



HIV JournalView

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Partial Treatment Interruptions: Stopping NNRTIs May Be OK, but Not NRTIs

Deeks SG, Hoh R, Neilands TB, et al. *Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. J Infect Dis. November 1, 2005;192(9):1537-1544.*

One of the puzzles of modern day HIV care is how to deal with patients who have multidrug-resistant HIV. There is little guidance regarding what works and what doesn't. Steven Deeks and colleagues have been working for years to understand the relative value of discontinuing HIV treatment in these patients. In this study, they tried to assess whether there was any benefit in stopping *some*, but not all, of the HIV drugs in a patient's current regimen. Put another way, Deeks et al asked: In a patient with resistance to all the drugs he/she is taking at the time, do any of those drugs still have *any* antiretroviral activity?

Deeks et al studied 22 patients who stopped taking their protease inhibitor (PI; n=18), nucleoside/nucleotide reverse transcriptase inhibitor(s) (NRTI; n=6) or non-nucleoside reverse transcriptase inhibitor (NNRTI; n=6). This was an unblinded, nonrandomized study in which patients were followed for changes in CD4+ cell count and HIV viral load for up to 48 weeks. The median baseline CD4+ cell count was 333 cells/mm³ and the median viral load was 3.93 log₁₀ copies/mL.

Stopping the NRTIs in a regimen resulted in an increase in viral load of 0.66 log₁₀ copies/mL and a decrease in CD4+ cell count of 100 cells/mm³ by 16 weeks. Interruption of the PI resulted in no significant change in viral load out to 24 weeks and a nonsignificant trend toward a reduction of CD4+ cell count. Interruption of NNRTI treatment resulted in no change in viral load level and no reported change in CD4+ cell count. There was very little loss or evolution of viral resistance after discontinuation.

In addition, fasting lipids were monitored. Discontinuation of PI treatment resulted in significant

declines in triglyceride, total cholesterol and non-high-density-lipoprotein (non-HDL) levels, whereas discontinuation of NRTI treatment resulted in significant reductions in triglyceride levels.

This pilot study is important, because both patients and practitioners alike remain confused regarding the potential harm or benefit of treatment interruption strategies in patients with multidrug-resistant HIV infection. In some studies, a complete treatment interruption for up to four months has resulted in significant viral load increases and CD4+ cell count reduction; when followed by reinitiation of antiretroviral therapy, the result has been a reduction in viral load, a return of the CD4+ cell count to baseline (but not above it) and an increase in AIDS events (primarily presumptive esophageal candidiasis), but not death.¹

The suggestion from this study is that it is probably safe to discontinue the NNRTI in a highly active antiretroviral therapy (HAART) regimen for those patients with NNRTI resistance. By contrast, NRTI treatment, despite evidence of genotypic and phenotypic resistance, still has an antiviral effect, as evidenced by the viral load increase and CD4+ cell count decline in patients who discontinue their NRTIs.

Although PI discontinuation did not result in significant differences in CD4+ cell count after 24 weeks, there was a *suggestion* of a decline, and estimates presented in this paper indicate that a significant decline in CD4+ cell count (25% loss) might occur 37 weeks after discontinuation. Thus, there may be some benefit from continuing PI treatment, although this benefit would not be seen acutely.

This study also confirms what others have published^{2,3} about stopping lamivudine (3TC, Epivir) treatment despite evidence of lamivudine resistance: namely, that viral loads *do* increase and CD4+ cell counts *do* decline when lamivudine is stopped.

Since this was a small and uncontrolled study, more studies like this will need to be performed to gauge the longer-term benefit of partial treatment interruptions.

Induction/Maintenance With Lopinavir/Ritonavir Monotherapy Is Worth a Closer Look

Arribas JR, Pulido F, Delgado R, et al. *Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study).* *J Acquir Immune Defic Syndr.* **November 1, 2005;40(3):280-287.**

Although our choice of initial therapies has improved dramatically over the years, there is still some attempt to lessen the risk of toxicity that lifetime treatment no doubt brings. So another family of treatment interruptions is being studied in HIV-infected patients who do not have advanced disease or multidrug-resistant virus -- in fact, these patients have achieved and maintained an undetectable viral load with their current antiretroviral regimen. Several studies have been published recently, and are reviewed elsewhere,⁴ that look at such strategies as one week on, one week off;⁵ or one month on, one month off; or staying off antiretroviral treatment until some predetermined CD4+ cell count decline threshold is met. Some of these strategies have been abandoned due to the rapid development of antiretroviral resistance.

Another possible treatment interruption strategy is to initiate a patient on a three- or four-drug antiretroviral regimen, and then stop some, but not all, of the drugs once the patient has achieved a sustained, undetectable viral load. This strategy, called induction/maintenance, has been attempted previously⁶ with mixed results,⁷ probably related to the antiretroviral regimens being used. Nonetheless, in theory, a successful induction/maintenance strategy could maintain viral suppression, decrease potential toxicities and reduce pill burden. Many of the studies of this strategy start with four drugs and go to three drugs.

Jose Arribas and colleagues studied the induction/maintenance strategy using lopinavir/ritonavir (LPV/r, Kaletra) as a single agent to see if it could maintain viral load suppression.

Theirs was a randomized, open-label study conducted in Madrid, Spain. Patients were required to have no history of virologic failure, to have an undetectable viral load (less than 50 copies/mL) for at least six months, and to have been on a regimen consisting of lopinavir/ritonavir + two NRTIs

for at least the preceding four weeks. Patients were randomized to either continue their current regimen or stop the two NRTIs and continue treatment with lopinavir/ritonavir monotherapy.

Patients were followed for 48 weeks with laboratory safety monitoring and viral load and CD4+ cell count tests. Baseline characteristics were not significantly different between the arms. The cohort was 80% male, and the mean age was 42 years. Two thirds had a previous AIDS diagnosis. The mean CD4+ cell count was about 600 cells/mm³.

Forty-two patients were screened; 40 of them completed 48 weeks of follow-up (20 in each arm). Four of 21 patients in the monotherapy arm demonstrated virologic failure, but one of the four was lost to follow-up. The percentage of patients with an undetectable viral load at 48 weeks was 81% in the monotherapy arm and 95% in the triple-drug therapy arm (one patient in this arm discontinued therapy).

The four patients with virologic failure after a switch to monotherapy were further characterized. Three of the four had an adherence rate between 60% and 80% as measured by prescription refills. The remaining patient had a refill score of 100%. Plasma trough lopinavir levels were within the therapeutic range in three of the four patients. No significant primary protease gene mutations were found at the time of virologic failure. There were no significant adverse events or differences in serum lipids.

Further analysis indicated that patients who failed the monotherapy regimen had significantly more days without medication, more missed doses and less time with an undetectable viral load prior to randomization than those patients who were able to maintain virologic suppression on monotherapy. The three patients with virologic failure who were not lost to follow-up were able to re-achieve virologic suppression after the addition of two NRTIs to their regimen.

This is an important pilot study demonstrating the feasibility of using boosted-PI monotherapy to maintain patients who have achieved an undetectable viral load on standard combination antiretroviral therapy. Previous studies may have failed to demonstrate the success of such a strategy, because the monotherapy agent was probably not as potent as a boosted PI.

Of course, lopinavir/ritonavir may not be unique in this regard, since indinavir (IDV, Crixivan) boosted with ritonavir (RTV, Norvir) has also been shown to work as a monotherapy maintenance strategy.⁸ That indinavir + ritonavir study went from three drugs to boosted indinavir alone.

Although less-than-optimal adherence would seem to be the logical explanation for the virologic failure among patients on the lopinavir/ritonavir monotherapy, plasma lopinavir levels at the time of failure nonetheless appeared to be in the therapeutic range.

However, regardless of the cause of failure, it was assuring to note that no specific lopinavir-associated mutations were found at the time of virologic failure (although the analysis was performed with population sequencing, so the presence of specific mutations could not be completely ruled out in the absence of more sophisticated analyses), and that patients responded favorably to the reintroduction of NRTIs. Further study is required to determine the feasibility of this strategy, as well as whether the new tablet formulation of lopinavir/ritonavir, or the administration of lopinavir/ritonavir once daily, could also be used as a monotherapy maintenance strategy.

Fish Oil Can Help Some Lipid Levels -- But to What Extent?

Wohl DA, Tien H-C, Busby M, et al. *Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counseling for the treatment of antiretroviral therapy-associated hypertriglyceridemia. Clin Infect Dis. November 15, 2005;41 (10):1498-1504.*

Antiretroviral treatment has resulted in various lipid abnormalities in HIV-infected people. Probably related to these dyslipidemic disorders is an increased risk of cardiovascular morbidity and mortality. Many patients with lipid abnormalities are unable to control serum triglyceride and cholesterol levels through diet modification or exercise alone and require medical treatment to do so.

Omega-3 fatty acids derived from fish oil can lower serum triglyceride levels in people *without* HIV infection.⁹ David Wohl and colleagues therefore studied whether fish oil supplementation might

result in the same effects in patients *with* HIV infection.

Patients who had been receiving antiretroviral treatment for a minimum of three months and who had serum triglycerides greater than 200 mg/dL were randomized to one of two intervention groups: diet and exercise counseling alone or diet and exercise counseling along with daily omega-3 fatty acid supplementation (1,750 mg eicosapentaenoic acid, 1,150 mg docosahexaenoic acid) for 16 weeks taken with food. This dose was within the American Heart Association's recommended dose for fish oil supplementation. Fasting lipids and diet and physical activity logs were monitored.

Fifty-two patients were enrolled and 41 (79%) completed 16 weeks of observation. The study population was about 90% male and about 55% nonwhite, with a mean age of approximately 43 years. The mean body mass index was 27. The mean CD4+ cell count was about 500 cells/mm³ and the mean viral load was about 35,000 copies/mL. There were no significant demographic differences between the two study arms, although 19% were on a ritonavir-boosted PI in the fish-oil arm, versus 35% in the diet/exercise arm. Mean baseline triglyceride levels were 461 mg/dL in the fish-oil arm and 502 mg/dL in the diet/exercise arm.

After four weeks, mean triglyceride levels had decreased by 25.1% in the fish-oil arm and *increased* 2.8% in the diet/exercise arm ($P = .0074$). After 16 weeks, triglyceride levels had maintained a reduction of 19.5% in the fish-oil arm versus a 5.7% reduction in the diet/exercise arm, which was no longer statistically significant ($P = .12$). There were no significant changes within or between study arms in total cholesterol, low-density lipoprotein (LDL), HDL, lipoprotein A, insulin or glucose levels at either week 4 or 16. Both groups reduced their total caloric intake and fat intake and increased their exercise activity. None of these parameters were significantly different between arms. There were no significant adverse events in the fish-oil arm.

This study demonstrates that fish-oil supplementation can result in significant short-term decreases in serum triglyceride levels in HIV-infected people on antiretroviral therapy, at least when the supplementation is accompanied by a diet and exercise education plan. The reductions seen in this study were consistent with those seen in other studies¹⁰ in patients without HIV infection. The limitations of this study include a small sample size, the potential impact of exercise and diet, and the fact that the researchers did not control for treatment regimen or the presence of baseline lipid disorders prior to antiretroviral treatment initiation.

Although the use of fish oil resulted in a modest decline in triglycerides in this study, whether this treatment strategy should *substitute* for other triglyceride-lowering medications, such as fibrates, remains to be determined.

For Lipid Relief, Switching From Stavudine to Tenofovir May Help

Schewe CK, Maserati R, Wassmer G, Adam A, Weitner L. *Improved lipid profiles and maintenance of virologic control in heavily pretreated HIV-infected patients who switched from stavudine to tenofovir treatment.* *Clin Infect Dis.* January 1, 2006;**42(1):145-147.**

Previous studies¹¹ have indicated that stavudine (d4T, Zerit) is associated with increased serum lipids in HIV-infected patients. There is also some suggestion that patients who switch from a stavudine-containing regimen to one containing tenofovir (TDF, Viread) may see an improvement in their lipid profile. Carl Knud Schewe and colleagues conducted a retrospective chart review of patients in a German HIV clinic who had been receiving a stavudine-containing regimen and were switched to one containing tenofovir.

Schewe et al identified 66 patients (58 men and 8 women, mean age 46 years) in this clinic who had made such a change, but who had made no other antiretroviral regimen change or change in lipid-lowering medications. Median duration of prior antiretroviral treatment was 8.7 years; median duration of stavudine treatment was 54 months. Fifty-one of the 66 patients had an undetectable viral load (less than 50 copies/mL) at the time of the switch. The reasons for discontinuation of stavudine included lipodystrophy, lipid abnormalities, neuropathy, abnormal liver function tests and virologic failure. At the time of the antiretroviral regimen switch, 49 of the 66 patients were changed to a tenofovir-containing regimen without PIs. Median follow-up was 18 months.

Mean total cholesterol at the time of the switch was 227 mg/mL; this decreased significantly -- by 18 mg/mL -- after three months on tenofovir ($P = .003$). Although mean total cholesterol

increased slightly between months 12 and 18, it remained significantly lower after 18 months (mean decrease 36 mg/mL; $P = .002$) when compared to baseline levels. LDL levels decreased slightly, but not significantly, over the same period. The mean triglyceride level at the time of the switch was 289 mg/dL and dropped significantly -- by 84 mg/dL -- after three months on tenofovir ($P < .001$). However, triglyceride reductions were *not* maintained, and by month 18 their levels had increased back almost to pre-switch values.

This study confirms that changing an antiretroviral regimen by only substituting tenofovir for stavudine can result in significant short-term reductions in total cholesterol and triglyceride levels, and *sustained* reductions in total cholesterol.

The study is limited due to the fact that it is a retrospective chart review. In addition, it does not reveal whether patients had preexisting lipid abnormalities *prior* to antiretroviral treatment, what the other background antiretroviral medications were or whether there were any differences in lipid changes in patients who were on NNRTI- or PI-based regimens.

Nevertheless, these study results certify that it is important for physicians and patients to consider *all* lipid-lowering strategies, including the replacement of medications within antiretroviral regimens that could be contributing to a lipid abnormality.

Tenofovir + Didanosine Can Make a Good Team, if the Didanosine Dose Is Lowered

Karrer U, Ledergerber B, Furrer H, et al, and the Swiss HIV Cohort Study. *Dose-dependent influence of didanosine on immune recovery in HIV-infected patients treated with tenofovir.* **AIDS. November 18, 2005;19(17):1987-1994.**

As more and more people use once-daily antiretroviral regimens for HIV treatment, attention has increasingly turned to the combination of didanosine (ddI, Videx) and tenofovir as a once-daily duo that can be incorporated into a regimen with additional NRTIs, an NNRTI or a PI.

Previous data¹² have suggested that a dose reduction of didanosine, from 400 mg to 250 mg once daily, is necessary when combined with tenofovir, as the latter results in increased didanosine plasma levels and the potential for greater didanosine-related toxicity. In addition, there have been reports¹³ suggesting that the combination of didanosine at 400 mg daily with tenofovir can result in CD4+ cell count declines despite virologic control.

Data are lacking regarding whether the same reduction in CD4+ cell count occurs when the dose of didanosine is reduced. Urs Karrer and colleagues conducted a retrospective study using data from the Swiss HIV Cohort Study of patients who were treated with tenofovir with or without didanosine at different dosing levels.

Patients were included if they had received tenofovir and/or didanosine for at least six months. A total of 614 patients met the inclusion criteria; 393 were treated with tenofovir without didanosine and 221 were treated with tenofovir + didanosine. There was no significant difference between the two groups in terms of baseline demographics (age, gender, mode of transmission, hepatitis C coinfection, CD4+ cell count and CD4+ cell percentage). Didanosine dose was stratified by weight adjustment into low dose (less than 3.3 mg/kg; median 2.9 mg/kg), intermediate dose (3.3 to 4.1 mg/kg; median 3.7 mg/kg) and high dose (more than 4.1 mg/kg; median 5.0 mg/kg). CD4+ cell count slopes and co-factors affecting CD4+ cell count slopes were analyzed in univariate and multivariate analyses.

Median viral load at follow-up was comparable and not significantly different in terms of the percentage of people with an undetectable viral load (less than 50 copies/mL) between the tenofovir (86%) and tenofovir + didanosine (81%) groups. Viral load response was the same in all the tenofovir + didanosine groups regardless of the didanosine dose.

In the univariate analysis, patients treated with tenofovir and more than 4.1 mg/kg of didanosine had, on average, a CD4+ cell count increase that was 51 cells/mm³ less than patients treated with tenofovir without didanosine or tenofovir + didanosine at less than 4.1 mg/kg daily. In the multivariate analysis, increased age, decreased body weight (not related to didanosine dose), higher absolute CD4+ cell count and an undetectable viral load all significantly affected the CD4+ cell count slope. In addition, high-dose didanosine (more than 4.1 mg/kg) was significantly associated with a negative CD4+ cell count slope of -47 cells/mm³/year.

This study confirms previous findings that the standard dose of didanosine (400 mg daily) in combination with tenofovir has a profoundly negative effect on CD4+ cell count and immune recovery. The good news is that when didanosine doses are reduced when given in combination with tenofovir, no such negative impact on CD4+ cell count was found. In addition, there were no differences in virologic outcome when reduced doses of didanosine were given with tenofovir.

The study is limited by its lack of reported toxicity data, and by the fact that it is a retrospective analysis in a heterogeneous population. Why there is such a profound effect of this combination on CD4+ cell count -- and, in all probability, function as well -- is not clear.

Nonetheless, this study gives assurance to providers and patients that the combination of tenofovir + didanosine can be given safely, as long as the dose of didanosine is reduced to maximize CD4+ cell count recovery and still achieve virologic suppression.

In Rich Countries or Poor, Antiretroviral Therapy Programs Work

Severe P, Leger P, Macarthur C, et al. *Antiretroviral therapy in a thousand patients with AIDS in Haiti. N Engl J Med. December 1, 2005;353(22):2325-2334.*

Although today in the United States we pretty much take for granted the availability and benefits derived from antiretroviral treatment for HIV infection, this clearly cannot be said for the developing world. Much has been discussed about the limited access to combination antiretroviral treatment in developing countries and over whether, even if treatment were available, HIV-infected people in developing countries would have the inclination to take these medications over the long haul.

Although earlier studies have suggested that these obstacles to treatment in the developing world are more myth than reality, few large-scale studies have proved it -- until now. This study by Patrice Severe and colleagues highlights the successful application of combination antiretroviral treatment in Haiti, a country with political instability and where approximately 3% of the adult population is infected with HIV.

Antiretroviral therapy was prescribed to adults and children with an AIDS-defining illness or a CD4 + cell count below 200 cells/mm³. Of 3,978 patients who were HIV-1 seropositive, 1,004 met criteria for antiretroviral treatment (94 children and 910 adults and adolescents). Of the adult population, 55% were female and 71% were between the ages of 30 and 49. The baseline median CD4+ cell count was 131 cells/mm³; 52% of the enrolled patients had an AIDS-defining illness.

The study participants were prescribed a regimen consisting of generic versions of efavirenz (EFV, Sustiva, Stocrin) + lamivudine + zidovudine (AZT, Retrovir). Alternatively, stavudine could be substituted for zidovudine, and nevirapine (NVP, Viramune) could be substituted for efavirenz.

A multidisciplinary team consisting of peer counselors, social worker, pharmacist, nurses and physicians oversaw the program in the capital city of Haiti, Port-au-Prince. Routine laboratory monitoring, body weight and adherence via pill counts were monitored. The cost of antiretroviral treatment ranged from US\$550 to US\$750 per person per year, and the total cost for all care was estimated to be approximately US\$1,600 per person per year. The observation period was one year.

Of the 910 adults and adolescents who participated in this study, 127 died through one year of follow-up -- and 100 of the 127 died within the first six months of antiretroviral treatment. Thus, 90% of the study patients were alive at six months and 87% were alive at 12 months. There were significant increases in weight and CD4+ cell count at months 6 and 12. Among the 94 children, 98% were still alive at one year.

There were a limited number of patients (n=100) who had viral load test results available after one year. However, 76 of the 100 patients tested had undetectable (less than 400 copies/mL) viral load levels.

Twenty-five percent of the adults and 10% of the children required an antiretroviral change; the primary reasons were toxicity or medication supply issues. In addition, it is worth noting that 12% of the patients were also being treated concurrently for active tuberculosis (TB). Since both HIV infection and TB require treatment, some although not all patients can successfully be treated for

both simultaneously. In this study, TB treatment was started first, and if a patient's CD4+ cell count was more than 200, HIV treatment was deferred; if the CD4+ cell count was between 50 and 200, TB treatment was given for two months and then HAART was started; if the CD4+ cell count was less than 50, TB and HIV treatment were started together.

This study presents dramatic results demonstrating how an internationally supported antiretroviral program can be successfully executed in Haiti. Epidemiological studies have indicated that the one-year survival rate of patients with AIDS in Haiti is about 30%. It is thus remarkable that, in this study, 87% of adults and 98% of children with AIDS survived for one year. The authors point out that the virologic and immunologic results obtained in this study are consistent with results seen in U.S.-based clinical trials and cohorts.

This is one of the first trials to demonstrate large-scale feasibility and success of an antiretroviral program in the developing world. Although medication supply issues and other logistical problems were evident, the broad level of success in Haiti demonstrated in this study should be repeatable in many other developing countries, as long as the same level of international support is provided. This study was supported by the World Health Organization, Global Fund, PEPFAR (President's Emergency Plan For AIDS Relief) and an international team of investigators.

Male Circumcision and HIV Risk: A Little Snip Can Make a Big Difference

Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. *Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Medicine. November 2005;2(11):1112-1122.*

Several observational studies have indicated that the prevalence of HIV infection among men who have been circumcised is less than among men who remain uncircumcised.¹⁴ It is not clear why this might be so, but it may be related to the keratinization of the glans penis in circumcised men, which might prevent the penetration of HIV. By contrast, the retained foreskin in uncircumcised men provides a mechanism for sheltering genital secretions after sexual contact; this allows for easy entrance of HIV through the foreskin membrane.

To better understand whether male circumcision results in reduced HIV infection, Bertran Auvert and colleagues performed a prospective, randomized trial in South Africa in which adult males were circumcised or left uncircumcised and followed prospectively to determine rates of HIV infection. The study included males between the ages of 18 and 24 (mean age: 21 years). There were no significant demographic differences between the control and intervention groups. Male circumcision was performed by experienced general practitioners. Follow-up visits were scheduled for three, 12 and 21 months after enrollment. Trial participants underwent genital examinations, blood testing and extensive questioning regarding their sexual history and habits. Patients were offered risk-reduction counseling and condoms. Mean follow-up was 18 months; 8% of the total population was lost to follow-up.

A total of 3,274 men were enrolled in the trial and 1,568 circumcisions were performed. There were 60 adverse events (4%) reported after surgery; these were primarily related to pain, bleeding and swelling immediately after surgery. Late adverse events were noted at month 21 in 11 participants (1%); they included urination problems, erectile dysfunction and dissatisfaction with the appearance of the penis.

During the study, 20 trial participants acquired HIV infection in the circumcised group, versus 49 trial participants in the uncircumcised group ($P < .0005$). The relative risk of HIV infection after circumcision was 0.4 compared to the control group. Stated another way, circumcision resulted in a 60% reduction in the risk of acquiring HIV infection. In a multivariate analysis looking at the attribution of sexual behavior factors, the reduction of HIV infection after circumcision was not affected by changes in reported behavior, including condom use.

This is a remarkable study demonstrating that a relatively simple and cost-effective intervention results in a dramatic reduction in the incidence of new HIV infection among men. The study was stopped early by the Data and Safety Monitoring Board because of the profound reduction in HIV infection found in the circumcised group. Although the study did not address the impact of male circumcision on *female* acquisition of HIV infection, its findings are nonetheless important.

The authors state that the impact of this intervention would be comparable to the preventative rates an HIV vaccine could achieve, but at a more affordable cost. Although the study was only

conducted in South Africa, there is no reason why these findings would not be translatable to any other country with high rates of HIV infection.

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