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Choosing this month's articles to review was a challenge. The past 2 months in the world of HIV research have been productive, with the publication of many excellent reports that are sure to change HIV clinical practice. As occasionally happens, several reports described different aspects of the same problems. For instance, new information related to metabolic complications of HIV and its therapies were found in abundance in the major HIV/AIDS journals. In addition, a few novel antiretroviral treatment strategies were reported that are, at the least, thought provoking. Rounding out these themes is a reassuring paper regarding the use of the influenza vaccine among HIV-infected patients that arrives in time to prepare for flu season, as well as an article examining surrogate markers for CD4+ cell count in areas where such testing is inaccessible.

Metabolic Complications of HAART

Seaberg EC, Munoz A, Lu M, et al, for the Multicenter AIDS Cohort Study. *Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003*. **AIDS. *June 10, 2005;19(9):953-960.***

Many of us have had a sneaking suspicion that combination antiretroviral therapy contributes to hypertension. Patients with normal blood pressure would start highly active antiretroviral therapy (HAART) and experience incremental increases into the hypertensive range soon thereafter. Later, with a switch in regimen, blood pressures would return toward normal. But, because these experiences have been anecdotal and the benefits of HAART are so striking, our concern regarding hypertension has not risen to the levels seen for hyperlipidemia or body shape changes.

Muddying the waters is the fact that hypertension becomes more prevalent with increasing age and weight -- both HAART byproducts. So, linking hypertension to HIV therapy has been tricky

business. A few years ago, some reports began to trickle in regarding protease inhibitor (PI) therapy and hypertension. Hewitt et al described an association between indinavir (IDV, Crixivan) and elevated blood pressure in a retrospective review of a clinical cohort.[1] This was followed by additional studies reporting results that have been conflicting -- possibly reflecting disparate research designs and populations scrutinized.[2-3]

An ideal way to address the question of the role of HIV therapy in blood pressure would be to look at trends in hypertension in a large cohort of HIV-infected patients who were evaluated with serial blood pressure measurements before and after the initiation of a variety of antiretrovirals. Better yet would be to compare these individuals to a group of HIV-uninfected controls who were similarly evaluated. This is exactly what Eric Seaberg and colleagues in the Multicenter AIDS Cohort Study (MACS) did.

MACS has been following a cohort of more than 5,500 gay men since 1984 in 4 U.S. cities (Baltimore/Washington, D.C.; Chicago; Los Angeles; Pittsburgh). The participants are seen regularly and blood pressure is obtained, along with treatment history and blood for laboratory analyses. Importantly, not all of the cohort is HIV infected; in fact, by 2003, the last year of data contributed for this study, 60% remained HIV uninfected. Almost all of the original MACS participants were available for the hypertension analysis.

To look at the baseline characteristics of the cohort is to look through a retrospect-o-scope back on the gay American man in the 1980s.

At baseline, the median age was 32 years old, 83% were Caucasian and almost 60% had a history of smoking, with about 40% current smokers. The median body mass index (BMI) was a trim 23 kg/m^2 (25 kg/m^2 is considered overweight and 30 kg/m^2 is obese). Blood pressure in this young group of mostly lean men, "back in the day," was a median 120/80.

By 2003, the average BMI of the cohort increased to 26 kg/m^2, but smoking declined to just 18% of these men. Among those participants who are HIV infected, the percentage who were taking HAART at any one of the semiannual study visits was approximately 37%, but varied considerably over time.

The prevalence of both systolic (>140 mmHg) and diastolic (>90 mmHg) hypertension at baseline was 5.9%. Men who were older than 50 years, are African American or had a BMI greater than 25 kg/m^2, had a higher prevalence of hypertension. Over time, hypertension became more common, particularly among the groups listed above, as well as those taking HAART. Systolic hypertension was detected during 12% of the study visits made by the trial participants on HAART, while diastolic hypertension was registered during 9.2% of these visits. These rates were higher than those observed during the visits of the overall cohort (7.3% with systolic hypertension and 8.0% with diastolic hypertension).

Interestingly, the rate of diastolic hypertension during the first 5 years of HAART was no different than that observed among HIV-uninfected men. However, after 5 years, the rate shot up. For systolic hypertension, the rate was stable for the first 2 years of HAART and increased sharply after that.

Multiple regression analyses found some expected independent factors associated with hypertension, including greater age, African-American race, higher BMI and, for systolic hypertension alone, smoking. But, when looking at HIV therapy, the results were more surprising. Men who were HIV infected and were not on antiretrovirals or were on therapy that was not HAART (i.e., monotherapy or dual-nucleoside therapy), had a *lower* prevalence of hypertension than HIV-uninfected men. (Why this is, is not clear or discussed in the paper, although perhaps suboptimal HIV therapy is a marker of substance abuse, nonadherence or other characteristics that may lead to poor nutrition and overall health and a lower blood pressure.) Among those on HAART for less than 2 years, the prevalence of systolic hypertension was no different than that in HIV-uninfected men, though, as described above, it increased substantially thereafter. The risk of systolic hypertension was 51% higher after 2 years of HAART than for an HIV-uninfected man.

To see if PIs were the culprit, as has been suggested in some reports, exposure to the class, as well as to individual agents of the class, was examined. The results indicate that PIs (overall and specific agents) *did not* contribute to systolic hypertension above and beyond the other independent factors described above. The odds ratio for PI-containing HAART was exactly the same as for non-PI-containing HAART, 1.37 ($P<.05$). HAART was not independently associated with diastolic hypertension in the regression analysis, regardless of the duration of therapy.

The Bottom Line

The association of HAART with systolic hypertension is concerning because isolated systolic blood pressure elevation is linked in the Framingham Study to atherosclerotic disease, including myocardial infarction and stroke. Isolated systolic hypertension is usually a manifestation of decreased arterial compliance following deposition of atherosclerotic plaques and reduced aortic distensibility. Therefore, this finding fits with an emerging picture regarding the effect of HAART on arterial function. However, the study only included men, which has always been a limitation of MACS. Further, the cohort is largely Caucasian and affluent. As our clinic cohorts are increasingly exactly the opposite and comprised of more women, one should apply these findings broadly only with caution.

Clinicians should take from this report a heightened awareness of the role of HAART in blood pressure elevation. Specifically, in addition to the "no-brainer" risk factors for elevated blood pressure (age, increased weight, being African American and smoking), HAART (be it PI sparing or containing) is *independently* associated with an increased systolic blood pressure in men like those in MACS. Monitoring blood pressure and treating according to published guidelines makes good sense and good practice.[4]

Efavirenz Reduces Plasma Levels of Popular Statins

Gerber JG, Rosenkranz SL, Fichtenbaum CJ, et al, for the AIDS Clinical Trials Group A5108 Team. *Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study*. **J Acquir Immune Defic Syndr. *July 1, 2005;39(3):307-312.***

Managing the dyslipidemia that accompanies antiretroviral therapy is complicated by drug-drug interactions among several major HIV and lipid-lowering therapies. Further, some of the most lipid-offensive antiretrovirals are the most likely to influence the metabolism of the drugs used to reduce lipids, especially the HMG-CoA reductase inhibitors (more commonly known as statins).

In this report, John Gerber and colleagues in the AIDS Clinical Trials Group (ACTG) investigated the effect of the popular antiretroviral efavirenz (EFV, Sustiva, Stocrin) on 3 commonly used statins: simvastatin (Vytorin, Zocor), atorvastatin (Caduet, Lipitor) and pravastatin (Pravachol).

Fifty-two healthy, HIV-uninfected study participants were administered 1 of these statins for 3 days, during which the levels of the drug were checked over a 24-hour period. Efavirenz was then administered alone for 12 days and then together with the statin for an additional 3 days -- allowing for the levels of both drugs when co-administered to be compared with those obtained earlier in the study. The dosage for each statin was as follows: simvastatin 40 mg daily, atorvastatin 10 mg daily and pravastatin 40 mg daily.

Of those enrolled, 42 participants contributed to the final analyses. The remainder either discontinued due to side effects or had improper specimen collection. Of the study patients who remained in the trial, most were men and two thirds were Caucasian.

Co-administration of efavirenz with simvastatin led to a 58% decline in area under the curve (AUC) and a similar decline in the active metabolite HMG-CoA reductase AUC. For atorvastatin, there was a median 42.7% decline in the AUC of this drug and a 34.5% drop in levels of its active metabolites in the presence of efavirenz. Likewise, the pravastatin AUC was reduced by a median of 40.4% with efavirenz. Efavirenz concentration was unaffected by the statins.

To demonstrate that these changes in AUC are potentially clinically meaningful, the investigators examined the low-density lipoprotein (LDL) cholesterol levels of the participants after the first short course of their statin alone and after the statin with efavirenz. They found a trend toward attenuation of the lipid-lowering effect of the drugs.

The Bottom Line

This extremely helpful study defines an important and commonplace drug-drug interaction. Efavirenz can contribute to increases in lipids, therefore, the prospect of concomitant administration of this non-nucleoside reverse transcriptase inhibitor (NNRTI) and a statin is indeed real. As a potent inducer of the metabolism of these 3 statins, efavirenz (and probably nevirapine

[NVP, Viramune], given its known induction of CYP3A4) can significantly reduce the levels of these drugs. As such, the dosing of the studied statins, when co-administered with efavirenz, will likely need to be increased to achieve a desired lipid-lowering effect. Clinicians can feel less anxious about initiating a higher dose of statin than usual (above the lowish starting doses we typically use) when NNRTIs are on board, but should continue to apply the proper side-effect surveillance.

Carotid Intima-Media Thickness Not Associated With Protease Inhibitor Use

Currier JS, Kendall MA, Zackin R, et al, for the AACTG 5078 Study Team. *Carotid artery intima-media thickness and HIV infection: traditional risk factors overshadow impact of protease inhibitor exposure*. **AIDS.** ***June 10, 2005;19(9):927-933.***

Carotid intima-media thickness (CIMT), as assessed by ultrasonography, is a validated early marker of early atherosclerosis. Whether HAART, and PIs in particular, increase CIMT has been unclear, since different studies have reached opposing conclusions.[5-10] To better evaluate the effect of PIs on CIMT, Judith Currier and colleagues conducted a carefully designed study in which 3 groups were enrolled:

- Group 1 -- HIV infected, with a viral load of 10,000 copies/mL or less and currently receiving a PI for 2 or more years
- Group 2 -- HIV infected, with a viral load of 10,000 copies/mL or less and treatment experienced, but never with a PI
- Group 3 -- HIV uninfected

A patient from each group was enrolled together as a triad and matched for age (+/- 5 years), race, sex, blood pressure status, smoking history and, for the few women in this study, menopause status. Patients with diabetes, obesity, family history of early myocardial infarction or a personal history of cardiovascular disease were excluded. CIMT was to be measured at baseline and at weeks 2, 24, 48, 72 and 96. A comparison of baseline characteristics and CIMT is presented in Currier et al's paper.

A total of 134 patients on 45 triads were enrolled (40 male and 5 female). Three quarters of the study patients were Caucasian; 55% had never smoked. There were some notable differences between the groups. The waist/hip ratio was higher among participants with a history of PI use. Similarly, the PI-exposed participants had higher total cholesterol and triglyceride levels. Compared to the PI-experienced patients, the other group of HIV-infected patients had a lower CD4+ cell count (481 cells/µL versus 530 cells/µL) and a lower proportion had a viral load less than 50 copies/mL (69% versus 75%).

CIMT at baseline was 0.690, 0.712 and 0.698 mm in groups 1, 2 and 3, respectively. There were no significant differences between groups, no matter which pair-wise comparison was made or when combining the HIV-infected groups. In a multivariable model, increases in CIMT were associated significantly with older age and increased BMI. High-density lipoprotein (HDL) cholesterol was protective, especially when triglyceride levels were high.

The Bottom Line

These results may be counterintuitive to many -- certainly, if the researchers had found that CIMT was associated with PI therapy, it would hardly have been shocking, given the contribution of this antiretroviral class to LDL cholesterol and triglyceride elevations. The authors state several possible explanations for the *lack* of an effect of PIs on CIMT, including one critical explanation: Perhaps PI-mediated atherosclerotic disease takes time to develop and the exposure (median 216 weeks) was too short in this study to see an effect on this particular artery. Also, the participants in this study were a bit more pristine than those in the average clinical cohort, since patients with major cardiovascular disease risk mediators, such as diabetes and personal or family history of heart disease, were excluded. The effect of PIs on CIMT may be more rapid and evident in such patients.

Furthermore, the site of action for PI-mediated cardiovascular disease may not be in the carotid intima, but elsewhere, and thus went undetected in this study. Lastly, and probably most convincingly, traditional risk factors for cardiovascular disease, which were controlled for in this study, may conceivably trump any effect of PIs (or any antiretroviral therapy) on subclinical atherosclerosis (e.g., HAART is a drop in the bucket compared to elevated blood pressure, smoking, etc.). This study is unlikely to be the final word on the CIMT story and results of the

follow-up phase of this study will be of great interest; however, for the moment, redemption for the much-maligned PI is in the air.

Managing Dyslipidemias: Is It Better to Fight or Switch?

Calza L, Manfredi R, Colangeli V, et al. *Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia*. **AIDS. *July 1, 2005;19(10):1051-1058.***

When confronted with serious antiretroviral therapy-induced dyslipidemias, a clinician must choose between initiating lipid-lowering therapy and switching the medication(s) most likely to be the culprit. When a switch is desired, swapping a PI for an NNRTI has been the typical approach. But, in cases where there are limited options for a switch -- due to pre-existing resistance, a history of intolerance or, in many cases, when modifying the regimen is considered too risky -- lipid-lowering therapy is often prescribed.

In this clever study from Italy, patients on their first antiretroviral regimen, consisting of 2 nucleoside/tide reverse transcriptase inhibitors (NRTIs) and one or more PIs at baseline, had to have:

- a viral load of less than 50 copies/mL;
- a CD4+ cell count greater than 350 cells/µL;
- a fasting triglyceride level that was greater than 200 mg/dL, but less than 750 mg/dL; *and*
- a total cholesterol of greater than 250 mg/dL, but less than 350 mg/dL.

A total of 130 patients meeting the entry criteria enrolled. Of these, 78 were male. The mean baseline triglyceride and total cholesterol levels were 293 mg/dL and 267 mg/dL, respectively. One of the NRTIs being taken at baseline by 46% of the patients was stavudine (d4T, Zerit). Of the PIs, mostly lopinavir/ritonavir (LPV/r, Kaletra) (28%), nelfinavir (NFV, Viracept) (21.5%), or indinavir (IDV, Crixivan) (17%) were taken at baseline. The mean duration of PI-based HAART was 29 months.

Patients were randomized to 1 of the 4 arms:

- switch their PI to nevirapine;
- switch their PI to efavirenz;
- continue their PI and add 20 mg pravastatin; or
- continue their PI and add 400 mg bezafibrate.

All patients were advised to start a low-fat diet and to exercise. After 6 months, triglycerides fell 26% in the nevirapine arm, 9.8% in the efavirenz arm, 42% in the pravastatin arm and 47% in the fibrate arm. When combined and when considered individually, the lipid-lowering arms were significantly superior to both the switch arms taken together. Nevirapine was better than efavirenz, but no difference was seen between the statin and fibrate with regard to triglyceride reduction. These reductions were essentially unchanged at 12 months.

At 6 months, total cholesterol was reduced from baseline by 28% for nevirapine, 11% for efavirenz, 44% for pravastatin and 37% for the fibrate. LDL cholesterol declines were almost identical. For both total and LDL cholesterol, the statistically significant differences followed the same pattern as seen for triglyceride reduction (lipid-lowering therapy was better than the switch, nevirapine was better than efavirenz and pravastatin was as effective as the fibrate).

For HDL cholesterol, despite all the noise made about how NNRTIs increase this cholesterol fraction, the rise seen with these antiretrovirals was minimal (2-3%) compared to the increase seen with the fibrate (8%) and the statin (10%). All these changes persisted at 12 months of follow-up.

After a year, the rates of suppression of plasma HIV viremia were no different between the 4 arms; they ranged from 96.5% in the nevirapine arm to 100% in the pravastatin arm. There were no reports of treatment-limiting toxicity in any of the arms and lesser toxicities occurred at similar rates across the arms.

The Bottom Line

Although this study is relatively small, it is a wake-up call to stop futzing around with antiretroviral switches and start appropriate lipid-lowering therapies. Even trading to the drug nevirapine, purported to be a lipid-friendly agent, led to normalization of triglyceride and total cholesterol levels in only 31% and 9% of patients, respectively, whereas pravastatin, which is *not* an extremely potent statin, achieved a rate of triglyceride normalization of 44%. As expected, the fibrate performed well, with 58% of the patients who were assigned to this agent normalizing triglycerides.

Certainly, some switches make more sense than others, and few clinicians would advise patients who are experiencing dyslipidemia while taking stavudine to suck it up and start a statin rather than switch to a more lipid-favorable NRTI. And, with the advent of atazanavir (ATV, Reyataz), a strategy not studied here, switching older PIs to this agent has become attractive, especially given its convenient once-daily dosing. However, expecting a switch to ritonavir (RTV, Norvir)-boosted atazanavir to produce results that would best those seen with nevirapine is a stretch, despite whatever belief system regarding this boosted PI we are creating for ourselves.

When there are additional reasons (ease of dosing, other toxicities, low-level viremia) to prompt a treatment switch and a new prescription is undesirable (another co-pay, toxicity potential, pill burden), a switch can be justified. However, this study tells us not to expect too much from an antiretroviral switch by way of lipid changes. Clearly, when drastic lipid reductions are required, lipid-lowering therapy is the best option.

Exporting Lipodystrophy

Pujari SN, Dravid A, Naik E, et al. *Lipodystrophy and dyslipidemia among patients taking first-line, World Health Organization-recommended highly active antiretroviral therapy regimens in western India*. **J Acquir Immune Defic Syndr.** ***June 1, 2005;39(2)199-202.***

This report was not unexpected. The heavy reliance on stavudine in much of the developing world has made such a study, detailing the toxicity of combination antiretroviral therapy in such locales, inevitable. This drug, now considered too toxic for use in the United States, has become one of the most popularly used antiretrovirals in Africa and Asia. Typically, stavudine is contained in a fixed-dose combination with two other antiretrovirals: lamivudine and nevirapine. Produced in India by Cipla LTD, this fixed-dose combination goes by the brand name Triomune. This is a cheap and potent antiretroviral combination -- too attractive for antiretroviral-starved HIV epidemic hot spots to disregard, despite its warts. Some hoped that the apparently higher prevalence of lipodystrophy (at least the body shape changes) in Caucasians taking stavudine would mean metabolic abnormalities would not be a significant problem when taken by those with darker skin color and disparate genetic backgrounds. But, this turns out not to be the case, as clinicians working in the Dominican Republic, India and Thailand can attest.

In this report from Pune, India, 180 consecutive patients receiving either stavudine/lamivudine/nevirapine (150 patients) or zidovudine (AZT, Retrovir)/lamivudine/nevirapine (30 patients) for a minimum of 1 year, were evaluated for body shape changes, dyslipidemia and hyperglycemia and compared to 126 HIV-infected, treatment-naive patients. To be included in the trial, the HIV-therapy-treated patients had to be considered adherent by self-report, laboratory results, clinical improvement and elevated MCV (mean corpuscular value) (for those on zidovudine).

Body shape changes were assessed by both patient and clinician report. Lipids and glucose levels were obtained after a 12-hour fast. The patients were mostly male and lean (BMI in the controls was 21.3 kg/m^2, in the stavudine/lamivudine/nevirapine arm it was 22.7 kg/m^2 and in the zidovudine/lamivudine/nevirapine arm it was 24.0 kg/m^2). All cases had a CD4+ cell count less than 200 cells/µL prior to treatment, the mean duration of which at study entry was 19.5 months for the stavudine arm and 24.3 months for the zidovudine arm. At study entry, CD4+ cell counts were 407 cells/µL and 460 cells/µL in the stavudine and zidovudine groups, respectively, compared to 260 cells/µL in the control arm.

The overall prevalence of body shape change among the treated patients was 46%; lipoatrophy was documented in 27% of those who were taking stavudine and 10% of those receiving zidovudine (P = .08). On regression analysis, stavudine was significantly associated with lipoatrophy (OR = 3.3 [95% CI 1.3-11.3]). Fat accumulation was reported in 23% of the stavudine group and 17% of the zidovudine group (P =.57). A mixed picture of fat accumulation and wasting was observed among 10% and 7% of those taking stavudine and zidovudine, respectively (P = .8). Those on HIV therapy had higher total cholesterol, LDL cholesterol and fasting blood glucose than the untreated controls, although there were no differences between the study arms. The proportion of patients on stavudine with an LDL cholesterol of more than 130 mg/

dL was 31% compared to 27% in the zidovudine arm and 4% among the controls. Likewise, triglyceride levels above 500 mg/dL were observed in 4% of the stavudine-treated patients, but none of the zidovudine or control patients. HDL cholesterol was higher in the treatment arms than the controls, as would be expected given the use of nevirapine.

The Bottom Line

This report has a number of limitations, including its low sample size, poor power to detect differences between stavudine and zidovudine-based treatment regimens, lack of objective measures of body shape and limited data regarding the weight of the patients receiving full-dose stavudine. However, the general results suggest that in this Asian clinic where stavudine-heavy World Health Organization (WHO)-recommended first line therapies are employed, metabolic complications are being experienced at a high rate. The trend for a greater prevalence of complications -- especially body shape abnormalities -- among those receiving stavudine signals the justified concern over the widespread application of this agent. The authors themselves call for increased access to alternative drugs such as abacavir (ABC, Ziagen) and tenofovir (TDF, Viread) at affordable prices.

It is certain that additional reports will emerge describing high rates of metabolic complications among patients in Africa and Asia who are receiving similar therapies. When the chorus becomes loud enough, the pictures of lipoatrophied faces become ever-present at large HIV conferences and the *New York Times* does a cover story on the reliance on cast-off therapies for the treatment of HIV in the developing world, then maybe there will be sufficient pressure to produce an alternative to the cheap stavudine-based regimens people in these regions have no choice but to swallow.

New Approaches to HIV Therapeutics

Lopinavir/Ritonavir PLUS Efavirenz -- Worthy or Wacky?

Allavena C, Ferre V, Brunet-Francois C, et al, and the Bitherapy Kaletra-Sustiva Study Group. *Efficacy and tolerability of a nucleoside reverse transcriptase inhibitor-sparing combination of lopinavir/ritonavir and efavirenz in HIV-1-infected patients*. **J Acquir Immune Defic Syndr. *July 1, 2005;39(3):300-306.***

If efavirenz is the King Kong of the HIV therapy market, lopinavir/ritonavir has got to be the Godzilla. Both are big and powerful, and neither has been bested to this day in a head-to-head contest. Both drugs are listed in the U.S. Department of Health and Human Services antiretroviral guidelines[11] as preferred regimen anchors. There has yet to be a direct comparison of these potent agents, and while that will be of intense interest (the ongoing ACTG study A5142 is performing such a comparison in naive patients), this report from France looks not to pit these behemoths against one another, but rather to make nice and team them up together in a nucleoside-sparing regimen.

In this pilot study, 65 antiretroviral-naive and 21 treatment-experienced patients received lopinavir/ritonavir (533/133 mg, 4 capsules) twice daily plus efavirenz (600 mg) once daily for 48 weeks. The treatment-experienced patients were all NNRTI naive and 12 had only received NRTIs previously. If they had prior PI exposure, they could not have more than 1 virologic failure on a PI-containing regimen and had to have less than 5 primary mutations that reduce susceptibility to lopinavir (LPV). Patients' median CD4+ cell count was 276 cells/µL and the median viral load was 4.87 $\log_{10}$ copies/mL.

During the 48-week study, 24% (21) of the patients discontinued study therapy. There were 7 adverse event-related discontinuations (see below), and 6 patients were lost to follow-up. Two trial participants experienced protocol-defined virologic failure. The other premature discontinuations were due to pregnancy, nonadherence, withdrawal of consent, protocol violation, psychiatric illness, tuberculosis and pruritus. At week 24, 69% of the patients had a viral load below 50 copies/mL. This persisted to week 48 by intent-to-treat analysis. There were no differences in viral suppression between patients who were naive to therapy and those who were not, or when patients were stratified by a baseline viral load of greater than or less than 100,000 copies/mL. The mean CD4+ cell count increase was 238 cells/µL at week 48.

Treatment-limiting adverse events attributed to study therapy included grade 3 central nervous system disturbances (in 3 patients), rash (in 3 patients) and grade 4 dyslipidemia (in 1 patient). Lipids seemed to increase in most patients, but the authors are a bit cagey about describing lipid

details. Apparently, fasting cholesterol increased by about 60 mg/dL and triglycerides by 119 mg/dL -- changes which may not have been statistically significant. Mean HDL cholesterol did increase significantly at week 48, from 42 to 49 mg/dL. LDL cholesterol changes were not reported, although we are informed that an LDL cholesterol of more than 160 mg/dL was seen in 2% of antiretroviral-naive patients at baseline and 35% at week 48. Among the treatment-experienced subset of patients, 12% had an LDL of more than 160 mg/dL at baseline and this increased to 20% at week 48. Despite this, only 3 patients started lipid-lowering therapy.

Genotyping of retrieved virus from patients who failed therapy revealed only NNRTI resistance (K103N) and no new mutations in the protease region.

The Bottom Line

This pilot study provides early data on a novel combination that has some obvious advantages and disadvantages. Sparing NRTIs, especially during first-line therapy, may provide potent and convenient secondary treatment options and avoid NRTI-associated adverse effects. On the other hand, the study combination may not be the easiest regimen to adhere to and it risks the elevation of lipid levels.

This study suggests that the lipid elevations, even on the presumably rich French cuisine, are not as bad as one would have expected and that when failure occurs, PI resistance is unlikely. This last point jibes with the general clinical experience that resistance to ritonavir-boosted PIs is hard to come by.

This study is not the final word on this NNRTI-PI combination. As part of the large ACTG study comparing 2 NRTIs + efavirenz to 2 NRTIs + lopinavir/ritonavir in treatment-naive patients, there is a third arm being studied: lopinavir/ritonavir + efavirenz alone. So, in the not-too-distant future, we will have the opportunity to see just how well these antiretroviral giants perform against one another and judge whether this NRTI-sparing regimen is just as good as the 2 top NRTI-based regimens or just too much. Until then, this is a combination to be used only when necessary (i.e., when you have to).

Putting Atazanavir + Ritonavir on the Map

Johnson M, Grinsztejn B, Rodriguez C, et al. *Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures*. **AIDS.** ***April 29, 2005;19 (7):685-694.***

This study, the first to examine ritonavir-boosted atazanavir and one which helped the drug receive U.S. Food and Drug Administration approval, has been presented previously at a series of HIV conferences and has now finally been published. The study launched the current wave of boosted-atazanavir use even though, as described below, the setting in which it was studied was limited to patients who had prior antiretroviral experience and detectable HIV-RNA levels.

The open-label trial was designed to test 3 different treatment strategies:

- atazanavir 300 mg + ritonavir 100 mg once daily,
- atazanavir 400 mg + saquinavir (SQV, Fortovase, Invirase) 1,200 mg once daily, and
- lopinavir/ritonavir 400/100 mg twice daily

plus tenofovir 300 mg daily and another NRTI choice based on phenotypic resistance testing at screening.

Trial participants were patients who had failed 2 or more HAART regimens that included 1 or more NRTIs, an NNRTI and a PI. However, participants had to have had a 1.0 $\log_{10}$ decline in viral load or suppression to less than 400 copies/mL on a prior HAART regimen. Also, their baseline HIV-RNA level had to be greater than 1,000 copies/mL and their CD4+ cell count more than 50 cells/µL.

The primary outcome was based on the time-averaged difference in the reduction of HIV RNA through week 48, with the proportion less than 50 and 400 copies/mL at week 48 seen as the secondary outcomes. This was a non-inferiority trial in which the study arms were compared to assess whether they are not inferior to the comparator (in this case the lopinavir/ritonavir arm). Keep in mind that, statistically speaking, *not* being inferior to something is different than being superior to it or even equal to it. It only means that you were (probably) not worse.

A total of 347 patients were enrolled to the 3 arms. Participants were about 80% male and 70% white. A third had a diagnosis of AIDS, 60% were on an NNRTI prior to entry and 34% were on a PI. The median number of baseline NNRTI mutations was 3 and to PIs was 2. The median baseline HIV-RNA level was about 4.44 $\log_{10}$ copies/mL and the median CD4+ cell count was approximately 300 cells/µL.

In the analysis used, boosted atazanavir was not found to be inferior to lopinavir/ritonavir; however, the atazanavir + saquinavir combo *was* inferior to lopinavir/ritonavir. Looking at more usual metrics of performance, the mean reduction in viral load was -1.93 $\log_{10}$ for the atazanavir + ritonavir arm, -1.55 $\log_{10}$ for the atazanavir + saquinavir arm and -1.87 $\log_{10}$ for lopinavir/ritonavir. The proportion of patients with a viral load less than 50 copies/mL was 46% for those on lopinavir/ritonavir, compared to 38% for those who were on boosted atazanavir and 26% for those on atazanavir + saquinavir.

The differences between the ritonavir-boosted atazanavir and lopinavir arms was not statistically significant (statistically, atazanavir + saquinavir tanked). Increased baseline resistance predicted muted response to the treatment assignment; this was most profound for the ill-fated atazanavir + saquinavir arm, which had low levels of response, with an accumulation of PI mutations.

CD4+ cell counts increased by 110, 121 and 72 cells/µL in the atazanavir + ritonavir, lopinavir/ritonavir and atazanavir + saquinavir arms, respectively.

Treatment-related adverse effects at a grade 2-4 level were reported by about a quarter of the patients in each arm and serious adverse events in approximately 10% of each arm. Jaundice was reported in 6% of the atazanavir + ritonavir patients and none of the lopinavir patients. In addition, 11% of the lopinavir-receiving patients had diarrhea, compared to 3% of the boosted-atazanavir patients. Total bilirubin increased, as expected, in the atazanavir + ritonavir arm. A total of 49% of the patients who were assigned to this arm experienced a grade 3-4 bilirubin elevation during the study. Liver transaminases increased in very few patients (4%) and were equal to that seen in the other study arms.

Lipid differences were what made headlines when this study first was presented and favored the atazanavir + ritonavir arm over the lopinavir/ritonavir arm. LDL cholesterol decreased 10% in the atazanavir + ritonavir arm and increased 1% in the lopinavir/ritonavir arm (P = NS). Likewise, fasting triglycerides dropped 4% in the atazanavir + ritonavir arm and rose 30% in the lopinavir/ritonavir arm (P<.005). Lipid-lowering therapy was initiated during the study in 14% of the patients taking lopinavir/ritonavir, but in only 3% of those who were on atazanavir + ritonavir.

The Bottom Line

This is an important study that showed boosted atazanavir could go toe-to-toe with lopinavir/ritonavir in patients with some, but not a lot, of PI resistance detected at baseline. The impressive responses seen with this new PI, and the lipid improvements after switching from NNRTI- (60%) and PI- (34%) based regimens, have led to considerable enthusiasm regarding the use of atazanavir with ritonavir in such patients. Although the jaundice and bilirubin abnormalities seen were significant, they did not lead to excess treatment discontinuation -- a finding that predicted clinical experience. An important caveat is to recognize that the improved lipids do not mean that boosted atazanavir is lipid neutral. There are no data describing the effects of ritonavir + atazanavir on the lipid levels of treatment-naive patients. It is likely that this combination does increase lipid levels, but to a lesser extent than that seen with lopinavir/ritonavir.

Induction-Maintenance With Zidovudine/Lamivudine/Abacavir

Markowitz M, Hill-Zabala C, Lang J, et al, for the ESS40013 Study Team. *Induction with abacavir/lamivudine/zidovudine plus efavirenz for 48 weeks followed by 48-week maintenance with abacavir/lamivudine/zidovudine alone in antiretroviral-naive HIV-1-infected patients*. **J Acquir Immune Defic Syndr.** ***July 1, 2005;39(3):257-264.***

In the wake of ACTG Study 5095[12] and the finding of a suboptimal response to the fixed-dose combination of zidovudine/lamivudine/abacavir (AZT/3TC/ABC, Trizivir) compared to a regimen of efavirenz combined with either zidovudine/lamivudine (AZT/3TC, Combivir) or zidovudine/lamivudine/abacavir among treatment-naive patients, use of this triple NRTI alone has become rare. This interesting study, sponsored by the good people at GlaxoSmithKline, the maker of zidovudine/lamivudine/abacavir, aims to see if a prolonged induction treatment with a potent

combination of zidovudine/lamivudine/abacavir + efavirenz can be followed by use of zidovudine/lamivudine/abacavir alone. The benefits of such a strategy are threefold: reduced exposure to efavirenz, and therefore removal of the adverse lipid effects and possibly persistent central nervous system disturbances of this agent; simplification of therapy; and lower expense of treatment.

Treatment-naive (less than 2 weeks of prior therapy) patients with an HIV-RNA level greater than 5,000 copies/mL were included in this study. All patients received zidovudine/lamivudine/abacavir + efavirenz at standard doses. Those with a viral load less than 50 copies/mL at weeks 36 and 44 were randomized at week 48 to continue or discontinue efavirenz.

A total of 448 patients were enrolled across the United States (~85% male, 50% non-white). The median HIV-RNA level was a little over 5 $\log_{10}$ copies/mL and the median CD4+ cell count was about 212 cells/µL. More than half of those enrolled had a viral load over 100,000 copies/mL at baseline. Of these initial patients, 166 (37%) discontinued study treatment during the first 48 weeks due to the following reasons: adverse events (33% of those discontinuing), withdrawn consent (20%), loss to follow-up (17%) and virologic failure (15%). Of those who entered the induction phase, 61% had a viral load less than 50 copies/mL at week 48 in an intent-to-treat analysis. This is not a stellar response and pales in comparison to the rates of viral suppression being seen in recent clinical trials of treatment-naive patients. The reason for the low rate of success at the end of the induction phase was mostly related to dropouts due to adverse effects and loss to follow-up. Seven percent of the patients experienced suspected abacavir hypersensitivity reactions and 2% experienced treatment-limiting rash. Of those who made it to week 48, however, 90% had a viral load less than 50 copies/mL.

A year after the randomization, 79% of those remaining on the quadruple therapy had suppression of their viral load to less than 50 copies/mL, as did 77% of those on zidovudine/lamivudine/abacavir alone (P =.7). Virologic failure after randomization occurred in 16 patients in the zidovudine/lamivudine/abacavir arm and in 8 patients in the quad therapy arm (P =.13). CD4+ cell count increased nicely in both arms to a median level of 425 cells/µL in the quad therapy arm and 453 cells/µL for the zidovudine/lamivudine/abacavir arm. There was a trend toward greater self-reported adherence among the zidovudine/lamivudine/abacavir alone arm than the quad therapy arm, 88.8% versus 79.6%, respectively (P =.057).

Of those who experienced virologic failure during the induction phase, the most common resistance detected was to efavirenz and/or lamivudine. Two patients had resistance to these plus zidovudine detected and, curiously, 2 additional patients selected for the K65R mutation (something zidovudine is supposed to prevent). During maintenance, the most common mutation detected was to lamivudine alone, although some patients did cultivate additional mutations, including thymidine analog and NNRTI resistance.

Lipids generally increased during induction, but dropped close to baseline in the zidovudine/lamivudine/abacavir-alone arm after randomization, while remaining elevated in the quad therapy arm.

The Bottom Line

The induction-maintenance concept is one that is attractive to clinicians familiar with the oncological therapy model. The idea is to hit hard and reduce viral burden to the point where suppression can be preserved with less-toxic and more-convenient therapy. Here, the problem was the somewhat surprising intolerance of the induction therapy. Zidovudine/lamivudine/abacavir + efavirenz has been administered in ACTG 5095 without anywhere near the 37% discontinuation rate seen here. In that study, only 7% of the overall participants discontinued therapy by week 32. Besides bad luck, it is hard to imagine a reason for the problems seen here in the first phase of the study -- although the high loss to follow-up/consent withdrawn rate may hint at some participant disgruntlement. It is important to note that of those who did make it to a year on induction therapy, almost all (90%) were undetectable. Furthermore, following the switch, persistence of viral suppression was comparable between the arms (77%-79%).

Is this approach ready for prime time? As a general strategy, not quite. Induction-maintenance for HIV infection has a checkered past. However, there are situations in which these results provide reassurance. Last week I saw an elderly woman who has been on zidovudine/lamivudine/abacavir + efavirenz for over 2 years, with viral loads uniformly less than 50 copies/mL and a CD4+ cell count that is now over 500 cells/µL. She complained of persistent dizziness since starting her regimen, which prevents her from tending her garden. She can pinpoint the start of her symptoms to the day she started her efavirenz. After reading this paper (and having a long discussion with her and her family), I decided to remove the efavirenz and continue the zidovudine/lamivudine/

abacavir alone. In such cases, where success of the induction therapy has been made clear, discontinuation of the NNRTI seems more attractive, particularly when dealing with toxicity. In other cases, I would be hesitant to alter therapy.

Refining Treatment Strategies

Predicting CD4+ Cell Counts Where There Are None

Costello C, Nelson KE, Jamieson DJ, et al. *Predictors of low CD4 count in resource-limited settings: based on an antiretroviral-naive heterosexual Thai population*. **J Acquir Immune Defic Syndr.** ***June 1, 2005;39(2):242-248.***

Can you imagine trying to manage HIV therapy without the benefit of HIV-RNA testing or even CD4 + cell counts? That is the circumstance that most clinicians in Africa and Asia find themselves working in. In some places, CD4+ cell counts are available, but cost more money than the patient can afford or rely on overworked machines and personnel. As HIV therapies penetrate into resource-poor regions, having a marker to assist in determining when to start therapy, to monitor response to treatment once started and to indicate when there is a need for prophylaxis for opportunistic infections will be essential. Recognizing the problem, the WHO has published alternative recommendations for the initiation of HIV therapy in places where CD4+ cell count testing is unavailable. Based on the correlation between CD4+ cell count and the total lymphocyte count (TLC),[13] these guidelines are as follows:

CD4	TLC
<200 cells/µL	<1,200
<350 cells/µL	<1,500

To determine whether the addition of other readily available information can increase the sensitivity of the WHO recommendations, investigators from the U.S. Centers for Disease Control and Prevention examined data from a cohort of 839 patients participating in a clinical study in Thailand. The population studied was diverse with regard to age, gender and CD4+ cell count. All were antiretroviral naive.

There was a high correlation between CD4+ cell count and TLC among men and women. The latest WHO guidelines indicating that a TLC of less than 1,200 predicted a CD4+ cell count of less than 200 cells/µL had a sensitivity of 34% in men and 32% in women, and a specificity of 90% for men and 86% for women. The authors found that with their real-life data, establishing a TLC of less than 1,500 as predictive of a CD4+ cell count of less than 200 cells/µL increased the sensitivity with minimal loss of specificity. The result is that more than twice as many patients with a CD4+ cell count of less than 200 cells/µL would be identified as individuals for whom HIV therapy would be recommended than would have been discovered with the lower cutoff. Similarly, for a CD4+ cell count of less than 350 cells/µL, increasing the TLC to 1,800 increased sensitivity without modification of specificity from that associated with the recommended 1,500 TLC.

Furthermore, the presence of anemia (defined as hemoglobin less than 12 g/dL for men and less than 11 g/dL for women), highly prevalent in this cohort, also predicted a CD4+ cell count less than 200 cells/µL. Adding it to the algorithm for both CD4+ cell counts less than 200 cells/µL and less than 350 cells/µL doubled the sensitivity above the current guidelines. Adding WHO stage II HIV infection classification to the CD4+ cell count less than 200 cells/µL model added further sensitivity. Therefore, the authors propose that the following guidelines be used when CD4+ cell testing is unavailable:

CD4	TLC
<200 cells/µL	TLC <1,500 or anemia and TLC <2,000 or WHO stage II HIV infection
<350 cells/µL	TLC <1,700 or anemia and TLC <2,000

The Bottom Line

It is likely that data available even in places with poor healthcare infrastructure can be applied to

provide improved surrogates for CD4+ cell counts. This analysis primarily adds the presence of anemia to the mix to increase the yield of slightly modified TLC cutoffs. The end result is fewer misclassified patients who, the current guidelines would suggest, are not eligible for HIV therapy although they have a CD4+ cell count less than 200 cells/µL.

Further testing of this helpful algorithm in other settings (e.g., Africa and China) is needed prior to broad application, but the results highlight the deficiencies of the current recommendations and the need to refine them based on available information.

Efficacy of Influenza Vaccine in HIV-Infected Patients

Yamanaka H, Teruya K, Tanaka M, et al, and the HIV/Influenza Vaccine Study Team. *Efficacy and immunologic responses to influenza vaccine in HIV-1-infected patients*. **J Acquir Immune Defic Syndr.** ***June 1, 2005;39(2):167-173.***

If I added all the time I spend each winter trying to convince HIV-infected people to take the influenza shot, I wonder how much time I would have. A week? A day? Enough time to run down to employee health to get a shot myself? Maybe a more important question is whether all that time is worth it, even if I could cajole enough of the needle-phobic to roll up their sleeves or could help patients put aside urban myths about the influenza vaccine *causing* the flu. Does the vaccine really work?

In this study, researchers in Japan gave the influenza vaccine (the trivalent shot used in 2002 in Japan) to 262 HIV-infected patients who agreed to participate. Their responses and influenza rates were compared to 66 patients who declined vaccination. Three quarters of the patients in each group were on HAART; the median CD4+ cell count was 380 cells/µL and the median viral load was 2.5 $\log_{10}$ copies/mL (these were almost identical between arms).

During the influenza season, one of the worst of the decade, 30 participants had documented influenza infection -- 16/252 were in the vaccinated group while 14/66 were in the non-vaccinated group ($P<.001$). The relative risk of influenza in the vaccinated group was 0.29 (CI: 0.14-0.55); therefore, they had a risk of infection that was 29% lower than participants who were not vaccinated. In other words, the vaccine worked.

Of those who were vaccinated and became infected, 3 had a CD4+ cell count less than 200 cells/µL. Two of the unvaccinated patients with influenza had a low CD4+ cell count.

Looking at the immune responses to the vaccination, the researchers found that among patients *without* baseline antibody responses to the vaccine, immune responses to vaccination were more robust among those whose CD4+ cell count was greater than 200 cells/µL. Of those patients who had antibodies present at baseline (~30%), responses to the vaccine were excellent, regardless of CD4+ cell count. As expected, the patients who became infected with the virus despite vaccination mostly had suboptimal responses. Those patients who were on HAART had better specific CD4+ cell responses to influenza antigen.

The Bottom Line

The bottom line is that influenza vaccination is effective in preventing flu among HIV-infected individuals. These results suggest annual vaccination is worthwhile. The observed differences in response to the vaccine based on the presence of influenza antibodies likely reflect preserved immune responses. Patients who continue to produce antibodies respond briskly, whereas other patients who do *not* continue to produce antibodies respond only when their CD4+ cell count is high. This is interesting, but of minimal clinical value since such testing is not feasible. The point is that the majority of patients will respond, and this message needs to be communicated to patients.

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