achieved by interrupting treatment for a few weeks.

The promise of a better response to salvage therapy on the one hand may be offset by the risk of increased immune suppression on the other. Such situations of equipoise call for randomized, prospective clinical trials. Three have been completed, and the results of the largest are reported by Lawrence et al. in this issue of the *Journal* (pages 837–846). Patients with multidrug-resistant HIV and HIV RNA levels of more than 5000 copies per milliliter either started a salvage regimen immedi-

ately (the control group) or stopped antiretroviral treatment for four months before starting the salvage regimen (the treatment-interruption group). Recruitment was stopped prematurely because the treatment-interruption group did worse than the control group: 22 cases of disease progression or death, as compared with 12 cases. Unexpectedly, most end points occurred after the interruption of treatment. There was no evidence of a favorable effect on surrogate markers. As expected, CD4 cell counts declined during treatment interruption and remained lower than those in the control group during the 20-month follow-up. Regarding HIV RNA concentrations, the salvage regimen had similarly disappointing results in the two groups: in only one in five patients was the viral load reduced to less than 400 copies per milliliter.

Do these results settle the issue? Doubts remain because the results of the concurrently published GIGHAART study seem to differ from those of Lawrence et al. (see Table). The decrease in the viral load at week 12 in the treatment-interruption group was much greater in the GIGHAART study than in the study by Lawrence et al. and remained greater up to week 48, with corresponding differences in the CD4 cell counts.

The Table shows that there were important differences among the three completed randomized trials in the degree of immunodeficiency, the duration of the treatment interruption, and the choice of salvage therapy. Lawrence et al. selected salvage therapy on the basis of the resistance genotype and phenotype and administered a mean of 3.6 drugs. The Retrogene study used a standardized regimen of lopinavir (enhanced by ritonavir), saquinavir, abacavir, didanosine, and lamivudine, whereas the GIGHAART study used all available drugs—a mean of 7.3—including nonnucleoside and nucleoside reverse-transcriptase inhibitors and protease inhibitors.

What are clinicians to do when faced with studies with divergent results, one of which was large and included clinical end points, the others of which were smaller and used surrogate markers as end points? They must go with the results of the large study. Partial or complete interruption of treatment may still have a role before the initiation of salvage therapy; perhaps the duration should be shorter than four months. Partial interruption of treatment involves stopping the drugs in which resistance has little influence on viral fitness while keeping those, such as lamivudine, that lead to less-fit resistant mutants. This interesting approach to treatment awaits clinical trials. Thus, for the time being, unless there are unbearable side effects, patients should continue treatment while awaiting salvage therapy. Maintaining the selection pressure may also reduce the virulence of the virus and therefore benefit the patient.

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4. Mellors J, Palmer S, Nissley D, et al. Low frequency non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant variants contribute to failure of efavirenz-containing regimens in NNRTI-experienced patients with negative standard genotypes for NNRTI mutations. *Antiviral Ther* 2003;8:Suppl:S150. abstract.

Key Data from Three Trials Investigating the Value of Treatment Interruption before the Initiation of Salvage Therapy.*			
Variable	Current Study (N=270)	Retrogene Study (N=46)	GIGHAART Study (N=68)
Median CD4 count at start of study (no./mm ³)	144	339	27
Duration of treatment interruption (wk)	16	12	8
Mean no. of drugs in salvage regimen	3.6	5.0	7.3
Mean change in viral load at wk 12 (log copies/ml)			
Control group	-0.86	-1.63	-0.37†
Treatment-interruption group	-0.78‡	-1.50	-1.91†
Mean change in CD4 cell count at wk 48 (no./mm ³)			
Control group	42	61	7†
Treatment-interruption group	14§	20	69†

* Data on the Retrogene Study (*Journal of Infectious Diseases*) and the GIGHAART study (*AIDS*) are in press.

† The median value is given.

‡ The value was obtained three months after salvage therapy was initiated.

§ The value was obtained 12 months after salvage therapy was initiated.