

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Report From Boston: The 12th Conference on Retroviruses and Opportunistic Infections (CROI)

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Complications/Toxicity of HIV Therapy

By Richard D. Moore, M.D., M.H.S. and Joseph Cofrancesco, Jr., M.D., M.P.H.

The number of sessions and abstracts at CROI devoted to complications and toxicity of HIV therapy attests to the growing prominence of these issues. We will focus on the clinically relevant issues.

Lipodystrophy

The impact of antiretroviral therapy (ART) on body shape and fat distribution was evaluated in substudy A5005s of ACTG 384 [Mulligan K, et al. [Abstract 38](#)]. In ART-naïve patients randomized to receive ddI + d4T or AZT/3TC with either EFV, NFV or both, the proportion of patients with a waist-hip ratio (WHR) above the value that has been previously associated with an increased risk of cardiovascular disease (>0.90 in women, >0.95 in men) was 35% at baseline and 47% after 64 weeks of therapy. There was no single pattern of fat changes: 52% had an increase in waist and hip circumference, 24% had increased waist and decreased hip circumference, and 22% had a decrease in both. DEXA results were similar. There was no difference by specific HAART regimen, although the statistical power to detect a difference was limited. Some patients, especially those with increases of fat in all body compartments, may be “returning to normal” from a wasted AIDS state, or were becoming obese.

In data from the Multi-center AIDS Cohort Study (MACS), HIV-infected men on ART were compared with HIV-negative men [Brown T, et al. [Abstract 849](#)]. Over a four year period, both groups had increased waist size, suggesting an aging effect, but hip circumferences increased more slowly in those on ART, resulting in a significant increase in WHR only for those on ART. In addition, thigh circumference increased only in HIV-negative group. Cumulative nucleoside reverse transcriptase inhibitor (NRTI) use, but not protease inhibitor (PI) use, was associated with decreased waist, hip, arm and thigh circumference as well as increased WHR and decreased body mass index. The study was not able to implicate specific NRTIs, but confirms the role of NRTIs in a number of body shape changes.

Switch Studies

The TARHEEL and MITOX studies previously demonstrated partial reversal of lipoatrophy by switching from stavudine

(d4T) to abacavir (ABC) or zidovudine (AZT) (TARHEEL) [McComsey GA, et al. *Clin Infect Dis* 2004;38:263], or from d4T or AZT to ABC (MITOX) [Martin A, et al. *AIDS* 2004;18:1029]. A number of switching strategies were presented at the 12th CROI. Graeme Moyle presented 48-week results from the RAVE study, in which 105 patients experiencing lipoatrophy on either d4T (N=71) or AZT (N=34) were randomized to switch to either tenofovir DF (TDF, N=52) or ABC (N=53) [[Abstract 44LB](#)]. More than 90% of subjects were also on lamivudine (3TC). This is the first head-to-head comparison of switching to ABC vs TDF for fat loss. As measured by DEXA, limb fat increased from baseline in both groups with no between-group differences (393 g for TDF, 316 g for ABC, P=0.97). Similar increases of 12% to 15% were seen in visceral and subcutaneous trunk fat by

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computerized tomography. There was no significant difference in virologic suppression, CD4 cell change, bone mineral density, or serum creatinine levels. Triglycerides and total and LDL cholesterol declined in both arms, though the decline was significantly greater with TDF. However, a higher proportion of patients switched to TDF than to ABC who had received d4T at baseline, which may have explained the differences in lipid results.

Additional studies confirmed the utility of changing from d4T to TDF. Fifty-three patients with controlled HIV and lipoatrophy on d4T-based regimens were switched to TDF and followed for 18 months [Ribera E, et al. [Abstract 860](#)]. Virologic and immunologic control was maintained and there were significant improvements in lactate levels, triglycerides and malar fat thickness (measured by bioelectrical impedance analysis and sonography), and non-significant increase in ratios of PBMC mitochondrial DNA to nuclear DNA. A randomized open-label study demonstrated a decrease in total fat and limb fat (measured by dual energy X-ray absorptiometry, DEXA) at 6 months as well as a decrease in triglycerides and cholesterol by reducing the dose of d4T from 40 to 30 mg bid or switching to TDF; all improvements were greater with switching to TDF than reducing the d4T dose [Milinkovic A, et al. [Abstract 857](#)].

In a late-breaker, preliminary 24-week data were presented from ACTG 5110 [Murphy R, et al. [Abstract 45LB](#)]. One hundred patients with lipoatrophy either switched from d4T (76%) or AZT (26%) to ABC or discontinued all NRTIs and were treated with lopinavir/ritonavir (LPV/r) + nevirapine (NVP). By CT, there was an increase of 8.4% in thigh fat (TAT) with lopinavir/ritonavir (LPV/r) + NVP compared to no change with ABC. Increase in subcutaneous abdominal fat (SAT) was

16.6% with LPV/r + NVP and 9.2% with ABC. There was a 15% decline in visceral abdominal fat (VAT) in both groups. The VAT:TAT ratio declined similarly by 9% to 11% in both groups. Both groups maintained virologic control, though the LPV/r + NVP group had a greater increase CD4 level. In this study elimination of the thymidine analog was associated with improvements in perturbations an effect that was even more pronounced when NRTIs were eliminated altogether. However, longer follow-up is needed before broad conclusions can be reached. It may be that over time, patients in the LPV/r + NVP group will develop worsening metabolic parameters, insulin resistance and fat accumulation.

To that point, A5125s, a metabolic substudy of ACTG 5116, randomized 62 patients with viral loads ≤ 200 c/mL after 18 months on any antiretroviral regimen to take either LPV/r + efavirenz (EFV) or EFV + two NRTIs [Tebas P, et al. [Abstract 40](#)]. There were no differences in glucose, lipids, bone mineral density, or fat distribution by DEXA between the groups at time of switch. After 48 weeks, the LPV/r + EFV group experienced a median increase in limb fat of 562 g vs. a loss of 246 g in the EFV + 2 NRTI group. However, patients in the LPV/r + EFV group also experienced a greater increase in triglycerides and total and LDL cholesterol levels compared to the NRTI group. The study was not powered to detect a difference between the effects of d4T vs. AZT within the 2 NRTI group.

Additional studies assessed switching PIs. Patients on a stable PI-based HAART regimen with virologic suppression and an LDL cholesterol >130 mg/dL were randomized either to switch to atazanavir (ATV) at 400 mg qd (N=126) or to remain on their current PI (N=118) [Sension M, et al., [Abstract 858](#)]. Improvements in LDL cholesterol (-15%), total cholesterol (-18%),

apo-B (-19%), lipoprotein-a (-21%) and triglycerides (-35%) were seen at 48 weeks in the ATV group compared to the PI group. Virologic suppression was maintained, and there was no difference in rates of discontinuation. In another study, patients on PI-based (43%), NNRTI-based (24%) or NRTI-based (5.6%) HAART with persistent (>3 months) fasting triglycerides >500 mg/dL, total cholesterol >200 mg/dL, or LDL cholesterol >130 mg/dL were switched to ritonavir-boosted ATV [Martinez E, et al. [Abstract 850](#)]. The patients had median improvements in triglycerides (-43%), total cholesterol (22%), LDL cholesterol (-18%), and HDL cholesterol (+6%) at 12 months of follow-up. There was no change in virologic control.

Taken together, we have continued evidence that the thymidine analogs, in particular d4T, are responsible for most lipoatrophy, and may contribute to some metabolic toxicity as well. Switching to ABC or TDF is generally safe and improves fat and metabolic parameters. There is continued interest in “nucleoside-sparing” regimens, but the data are preliminary. Atazanavir, even when boosted with ritonavir, has a more favorable lipid profile than other PIs. As our understanding of antiretroviral drug toxicity becomes more sophisticated, it is clear we need to think less about “class effects” and more about the toxicities of individual drugs.

Pharmacologic Interventions

Two studies assessed treatment of lipid abnormalities or lipodystrophy. A randomized, double-blind trial of 146 patients who had fasting triglycerides >200 mg/dL evaluated *MaxEPA* 2 gm tid (a compound of omega-3 polyunsaturated fatty acids in fish oil) versus paraffin oil placebo for 8 weeks, followed by 8 weeks of open label *MaxEPA* [De Truchis P, et al.



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Abstract 39]. Of note, subjects received a triglyceride-controlled diet for 4 weeks prior to and during the intervention. After 8 weeks, *MaxEPA* was associated with a 25.5% decline in triglyceride levels (22% normalized) vs. a 12% increase (6.5% normalized) with placebo. During open-label follow-up, placebo recipients had a 21.2% decline in triglyceride levels on *MaxEPA*. This study demonstrated the utility both of diet and fish oil compounds in improving triglyceride levels in HIV-infected patients with high triglyceride levels. Although not assessed in this study, no pharmacokinetic interactions with HIV

medications are anticipated. Finally, both arms experienced diarrhea as the most common side effect, and although there was no difference between arms, the placebo recipients received a large amount of paraffin oil. It is likely that many patients prescribed relatively high doses of fish oil compounds will experience gastrointestinal side effects.

Yet another study of rosiglitazone (4 mg bid) failed to demonstrate improvement in limb fat at 24 weeks [Cavalcanti R, et al. **Abstract 854**].

In another trial, 142 patients on stable PI-based regimens with diet-resistant mixed

hyperlipidemia who had viral load <50 c/mL and CD4 >350 cells/mm³ were randomized to switch from a PI to NVP, switch from a PI to EFV, continue PI and receive pravastatin, or continue PI and receive bezafibrate [Calza L, et al. **Abstract 859**]. Over a 12 month follow-up period, reductions were seen in triglyceride and total cholesterol levels in all subgroups (see **Table, p 4**). Switching to NVP was more effective than to EFV. However, the greatest improvement in lipids occurred by adding

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Table. Change in Lipid Level By Study Group [Calza L., et al. Abstract 859]

Lipid	Study Group			
	Switch PI → NVP	Switch PI → EFV	Continue PI + Pravastatin	Continue PI + Bezafibrate
Triglycerides	-25.2%	-9.4%	-41.2	-46.6%
<400 c/mL, %	-27.1%	-10.2%	-45.8%	-37.6%

a lipid-lowering agent. This latter result is different than some earlier data where switching from a PI had a greater effect on lipids than adding a lipid-lowering drug.

Recombinant human growth hormone (rhGH) has previously demonstrated utility in decreasing visceral fat accumulation, but often at the expense of subcutaneous fat loss

and insulin resistance. This has generated interest in finding an optimal dose for this compound. Bickel and coworkers conducted an open-label study of 26 patients randomized to rhGH 4 mg qd or 3x/week for 12 weeks, followed by 2 mg qd maintenance for an additional 12 weeks [Bickel M, et al. Abstract 855]. Visceral adipose tissue was significantly and similarly reduced in both study arms, with significant reductions in total and LDL cholesterol and a significant increase in HDL cholesterol. However, there were also small reductions in facial and thigh fat in both arms of the study.

Previously reported data suggested that a growth hormone releasing hormone may decrease visceral fat without the deleterious side effects of growth hormone. Falutz and colleagues conducted a 12-week double-blind placebo-controlled trial of such a compound (TH9507) at 1 mg or 2 mg sc qd [Abstract 856]. There were no significant improvements in overall quality of life, but both doses were associated with significantly lower subjective reports of abdominal girth and bloating compared to placebo; abdominal pain was significantly improved at the lower dose only. It is too soon to make recommendations regarding this compound, but phase 3 studies are expected soon.

Cardiovascular Disease Risk

There are increasing data linking the metabolic abnormalities associated with HAART to an increased risk of cardiovascular disease (CVD). Further data were presented from D:A:D, the 11-cohort multicenter study of CVD in HIV-infected

patients in care in Europe, North America and Australia [El Sadr W, et al. Abstract 42]. Follow-up now extends to 76,577 person-years (PY), with 277 patients experiencing a myocardial infarction (MI, incidence rate of 3.6/1000 PY). MI incidence increased from 1.39/1000 PY in those not on ART to a high of 6.1/1000 PY in those on >6 years of HAART, a relative rate of 1.17 MI per additional year of HAART. The association of increased risk with HAART was maintained in a subanalysis by gender and age: (men >45 years, women >55 years). CVD risk factors in the D:A:D cohort, including age, diabetes, CV events, hypertension, lipid levels and smoking, have worsened over time, but after controlling for CVD risk factors and duration of HAART, the risk of MI had actually decreased [Sabin C, et al. Abstract 866]. The authors suggested that this may be due to the fact that clinicians are being more aggressive at managing other cardiovascular risk factors, including more effective treatment of hyperlipidemia.

In a follow-up analysis of Northern California Kaiser Permanente data, there were 81 hospitalizations for MI in HIV-infected patients during 25,251 PY of follow-up (age-adjusted incidence of 3.8/1000 PY) [Klein D, et al. Abstract 869]. In PI-treated patients, the rate was 4.4 compared to 2.9 with not taking PIs. The rate was 2.2 in HIV-negative controls from the same population. As in D:A:D, there was an increasing risk of MI with increasing duration of PI use (2.9 for <2 years, 4.4 for >6 years). In another study of 233 HIV-infected patients from the ARNS Aquitaine Cohort, during a 36-month follow-up carotid intima-media thickness (IMT), a marker for vascular damage, increased from 0.55 to 0.57 mm at month 12, but then decreased to 0.53 mm at month 36 [Thiébaud R, et al. Abstract 871]. This decrease was associated with increased use

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of lipid-lowering drugs, use of PI-free HAART regimens, and a small decline in smoking.

Taken together, the increased risk of CVD in patients on HAART appears to be real, but interventions that improve traditional risk factors (either by direct treatment or changing ART) can improve the risk. Many speakers stressed the importance of smoking cessation in risk reduction.

A number of other complications of HIV therapy were also presented. Two of these, hypertension and renal disease, are also associated with CVD risk, and the other complications examined attest to the potential for adverse effects inherent in current HIV therapy.

Hypertension

Hypertension is another major risk factor for CVD. Hypertension was examined as a possible complication of HIV therapy in 3 studies. A case-crossover analysis involving 404 patients from the MACS cohort was presented by Seaberg [Abstract 872]. Initiating HAART was associated with a significant increase during the next 6 months in systolic blood pressure (mean +1.8 mmHg) but not diastolic blood pressure (mean +0.6 mmHg). While on HAART the systolic pressure continued to increase over time by a mean of 0.3 mmHg every 6 months. Men with CD4 counts <200 cells/mm³ experienced greater increases in systolic pressure (mean +3.6 mmHg) and diastolic pressure (mean +2.5 mmHg) than men with CD4 counts >350 cells/mm³. A retrospective analysis of 607 patients at the University of Washington found that 9.9% of patients had a ≥10 mmHg increase in diastolic blood pressure or initiated antihypertensive drugs, and 13.2% had a ≥10mmHg increase in systolic pressure or initiated therapy after initiation of HAART [Crane H, et al. Abstract 873]. Adjusting for

age, race and sex, EFV (OR=3.0), LPV/r (OR=7.2) and NVP use (OR=2.1) were associated with increased systolic pressure.

Finally, development of pulmonary arterial hypertension (PAH) was assessed by 2D and Doppler echocardiography in a prospective study of 200 HIV-infected patients on HAART for at least 3 months [Rosenkranz S, et al. Abstract 874]. PAH was diagnosed in 7.5% of patients. Right ventricular dilation (>25 mm) was observed in 53% of those with increase plasma B-type natriuretic peptide (a marker of right-heart failure) in 40%.

Renal Insufficiency

Several studies emphasized the importance of estimating the glomerular filtration rate (GFR) in patients rather than relying solely on the serum creatinine to assess renal function. In data from the CHORUS cohort, 1298 patients, all of whom were receiving TDF, had serum creatinine measured and GFR calculated by the Modification of Diet in Renal Disease Study Group (MDRD) equation during 6 months of follow-up [Becker S, et al. Abstract 819]. Only 1.9% and 0.4% had ACTG grade 1 and 3 serum creatinine increases, respectively. In contrast, National Kidney Foundation (NKF) Stage 3 GFR (<60 mL/min/1.73 m²) occurred in 13.3% and Stage 4 (<40mL/min/1.73 m²) in 0.9%. Factors associated with GFR decline included past renal disease, older age, hypertension, abnormal renal function at baseline and concurrent nephrotoxic drugs. Joel Gallant and colleagues analyzed change in calculated creatinine clearance (using the Cockcroft-Gault equation) after starting TDF [Abstract 820]. Patients who started TDF (N=344) were compared to 314 patients who started an alternative NRTI as part of HAART. Over 1 year, the median decline in GFR was -13 mL/min with TDF and -7 with NRTI (P <0.01). The decline

with TDF was independent of other factors associated with decline in renal function, including a lower baseline creatinine clearance, diabetes and low baseline CD4.

In an analysis from the MACS, 42.2% had NKF stage 2 (<90 mL/min/1.73 m²) and 3.6% had stage 3-5 (<60 mL) by MDRD-calculated GFR [Reisler R, et al. Abstract 818]. Factors that increased the risk of a GFR <90 were: HAART use (OR=1.7) and use of TDF (OR=1.8).

Finally, using data from the FRAM cohort and the CARDIA study, microalbuminuria was found in 8% of HIV-infected participants but only 2% of HIV-negative patients [Szczech L, et al. Abstract 821]. By multivariate analysis, HIV infection was associated with microalbuminuria (OR=4.5). In HIV-infected patients, other factors associated with microalbuminuria were systolic hypertension and African-American race. As microalbuminuria is associated with an increased risk of chronic kidney disease, this result suggests a relatively high risk for this complication, and the results from all of these studies emphasize the importance of monitoring renal function in HIV-infected patients.

Peripheral Neuropathy

NWCS238, a substudy of ACTG 384, was conducted to determine if mitochondrial DNA polymorphisms were associated with peripheral neuropathy [Hulgan T, et al. Abstract 43]. Of 526 subjects who had mitochondrial DNA collected, 147 had ≥ grade 1 neuropathy (114 on ddI + d4T, 35 on AZT + 3TC) and 362 controls had no neuropathy. Mitochondrial haplotype T was present in 9% of Caucasians and <2% of African-Americans, with a relative odds of 2.8 for

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Pharmacology at the 12th CROI: Generic Antiretrovirals, Drug Interactions, and Therapeutic Drug Monitoring

By Adriana Andrade, M.D., M.P.H. and Charles Flexner, M.D.

Generic Antiretrovirals: Is Cheaper Better?

There is concern about the quality of generic antiretroviral (ARV) drugs, especially after the WHO withdrew several generic ARV formulations with inadequate bioequivalence from its list of prequalified products [<http://mednet3.who.int/prequal>]. This issue was addressed in two studies at the 12th CROI comparing trade and generic formulations of ARVs.

Hosseinipour presented the results of a study conducted in Malawi comparing the pharmacokinetic properties of the fixed-dose triple combination *Triomune 40* [stavudine (d4T)/lamivudine (3TC)/nevirapine (NVP)] 40/150/200 mg (Cipla, India) and trade formulations of the same drugs [Abstract 631]. Twelve HIV-infected subjects were randomized to take either *Triomune 40* or the same combination using brand name formulations: *Epivir* (3TC), *Zerit* (d4T), and *Viramune* (NVP). They then crossed over to the other formulation for 28 days. Average bioequivalence was determined according to FDA criteria [www.fda.gov/cder/guidance/]. AUC_{0-8hr} and C_{12hr} were similar for the generic and trade formulations. However, d4T C_{max} was significantly higher with *Triomune 40* than with the trade formulation. Nine of the 12 subjects had grade 1 or greater peripheral neuropathy while taking the generic formulation, and the authors speculated that this could have been caused by higher d4T concentrations.

Vezina and colleagues compared the pharmacokinetic parameters of the generic triple fixed-dose combination *Duovir-N* [NVP/zidovudine (AZT)/3TC] 200/300/150 mg (Cipla, India) and the trade formulations *Viramune* (NVP) 200 mg coadministered with *Combivir* (AZT/3TC) 300/150 mg [Abstract 669]. Fifteen HIV-negative Indian women were given a single dose of the generic or trade formulation,

and after a 14-day wash out period subjects crossed over to the other formulation. Mean NVP, AZT, and 3TC C_{max} , T_{max} , AUC, and $t_{1/2}$ were similar for the generic and trade formulations. The AZT C_{max} mean ratio did not meet the FDA bioequivalence criteria, although the clinical significance of this is unclear.

These findings emphasize the fact that pharmacokinetic bioequivalence of generic formulations is not guaranteed. This is a crucial issue, especially in resource-poor settings where generic ARVs are likely to become the standard of care.

Drug Interactions

Buprenorphine and Efavirenz

Buprenorphine (BUP; *Suboxone*) is a promising office-based treatment for opioid dependence [Lucas G, *HHR*2004;16(4):6]. Like methadone, BUP is a substrate of the cytochrome P-450 (CYP450) enzyme CYP3A4 and could be affected by adverse drug interactions. McCance-Katz and coworkers evaluated pharmacokinetic interactions between BUP and efavirenz (EFV) [Abstract 653]. Ten HIV-negative opioid-dependent adults on a stable BUP regimen were treated with EFV for 15 days. In the presence of EFV, the mean BUP AUC, C_{max} , C_{min} , and $t_{1/2}$ decreased by 51%, 55%, 49%, and 71% respectively, while clearance increased by 47%. There was no evidence of withdrawal symptoms and EFV plasma concentrations were not affected by BUP coadministration.

CYP3A4 is induced by EFV, which would explain the reduction in BUP concentrations. The lack of withdrawal symptoms is probably because of the high affinity of BUP for the μ -opioid receptor, which results in a prolonged pharmacodynamic effect. Whether BUP would be preferable to methadone for patients on EFV will require further study.

Rifampin and Atazanavir/Ritonavir

Rifampin (RIF) is a potent CYP3A4 inducer that markedly lowers plasma concentrations of all PIs. For this reason, coadministration of RIF with most PIs is contraindicated. Burger and colleagues evaluated the safety and pharmacokinetic of atazanavir (ATV) when combined with RIF [Abstract 657]. In this study 71 healthy volunteers received: ATV 400 mg qd from days 1 to 6 and then ATV/RTV 300/100 mg qd from days 7 to 16. Subjects were then subdivided in three groups and treated from days 17 to 26 with ATV/RTV 300/100 + RIF 600 mg qd, ATV/RTV 300/200 + RIF 600 mg qd, or ATV/RTV 400/200 + RIF 600 mg qd (N=18/group). ATV steady-state mean AUC was reduced by 28% in the ATV/RTV 300/100 + RIF 600 regimen, and 46% in the ATV/RTV 300/200 + RIF 600 regimen. Although coadministration of ATV/RTV 400/200 with RIF resulted in a 10% increase in the ATV AUC, the C_{max} and C_{min} decreased by 18% and 59%, respectively, when compared to ATV 400 alone. Coadministration of RIF and ATV was well tolerated.

Thus, increasing the dose of RTV and ATV was not enough to compensate for the inducing effects of RIF. It remains to be determined whether higher doses of RTV and ATV might compensate for this pharmacokinetic interaction, or whether ATV will join the list of other PIs that cannot be given with RIF. This is unfortunate, because unboosted ATV does not require refrigeration and, thus, it is one of the few PIs suitable for use in resource poor settings.

A second report monitored clinical outcomes and EFV plasma concentrations during and after treatment with RIF [Abstract 891]. Twenty HIV-infected South Africans with pulmonary tuberculosis received 3TC + didanosine (ddI) + EFV 600 mg QD with a RIF-containing regimen.



Nineteen subjects were cured of their TB and 80% achieved an undetectable viral load. Viral load remained undetectable in 65% of those remaining on ARV therapy after a mean 15 months of follow-up. Mean EFV trough concentrations (1,510 ng/mL on RIF and 1,377 off RIF) were within the therapeutic range (1,000-4,000 ng/mL).

These results suggest that EFV-based regimens are safe and effective in patients with TB/HIV co-infection in need of concomitant treatment with RIF. Some previous studies suggested that the EFV dose should be increased to 800 mg daily when coadministered with RIF [<http://www.cdc.gov/nchstp/tb/>]. However, EFV dosage modification was not needed in this study population.

Depo-Medroxyprogesterone Acetate and ARVs

Susan Cohn reported results of a study of drug interactions between the progesterone-based contraceptive Depo Medroxyprogesterone Acetate (DMPA; *Depo-Provera*) and selected ARV regimens: nelfinavir (NFV), EFV, or NVP + NRTIs compared to NRTIs only or no ARVs [[Abstract 82](#)]. In this prospective study, 65 HIV-infected women (20, 15, and 14 patients, respectively, on NFV, EFV, or NVP-based regimens, and 16 controls) underwent ARV pharmacokinetic assessment at baseline and week 4. Progesterone levels were also assessed with a concentration of >5 ng/mL presumptive of ovulation. Mean C_{max} , T_{max} , AUC_{0-12h} , of EFV, NFV, and M8 (an active NFV metabolite) were similar before and after DMPA administration. Mean NVP C_{max} and AUC_{0-12h} were higher with DMPA, although this increase did not appear to be clinically relevant. DMPA concentrations were not reported. DMPA was well tolerated and progesterone concentrations were below the level for ovulation in all participants.

Coadministration of DMPA with these selected ARV regimens did not compromise safety or efficacy. DMPA offers an alternative

to estrogen-based contraceptives whose metabolism is known to be adversely affected by a number of ARV agents. Further studies are needed with other PIs and NNRTIs.

Atazanavir and Proton Pump Inhibitors

ATV requires an acidic stomach environment for optimal absorption. Concurrent use of ATV with drugs that suppress acid secretion is therefore contraindicated. Agarwala and colleagues evaluated the effects of the proton pump inhibitor (PPI) omeprazole (OMP) on boosted ATV [[Abstract 658](#)]. Forty-eight healthy volunteers received ATV/RTV 300/100 mg qd for 10 days and then were randomized as follows: Group A - ATV/RTV 300/100 mg + OMP 40 mg qd for 10 days, Group B - ATV/RTV 300/100 mg + OMP 40 mg qd + cola (acidic beverage) for 10 days, and Group C - ATV/RTV 400/100 mg + OMP 40 mg qd for 10 days. In the presence of OMP, the mean ATV C_{min} decreased by 78% relative to ATV/RTV 300/100 alone. Mean ATV C_{min} was 66% and 73% lower in subjects given higher dose ATV or cola, respectively. ATV AUC and C_{max} were also significantly reduced.

An increase in the ATV dose or administration of an acidic beverage like cola did not compensate for the effect of OMP on ATV bioavailability. Patients should be cautioned about this drug interaction, and ATV should not be coadministered with PPIs. Until more studies are done, clinicians should also be cautious about using ATV with antacids or H2-blockers.

Atazanavir and Didanosine EC

Investigators from Bristol-Myers Squibb evaluated the effect of didanosine (ddI) EC on ATV steady-state pharmacokinetics [[Abstract 648](#)]. Thirty-two healthy volunteers went through four treatment phases: ddI EC 400 mg fasted on day 1, ATV 400 mg QD with food from days 2 to 7, ATV 400 mg QD + ddI EC 400 mg with food on day 8, ATV/RTV 300/100 mg

QD with food from days 9 to 18, and ATV/RTV 300/100 mg QD + ddI EC 400 mg with food. Reduced ddI EC plasma concentrations were observed with ddI EC + ATV 400 mg (34% and 36% decrease in AUC and C_{max} , respectively) or ddI EC + ATV/RTV 300/100 mg (34% and 38% decrease in AUC and C_{max} , respectively) when given with food. This reduction in ddI concentrations is consistent with what is already known about the effect of food on ddI absorption. Because ddI EC does not have a buffer, ATV concentrations were not changed. However, ATV and ddI EC have different food requirements, thus these drugs must be administered separately as recommended by the manufacturer.

Amprenavir, Lopinavir, and Efavirenz

Amprenavir (APV), lopinavir/ritonavir (LPV/r), and EFV are substrates, inhibitors, and inducers of the CYP3A4 enzyme. Consequently, there is a considerable potential for drug interactions when these agents are combined. Paul Pham and colleagues from Johns Hopkins conducted an open label, steady-state study to evaluate the pharmacokinetic parameters of combined APV and LPV and the effects of EFV on this dual-PI combination [[Abstract 79](#)]. Nineteen HIV-infected patients who were taking APV 750 mg bid and LPV/r 533/133 mg bid without EFV (Group A, N=12) or with EFV (Group B, N=7) for ≥14 days were enrolled. At the doses studied, EFV did not significantly alter LPV/r or APV PK parameters. LPV/r C_{min} in the two groups was similar to LPV/r historical controls. When compared to RTV-boosted APV, the FPV mean AUC was 35% and 52% lower in groups A and B, respectively. Conversely, the FPV mean AUC for groups A and B was comparable to that seen with FPV 1400 + LPV/r 533/133 historical

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control data. FPV C_{\min} was 55% lower in both study groups relative to boosted FPV historical control data, but comparable to FPV 1400 mg + LPV/r 533/133.

Although limited by a small sample size, this study provides clinicians with some guidance for dosing this complex salvage ARV regimen. Now that APV has been withdrawn from the market, FPV 1400 mg bid + LPV/r 533/133 mg bid may be a reasonable option for patients in need of a dual-boosted PI regimen.

Therapeutic Drug Monitoring

Enfuvirtide (ENF) is an attractive candidate for therapeutic drug monitoring (TDM) because of its high cost and parental formulation. Bonora presented the results of a prospective study investigating the determinants of virological response to ENF [Abstract 643]. Thirty-eight HIV-infected subjects starting a salvage ENF-based regimen underwent a full PK analysis at week 2 and trough concentrations at weeks 4 and 12 and had a virtual phenotype and genotype obtained at baseline. Receiver operating characteristic (ROC) curves were used to define cut-offs for ENF plasma concentrations predictive of virological suppression. Optimized background score (OBS), defined as the number of active drugs in the regimen by virtual phenotype, was also used to assess virologic response to ENF. Multivariate analysis revealed that ENF AUC, number of PIs, and presence of LPV/r in the optimized background score (OBS; number of active drugs in the regimen) were associated with viral load decrease at week 4. ENF $C_{\text{trough}} > 2200$ ng/mL and OBS were predictive of viral suppression at week 12. The correlation between plasma concentrations and viral load suppression suggests that ENF might be a good candidate for TDM. However, the utility of TDM for ENF-based regimens needs to be confirmed in prospective trials.

An important consideration in TDM is

the significant degree of intra-individual variability, which could decrease the clinical utility of TDM. Rick Nettles and colleagues from Johns Hopkins used frequent repeated sampling of ARV drug concentrations to assess intra-individual variability in an outpatient clinic population [Abstract 642]. Plasma samples of PIs and NNRTIs were collected at the same time of the day 3 times per week for up to 4 months in 10 HIV-infected patients fully suppressed on a stable ARV regimen. Intraindividual percent coefficient of variation (SD/mean x 100) for drug concentrations was high in most patients taking PIs and lower for NNRTIs: median 43% (N=12) and 26% (N=5), respectively. Virologic “blips” (26/713 samples) did not coincide with low ARV plasma concentrations.

These results challenge the potential utility of TDM; single samples to assess PI concentrations may have limited value and may even be misleading. These findings reinforce the need for more prospective studies of TDM.

Pharmacogenetics and ARV Therapy

Three studies by David Haas and colleagues investigated the role of genetic polymorphisms in response to ARV therapy, occurrence of toxicity and ARV pharmacokinetics.

The Adult AIDS Clinical Trials Group (AACTG) Protocol 384 investigated the relationship between allelic variants of the CYP450 enzymes and *MDR-1* transporter genes, and long-term responses to ARV regimens that included EFV and/or NFV [Haas DW, et al. Abstract 81]. EFV is metabolized by CYP2B6 and 3A4/5 pathways, while NFV and its main metabolite M8 are metabolized by the CYP2C19 and CYP3A4 enzymes, respectively. As previously reported by this group, the allelic variants CYP2B6 516GT and CYP2C19 681GA predicted higher EFV and NFV plasma concentrations,

respectively [Andrade A and Flexner C, *HHR* 2004;16(3):1]. No association was found between these allelic variants and time to treatment failure. However, the MDR1 3435TT polymorphism was strongly associated with decreased emergence of resistance to EFV but not with EFV plasma concentrations. No association was found with NFV outcomes. The favorable virologic response associated with the MDR1 3435TT genotype is consistent with the previous report of Fellay and colleagues [*Lancet* 2002;359:30-6] but inconsistent with findings in other large cohort studies. Although these results corroborate the notion that ARV pharmacokinetics and response to ARV therapy may be affected by genetic polymorphisms, they need to be validated in other large databases.

The same author examined whether there is an association between MDR1, CYP2B6, CYP3A4, and CYP3A5 polymorphisms and occurrence of NVP-associated hepatotoxicity [Abstract 833]. The investigators analyzed data from South African participants who initiated NVP in Gilead protocol FTC-302. Of the 385 participants, 66 (17%) experienced hepatotoxicity, and DNA analysis was performed 53/66 subjects. The investigators found a significant association between the MDR1 3435CT polymorphism and a lowered risk of hepatotoxicity. Although these associations are statistically significant, there was substantial overlap in risk. The extent to which genetics will impact ARV-induced toxicity deserves further investigation.

Because of its long half-life, EFV plasma concentrations may persist at therapeutic or subtherapeutic levels for prolonged periods of time following discontinuation, leaving patients on functional “monotherapy” and at increased risk for the development of NNRTI-resistance mutations. Although staggered interruption of EFV-containing regimens has been suggested to prevent the



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rise of mutations, to date there is no established approach for safely discontinuing EFV. Haas and colleagues investigated the relationship between CYP2B6 genotype and plasma EFV concentrations [Abstract 651]. One hundred fifty-two participants randomized to take EFV-containing regimens were recruited from the AACTG 5097 protocol that evaluated the relationship between EFV pharmacokinetic parameters and CNS effects. Patients with the TT genotype at CYP2B6 position 516 had a longer median half-life (48 hrs) compared to those with the GG (23 hrs) and GT (27 hrs) genotypes. The CYP2B6 516TT genotype, known to be more common in Africans and African Americans and associated with slower EFV clearance, was significantly associated with higher plasma EFV concentrations, which may increase the risk for developing resistance after stopping therapy. These findings suggest that the optimal approach for preventing NNRTI resistance with discontinuation of EFV-based regimens may be influenced by the CYP2B6 genotype and that a single strategy may not be suitable for all patients. ▲

ERRATUM

In the March, 2004 issue we published the following article: "Treatment of Experienced Patients and Antiretroviral Resistance Issues from the 12th CROI" [HHR 2004,17(2):1]. On page 2, in the second full paragraph, the second sentence should read: "Additionally, the percent of subjects achieving a viral load <50 c/mL and the average increase in CD4 cell count were significantly higher in TMC114 600/100 mg bid than in the 400/100 mg qd group." The title for table 2 should read: "Table 2. 24-Week Results of Optimized Clinical Background Plus 1 of 4 TMC114 Dosing Schemes or a Comparator PI." Finally, in table 2 the percent of patients taking TMC114 400/100 bid who experienced grade 3 or 4 adverse events should be 28% not 26%. We regret these errors. ▲

Complications/Toxicity of HIV Therapy

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peripheral neuropathy associated with haplotype T overall and a relative odds of 5.5 in patients receiving ddI + d4T. By multivariate analysis, the odds ratio (OR) was 2.57 for use of ddI + d4T, 1.05 for age increase of 5 years, and 2.89 for haplotype T. The polymorphism that defines this haplotype may point to variations in this gene that predispose individuals to mitochondrial toxicity.

Hepatic Complications

Mark Sulkowski presented data from Johns Hopkins showing that 74% of HIV/HCV co-infected patients had stable or decreased hepatic steatosis measured by paired liver biopsies 3 years apart [Abstract 831]. There was a trend toward worsening steatosis with d4T use in the previous 2 years (47% on d4T vs. 24% without d4T), but no association with age, gender, alcohol use, ALT, glucose, other ART use, HIV suppression or CD4.

Two studies examined the pharmacogenetics of NNRTI hepatotoxicity [Ritchie M, et al. Abstract 832 and Haas D, et al. Abstract 833]. In both studies, one from the US and one from South Africa, a genetic variant of MDR1, MDR1 3435C>T was associated with more than a 2-fold reduction in hepatotoxicity. A concurrent CYP2B6 516G>T polymorphism (previously shown to be associated with reduced EFV clearance) predicted hepatotoxicity with 70% accuracy in the US cohort, in which both EFV and NVP were assessed. In the South African cohort, only NVP was assessed, and the CYP2B6 SNP was not associated with NVP clearance. Though this finding needs further confirmation and has no current clinical utility, pharmacogenetics studies such as this may ultimately foster more rational prescribing of NNRTIs.

Abacavir Hypersensitivity

Factors associated with ABC hypersensitivity reaction (HSR) were evaluated among 9,330 patients receiving ABC in GlaxoSmithKline trials; the overall rate of HSR was 5.4% [Brothers C, et al. Abstract 836]. The rate of HSR was lower in those of African ethnicity, men, and those with CDC class C HIV disease. It was not affected by once- or twice-daily dosing. Rash alone was not sufficient for diagnosis of HSR; 95% of patients with an isolated rash were able to continue ABC. In the second study, the FDA reviewed HSR rates from 9 randomized controlled trials submitted as part of the NDA [James A and Johann-Liang R, Abstract 835]. There were 206 cases of HSR in 2,670 patients (8%) exposed to ABC. There was no difference in occurrence of HSR with once- or twice-daily dosing, although severe HSR was more common with once-daily dosing. These studies indicate HSR rates that may be higher than in earlier product labeling, but that once-daily dosing does not increase risk of HSR.

Injection Site Reactions

Injection site reactions (ISRs) to enfurvitide (ENF) were assessed in 2 studies. In the first of these, the FDA assessed ISRs in the New Drug Application for ENF [Gibbs N, et al. Abstract 837]. Ninety-eight percent of 663 patients reported ISRs (96% pain, 90% induration, 91% erythema, 80% nodules, 65% pruritis). Only 7% discontinued ENF due to ISRs. In the ALLIANCE trial, a 48-week open-label study of 59 patients who received ENF, 98% experienced ≥ 1 ISR, but no patient discontinued ENF because of ISRs over 48 weeks of follow-up [Cooper D, et al. Abstract 838]. Subcutaneous fat was measured by DEXA and was not associated with ISR occurrence, although having more subcutaneous fat was associated with less severe ISRs. ▲



Viral Hepatitis Treatment and Beyond: A Review of CROI 2005

By Lucy Wilson, M.D., Sc.M. and Kelly Gebo, M.D., M.P.H.

While viral hepatitis was well covered this year with an oral session and a number of interesting posters, there was less excitement than at last year's premiere of the HIV/HCV co-infection clinical trials. However, there were several topics of particular interest, including serologic markers for fibrosis, progression of liver disease, and treatment of hepatitis C. In addition, several oral abstracts and posters presented new work on hepatitis B treatment and occult hepatitis B.

Hepatitis C Progression

Several studies addressed the need for noninvasive serologic testing for liver fibrosis and liver fibrosis progression. Mark Sulkowski presented findings from a paired liver biopsy study among HIV/HCV co-infected patients in Baltimore [Abstract 121]. Surprisingly, biopsies performed a median of 2.84 years apart showed that 28% of those with minimal fibrosis (Ishak fibrosis score 0-1) at baseline biopsy had fibrosis progression of at least 2 stages, including some progressing to cirrhosis. These findings suggest that an interval of 3 to 5 years between biopsies, which is standard practice in HCV mono-infected populations, may be too long in HIV co-infected patients. These data argue that HIV/HCV-infected patients should be more closely monitored for liver disease progression than HCV mono-infected patients.

Al Mohu and colleagues from McGill University Hospital Center analyzed the APRI formula (a formula that includes AST and platelet count developed to predict stage of liver fibrosis) for predicting liver fibrosis progression in HIV/HCV or HIV/HBV co-infected subjects as a way to avoid repeat liver biopsy [Abstract 954]. Subjects were followed a median of 4.3 years. At baseline, those with HIV/HCV and HIV/HBV had a higher APRI score than those with HIV

alone. Male sex, lower CD4 and elevated HIV RNA correlated with APRI score. The estimated time to significant fibrosis from baseline in HIV/HCV-infected subjects was 5 years. Liver complications occurred in 6/117 (5%) of HIV/HCV co-infected and 4/53 (8%) of HIV/HBV co-infected patients compared with 5/437 (1%) HIV mono-infected patients. Baseline APRI and the change in APRI predicted liver complications in HCV-infected patients. HAART usage was not protective of liver fibrosis progression.

Sterling presented work from the APRICOT pegylated interferon (PEG-IFN) alpha 2a and ribavirin treatment study evaluating different combinations of routine serologic tests to predict mild, moderate, and severe liver disease [Abstract 120]. Using ROC curves, a model entitled FIB-4 that incorporated age, AST, INR, and platelet count, was the most predictive combination for determining the extent of liver fibrosis. The model was able to distinguish between Ishak fibrosis scores 0-3 versus 4-6, but was less able to distinguish between 0-1 and 2-6. This outperformed APRI and was able to predict fibrosis in 70% of HIV/HCV co-infected patients with 90% accuracy.

HCV Treatment

Data on treatment of acute HCV infection among HIV seropositives was presented. Chaix and colleagues studied 12 HIV-infected MSM with acute HCV infection, genotype 4d [Abstract 122]. Of the 12, ten were treated with early antiviral therapy consisting only of standard interferon. None of the ten achieved a sustained virologic response (SVR). Vogel and coworkers demonstrated that among chronically HIV-infected patients with CD4 counts >300 cells/mm³ and acute HCV infection treated with PEG-IFN and

ribavirin, SVR could be predicted by early treatment response [Abstract 922]. All treatment responders had HCV RNA <600 IU/mL at week 4 of treatment, while all non-responders had HCV RNA >600 IU/mL. Of those receiving HCV treatment, 14/18 (42%) had undetectable HCV RNA at the end of 24 weeks of therapy. This suggests that treatment of acute hepatitis C with PEG-IFN + ribavirin may be useful in certain subgroups of patients with acute HCV infection and that early response may be an appropriate marker to determine the benefit of continued therapy.

Several other studies analyzed the efficacy and safety of PEG-IFN alpha 2a plus ribavirin. Opravil and colleagues presented data from the APRICOT trial on the effect of baseline CD4 on the efficacy and safety of PEG-IFN + ribavirin [Abstract 926]. In the 271 patients with CD4 counts >200 cells/mm³ at study entry, baseline CD4 had minimal effect on SVR. There were only 17 patients with CD4 counts <200 cells/mm³; therefore, conclusions regarding the safety and/or efficacy of HCV treatment in this group could not be made. The frequency of adverse events was similar across all CD4 count strata. The authors concluded that in those with CD4 counts >200 cells/mm³, the safety of PEG-IFN alpha 2a and ribavirin was not adversely affected by baseline CD4 count in this study.

A study by Alvarez and colleagues demonstrated that co-infected patients treated with PEG-IFN + ribavirin and zidovudine (AZT) were more likely to suffer from anemia than those on non-AZT containing regimens [Abstract 927]. Among 217 patients who had completed 12 weeks of PEG-IFN (alpha 2a or alpha 2b) and weight-based ribavirin, there was a mean decrease in hemoglobin in those on AZT of 3.13 g/dL compared to 1.96 g/dL in those on non-AZT containing regimens.



Viral Hepatitis Treatment and Beyond: A Review of CROI 2005

As would be expected, ribavirin dose adjustments were more common in those on AZT regimens, as was use of erythropoietin. This suggests that co-infected patients treated with PEG-IFN and ribavirin who require AZT therapy should be monitored closely for treatment-related anemia, which may require use of erythropoietin. When possible, alternative nucleoside analogs may be preferable.

Hepatitis B Liver Progression

A study from Benhamou and colleagues in Paris examined 668 HBsAg-positive patients, of whom 164 were HIV-infected, for liver decompensation [Abstract 933]. Male age, HIV status, age over 35 years, and alcohol consumption were associated with highest risk of liver decompensation. Among HIV/HBV co-infected patients, age over 35 years and absence of HBV therapy were associated with increased risk of liver decompensation. This study demonstrated that HIV co-infection significantly increased the risk of liver decompensation among HBsAg carriers and that ART regimens that include drugs with activity against HBV and HIV should be included in the treatment of co-infected patients to prevent liver disease progression.

Hepatitis B Treatment

Treatment of hepatitis B, including the use of entecavir in HIV-HBV co-infected patients and a trial of tenofovir DF vs. adefovir in HIV-HBV co-infection, was highlighted in an oral session. Pessoa and colleagues presented data on entecavir in HIV/HBV co-infected patients [Abstract 123]. Entecavir is a guanosine nucleoside analog that is a selective inhibitor of HBV polymerase and has a low interaction potential with HIV medications. Sixty-eight HIV/HBV co-infected patients who experienced HBV viremia on 3TC treatment were randomized to receive

entecavir (N=51) or placebo (N=17) once daily for 24 weeks, followed by open-label entecavir. All patients also continued 3TC during the study. At 24 weeks, the mean reduction in HBV DNA from baseline was superior in the entecavir arm compared to placebo (-3.66 log vs. +0.11 log). After a mean follow-up of 40 weeks, side effect profiles were similar. No significant changes were seen in HIV viremia or CD4 count. These data suggest that entecavir is the first selective HBV antiviral agent to demonstrate safety and efficacy in the HIV-HBV co-infected population.

Peters presented the results of a randomized, double-blind study of 52 HIV/HBV co-infected subjects who received adefovir 10 mg plus tenofovir placebo or tenofovir 300 mg plus adefovir placebo [Abstract 124]. After a median follow-up of 75 weeks, the mean log₁₀ time-weighted average change from baseline to week 48 was -4.44 in those on TDF and -3.21 in adefovir (P=.017). Four subjects in each arm discontinued therapy prematurely, including one death in each arm (HCC and unknown cause). A limitation of this study was that seroconversion was evaluated at 48 weeks, which may be too early to assess hepatitis B treatment response.

Occult Hepatitis B

Several presentations highlighted the importance of occult hepatitis B, which is defined as detectable HBV DNA and anti-HBc antibodies in the serum in the absence of HBsAg. Pogany and colleagues demonstrated that occult HBV occurred in 4% of HAART-naïve individuals at their facility [Abstract 932]. All patients tested negative for HBV DNA one year after starting on HAART. They concluded that occult HBV infection is more of a diagnostic dilemma than a clinical problem. Another study by Selabe from South Africa evaluated 12 occult HBV/HIV co-infected

patients, 10 HBsAg-positive/HIV-infected patients, and 12 HBsAg-positive HBV-mono-infected patients [Abstract 935]. They found lower HBV viral loads in the occult co-infected patients compared to HBsAg-positive patients. They also demonstrated the evolution of YMDD mutations (mutations in the polymerase gene associated with the reappearance of HBV DNA) in occult patients, suggesting that such strains are able to emerge without 3TC therapy. While YMDD mutations are common in the developing world because of extensive lamivudine use, these results have implications for new treatment programs in the developing world, since this study suggests that occult HBV-infected patients will need to be monitored more closely for the development of HBV resistance.

Liver Transplant

Finally, Vogel and colleagues authored a report on 10 patients who had been listed with the Eurotransplant International Foundation (responsible for the mediation and allocation of organ donation procedures in several European countries) for liver transplantation and were known to be HIV-infected at the time of listing [Abstract 931]. The reasons for listing on the transplant list included fulminant HBV, chronic HBV/HCV and chronic HCV infection. Seven patients underwent transplant at a median of 315 days, two died while awaiting transplant, and one patient experienced significant improvement in liver function after initiating HAART. One transplanted patient died at 84 days from an intrathoracic hemorrhage; the rest were alive at a median of 432 days. The most common drug-drug interactions were between cyclosporine A and protease

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Reduced Bone Mineral Density in HIV-Infected Patients

By Todd T. Brown, M.D.

At the 7th Conference on Retroviruses and Opportunistic Infections in 2000, amid much discussion of buffalo humps, skyrocketing lipids, and disappearing fat, two groups reported an increased prevalence of osteopenia and osteoporosis in HIV-infected patients receiving highly active antiretroviral therapy (HAART) [Tebas P, et al. [Abstract 207](#) and Hoy J, et al. [Abstract 208](#), 7th CROI, 2000]. The initial concern was that reduced bone mineral density would be yet another toxicity of antiretroviral therapy. Since that time, the picture has become more complicated. There is no question that HIV-infected patients have a higher risk of osteopenia and osteoporosis, but the etiology appears to be multifactorial, and the role of antiretroviral therapy is controversial. Many questions still remain, particularly surrounding the utility of screening and the criteria for treatment. This review addresses our current state of knowledge regarding the pathogenesis of osteopenia and osteoporosis in HIV-infected patients and gives practical recommendations regarding screening and treatment. The gaps in knowledge are highlighted and, in the absence of data, an attempt is made to supplement evidence-based recommendations with clinical experience.

Definitions

Osteoporosis has been defined as a “systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and fracture” [[Am J Med 1993;94:646](#)]. There are three important features of this definition: 1) low bone mass, 2) abnormalities in bone structure, and 3) resulting fractures. Practically, osteoporosis is generally identified only by the first part of the definition, i.e. low bone mass, usually measured by dual x-ray absorptiometry (DXA). By criteria established by the World Health Organization,

osteoporosis is defined as a bone mineral density (BMD) over 2.5 standard deviations less than the mean healthy, young, race- and gender-matched control subjects (T-score <-2.5) [[World Health Organ Tech Rep Ser 1994;843:1](#)]. It should be noted that abnormalities in bone structure that may weaken bone and predispose it to fracture are not captured by this definition. Nevertheless, this definition has practical significance, in that the risk of fracture increases by a factor of 1.5 to 3.0 for each standard deviation decrease below the young normal mean [Marshall D, et al. [BMJ 1996;312:1254](#)]. One caveat is that the WHO definition was created to evaluate BMD in postmenopausal women. Its utility in men and in premenopausal women has not been clearly established. Despite these limitations, this definition is generally applied to all adult populations.

Other definitions are also important to review. Osteopenia is defined by the WHO as a BMD between 1 and 2.5 standard deviations less than mean BMD in young, healthy subjects. Because the risk of fracture increases linearly with reducing BMD, fracture risk is also increased in this group, at least in post-menopausal women. Osteomalacia describes the relative lack of mineralization in bone tissue that causes bones to be soft, weak, and prone to fracture. It cannot be definitively measured by DXA, but often the T-scores in these patients are reduced. In adults vitamin D deficiency is the most common cause.

Epidemiology of Reduced Bone Mineral Density in HIV-infected Patients

Most cross-sectional studies have shown that osteopenia and osteoporosis are 2-3 times more common in HIV-infected patients on HAART compared to HIV-seronegative control subjects [Tebas P, et al. [AIDS 2000;14:F63](#)], with prevalence

estimates varying from 55% to 89% [Gold J, et al. [J Acquir Immune Defic Syndr 2002;30:131](#); Knobel H, et al. [AIDS 2001; 15:807](#)]. Studies examining longitudinal changes in BMD in HIV-infected patients have had conflicting results [Mondy K, et al. [Clin Infect Dis 2003;36:482-490](#); Mallon PW, et al. [AIDS 2003;17:971-979](#)].

Abnormalities of bone turnover are also common in HIV-infected patients. Normally, bone is being constantly remodeled: old bone is resorbed by osteoclasts, and new bone is laid down by osteoblasts in a process that is tightly coupled. HIV-infected subjects have demonstrated enhanced bone resorption compared to HIV-negative control subjects but no difference in bone formation, suggesting an uncoupling of these two processes [Mondy K, et al. [Clin Infect Dis 2003;36:482](#); Brown TT, et al. [J Clin Endocrinol Metab 2004;89:1200](#)]. This imbalance between formation and resorption may lead to reduced BMD over time.

The most important question in the epidemiology of osteopenia and osteoporosis in HIV-infected patients has not yet been answered: Are HIV-infected patients at a higher risk of fracture? To date, there have been several case reports documenting atraumatic fractures in young HIV-infected patients [Forsyth SF, et al. [Int J STD AIDS 2002;13:645](#); Guaraldi G, et al. [AIDS 2001; 15:137](#); Nuevo JA, et al. [An Med Interna 2003;20:496](#)]. However, the risk of fracture in HIV-infected patients has not been determined in controlled, prospective studies. Because this population is relatively young and their baseline fracture risk is low, prolonged follow-up of large numbers of subjects is required to answer this question with adequate statistical power. There is active ongoing research in this area.

Pathophysiology and Risk Factors

Multiple factors contribute to reduced BMD in HIV-infected patients. Chronic



Reduced Bone Mineral Density in HIV-Infected Patients

HIV infection with ensuing systemic inflammation may play an important role. Cytokines such as TNF- α and IL-6 are potent stimulators of osteoclast activity and may lead to increased bone resorption. Markers of bone resorption in HIV-infected patients have been shown to be positively correlated with TNF- α activity [Aukrust P, et al. *J Clin Endocrinol Metab* 1999;84:145]. In addition, cytokine activation may account for low levels of 1, 25-dihydroxyvitamin D observed in patients with advanced HIV-disease [Haug CJ, et al. *J Clin Endocrinol Metab* 1998;83:3832]. Deficiency of the active form of vitamin D (1, 25 dihydroxyvitamin D) may impair the intestinal absorption of calcium and lead to osteomalacia. Taken together, these changes in cytokine expression and activity may account for the increased risk of reduced BMD in HIV-infected patients before the HAART era [Paton NI, et al. *Calcif Tissue Int* 1997;6:30].

Known risk factors and secondary causes of reduced BMD may also be more common among HIV-infected patients. Hypogonadism, previous steroid exposure, cigarette smoking, and heavy alcohol use all can contribute to osteopenia and osteoporosis. Low body weight and nadir body weight are also important risk factors in HIV-infected patients [Carr A, et al. *AIDS* 2001;15:703].

The contribution of antiretroviral therapy to reduced BMD has not been clarified. Some cross-sectional studies have shown an increased prevalence osteopenia and osteoporosis in HIV-infected patients exposed to protease inhibitors [Tebas P, et al. *AIDS* 2000;14:F63; McDermott AY, et al. *Am J Clin Nutr* 2001;74:679]. However, other studies have failed to find an association [Brown TT, et al. *J Clin Endocrinol Metab* 2004;89:1200; Huang JS, et al. *AIDS* 2001;15:975; Amiel C, et al. *J Bone Miner Res* 2004;19:402]. These conflicting data

might be due to the differential effects of individual protease inhibitors on bone metabolism. *In vitro* studies have shown that indinavir, for example, impairs bone formation, whereas ritonavir inhibits the formation of osteoclasts and may be bone sparing [Wang MW, et al. *J Clin Invest* 2004;114:206]. These *in vitro* findings have questionable clinical significance, however, since HIV-infected patients on indinavir actually experience an increase in bone mineral density over 40 months [Nolan D, et al. *AIDS* 2001;15:1275].

Nucleoside analogs, particularly thymidine analogs, have also been implicated in the pathogenesis of reduced BMD. In a longitudinal study, patients receiving d4T or AZT therapy had a significant decline in BMD over the 104 week observation period, while those who switched to abacavir remained stable [Martin A, et al. *AIDS* 2004;18:1029]. These results are consistent with the *in vitro* observation that AZT stimulates osteoclast activity [Pan G, et al. *AIDS Res Hum Retroviruses* 2004;20:608]. In addition, thymidine analogs may affect bone metabolism indirectly, through their effect on mitochondria. A large, cross-sectional study showed that an independent predictor of reduced BMD is the presence of lactic acidosis [Carr A, et al. *AIDS* 2001;15:703]. Metabolic acidosis decreases bone formation and increases bone resorption [Bushinsky DA, et al. *Am J Physiol* 1983;245:F204]. In addition to the thymidine analogs, the nucleotide analog, tenofovir DF, has also been associated with modest decreases in bone mineral density in a recent randomized trial [Gallant JE, et al. *JAMA* 2004;292:191]. In some patients, tenofovir impairs phosphate reabsorption in proximal tubule of the kidney, thereby leading to phosphate wasting and osteomalacia.

In addition, tenofovir can impair 1- α hydroxylase activity in the kidney, thereby

decreasing the relative concentration of 1, 25 dihydroxyvitamin D.

Screening Recommendations

With the lack of data regarding fracture risk and the relatively young patient population, the current recommendation is not to screen HIV-infected patients routinely for osteoporosis. However, those patients who have other risk factors for the development of osteoporosis or those with the history of atraumatic fracture should be offered screening [Schambelan M, et al. *J Acquir Immune Defic Syndr* 2002;31:257]. The risk factors that should be considered when making the decision to screen for reduced bone mineral density are not explicit in the current guidelines. In my practice, I screen men with hypogonadism, women who are post-menopausal or have amenorrhea, patients with a history of wasting, gastrointestinal diseases, such as celiac sprue or inflammatory bowel disease, or endocrine diseases associated with reduced BMD including hyperthyroidism and hyperparathyroidism. I also screen patients with a history of prolonged steroid exposure (>3 months). Because of the potential association between body fat changes and reduced BMD, patients with lipodystrophy may represent another population that merits screening [Brown TT, et al. *J Clin Endocrinol Metab* 2004; 89:1200; Huang JS, et al. *AIDS* 2001;15: 975; Rosenthal L, Falutz J. *J Bone Miner Metab* 2005;23:53]. At this point, however, the data are too few to support this recommendation.

Evaluation for reduced BMD is best done with DXA measurements. In standard protocols, bone density at the lumbar spine and the hip is measured. Treatment decisions should be based on the lowest

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score of the two sites. For the hip, the total hip and femoral neck are useful measurements; Ward's triangle is not.

It should be noted, however, that BMD by DXA explains only about 50% of fracture risk. Therefore, it is possible to have compromised bone strength and consequent atraumatic fracture without a T-score that meets WHO criteria for osteoporosis. Conversely, while the relative risk of fracture in HIV-infected patients with osteopenia and osteoporosis is probably higher compared to age-, race-, and sex-matched subjects, the absolute fracture risk is very small given the relatively young age of the HIV population.

Treatment Recommendations

The optimal treatment threshold in HIV-infected patients has not yet been established. Current recommendations are extrapolated from data on postmenopausal women in the general population, which suggest that treatment should be offered to those with a T score <-2.5 or a T score <-2.0 in patients with a history of atraumatic fracture. In the absence of specific data delineating the risk of fractures in HIV-infected patients, these guidelines should be followed. However, given the low absolute risk of fracture in a younger population, the optimal treatment threshold may actually be higher.

All those with osteopenia or osteoporosis should receive 1200-1500 mg of calcium daily and 400-800 IU of vitamin D. Ideally, both of these should be derived from the diet. In reality, most people fall well short of these recommendations with normal daily intake and therefore require at least some supplementation. Weight bearing exercise should also be recommended.

There are multiple effective medications for the treatment of osteoporosis. The safest and most effective of these are the bisphosphonates class. The newest

generation of oral bisphosphonates, risedronate and aledronate, are used to reduce the risk of fracture in postmenopausal patients. In HIV-infected patients, aledronate (70 mg/week) increased lumbar spine BMD by 5.2% over 48 weeks [Mondy K, et al. *J Acquir Immune Defic Syndr* 2005;38:426]. Bisphosphonates bind to the bone matrix and prevent bone resorption by osteoclasts. Both of these medications are poorly bioavailable and therefore must be taken on an empty stomach. Because of their long tissue half-lives, these drugs can be dosed once a week. However, longer dosing intervals and interrupted treatments strategies are currently being examined. The fraction that is not bound to bone is excreted unchanged by the kidney. Therefore, there is no pharmacokinetic interaction with anti-retroviral medications. The most common side effect is gastric and esophageal ulceration; as a result, these medications must be taken with a full glass of water and the patient must remain upright for at least 30 minutes after administration. For those subjects who cannot tolerate oral bisphosphonates, intravenous bisphosphonates (pamidronate or zoledronate) are reasonable alternatives, although these drugs are not FDA approved for this purpose.

For women with osteoporosis, selective estrogen receptor modulators such as raloxifene are reasonable alternative or adjunctive treatments to bisphosphonates. Hormone replacement therapy is also an effective treatment for postmenopausal women with osteoporosis. However, because of the risk of breast cancer and endometrial cancer, cardiovascular disease, deep vein thrombosis, and Alzheimer's disease, estrogen replacement therapy cannot be recommended as first line treatment. Intranasal calcitonin also has some effect and maintaining bone mineral density. Because this effect is rather modest,

other treatments should be considered first.

The newest drug available for the treatment of osteoporosis is recombinant parathyroid hormone. With intermittent exposure, parathyroid hormone stimulates bone formation particularly of cortical bone. Concomitant administration with bisphosphonates impairs the activity of parathyroid hormone. For this reason, bisphosphonates should be discontinued at least three months before starting PTH. PTH should be used only in those patients who continue to have fractures with bisphosphonates exposure, or those who are at a higher risk of fracture and not responding to bisphosphonates.

Evaluation of Secondary Causes

Patients who have been diagnosed with osteopenia or osteoporosis should be evaluated for secondary causes of reduced BMD, with an emphasis on those causes that can be treated. A suggested work-up is shown in the [Table 1, p 16](#). In addition, patients should be counseled to minimize modifiable risk factors, such as alcohol intake, inactivity, and smoking.

Conclusions

Reduced BMD is common among HIV-infected patients. However, the risk of fracture in this population is not known. Because osteoporosis is often an asymptomatic condition with a long latency until fracture, prevention of fractures through targeted screening and early treatment is a reasonable strategy. However, these benefits must be balanced with the actual risk of fracture and the costs and side effects of treatment. In HIV-infected patients, the cost:benefit ratio has not been determined. At this point, screening should be reserved for those patients with other risk factors for

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FDA Approves *Pegasys* and *Copegus* for Hepatitis C in Patients With HIV Co-infection

By John G. Bartlett, M.D.

On February 25, 2005 the FDA approved the use of *Pegasys* and *Copegus* for treatment of hepatitis C (HCV) in patients co-infected with HIV. *Pegasys* is the Roche formulation of peginterferon alpha-2a; *Copegus* is the Roche formulation of ribavirin.

Efficacy: The study that established efficacy in the treatment of HCV in HIV co-infected patients was a randomized trial of *Pegasys* (180 µg SC weekly) combined with ribavirin (800 mg PO daily) compared to interferon-alpha (*Roferon-A*, 3 MIU SC) plus ribavirin (800 mg PO daily) vs. *Pegasys* (180 µg SC) with ribavirin placebo. Results are summarized in the following table, which also shows results of *Pegasys* plus ribavirin at the same doses for HIV-negative patients. Both studies demonstrated that the lack of an early virologic response by week 12 strongly predicted non-response and was grounds for discontinuation of treatment. It was noted that median HIV viral loads did not increase above baseline during treatment or 24 weeks after discontinuation of treatment.

Black Box Warnings: *Pegasys* may cause or aggravate fatal or life threatening neuropsychiatric condition (depression), infectious disorders (serious bacterial infections), autoimmune disorders (myositis, hepatitis, immune thrombocytopenic purpura, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis and lupus) and ischemic disorders (hypertension, arrhythmias and myocardial infarction).

Ribavirin may cause birth defects and/or fetal death (pregnancy category X) requiring "extreme care to avoid pregnancy in female patients and in female partners of male patients". Ribavirin causes hemolytic anemia, and is genotoxic and mutagenic, suggesting carcinogen potential.

Table. Sustained Viral Response in Patients With HIV/HCV Co-Infection By Regimen

Genotype	HIV-Positive			HIV-Negative
	IFN + RIB N = 289	PEG-IFN + Placebo N = 289	PEG-IFN + RIB N = 290	PEG-IFN + RIB N = 361
Genotype 1	7%	14%	29%	40%
Genotype 2-3	20%	36%	62%	76%
Total	11%	20%	40%*	50%

*Of 85 patients who did not achieve undetectable HCV RNA or $\geq 2 \log_{10}$ reduction in HCV RNA at 12 weeks 2 (2%) had a sustained viral response.

Indications: *Pegasys* alone or in combination with ribavirin is indicated for patients with HCV who have compensated liver disease and who were not previously treated with interferon-alpha, including patients with HIV infection who are clinically stable (defined as not requiring antiretroviral therapy or on ART and stable). Ribavirin (*Copegus*) is indicated for patients with HIV-HCV co-infection as defined above. This drug is not effective as monotherapy.

Contraindications: 1) Hypersensitivity to *Pegasys*, 2) autoimmune hepatitis, 3) hepatic decompensation with a Child-Pugh score of ≥ 6 before or during therapy. The combination of ribavirin and *Pegasys* is contraindicated in: 1) patients with hypersensitivity to ribavirin, 2) pregnant women, 3) men with a female partner who is pregnant, and 4) patients with hemoglobinopathies such as thalassemia major or sickle-cell anemia.

Precautions: It is noted that experience is limited for *Pegasys* alone or in combination with ribavirin in patients with hepatitis B and in patients with HIV with a CD4 count < 100 cells/mm³.

Pegasys/Copegus combination therapy should not be used in pregnant patients or patients with hemoglobinopathies.

Doses: The standard regimen is *Pegasys* 180 µg SC weekly combined with ribavirin 800 mg PO daily for a total of 48 weeks.

How Supplied: *Pegasys* is supplied as single-dose vials, four-packs of single-dose vials, and prefilled single dose syringes.

Copegus is supplied in bottles of 168 200 mg tablets.

Additional information may be obtained from the package inserts:

Pegasys: <http://www.rocheusa.com/products/pegasys/pi.pdf>

Copegus: <http://www.rocheusa.com/products/copegus/pi.pdf>



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inhibitors. HCV infection, which recurred in all patients with pre-existing HCV disease, was successfully treated with early interferon + ribavirin combination therapy. These data suggest that liver transplant may be a reasonable treatment option for selected HIV-infected patients with end-stage liver disease, but that drug-drug interactions remain an important issue.

Summary

Overall, the viral hepatitis studies at CROI 2005 suggest that viral hepatitis co-infection in the setting of HIV infection results in progression of liver disease at a much faster rate than in hepatitis mono-infection. In addition, the treatment trials suggest that both hepatitis B and C can be treated, but larger trials, particularly for hepatitis B infection, will be required in the future before formal treatment recommendations can be made. ▲

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Table 1. Secondary Causes of Reduced Bone Mineral Density and Screening Modalities

Condition	Screening Test	Specific Treatment	Comment
Vitamin D deficiency	25-OH Vitamin D	Ergocaliferol to load (50K units 2x/wk x 6 wk)	Lower limit of normal: 20 ng/mL
Hyperparathyroidism	PTH, Ca++	Surgery	–
Hypogonadism	Testosterone (males); menstrual history (females)	Hormone replacement	Investigate potential underlying causes
Subclinical Hyperthyroidism	TSH	Antithyroid drugs/radioiodine	Investigate underlying cause
Idiopathic Hypercalciuria	24 h urinary calcium	Thiazide Diuretics	–
Celiac Sprue	Tissue Transglutaminase	Gluten-free diet	Can be seen in the absence of diarrhea
Phosphate wasting	Serum Phosphate	–	–

reduced BMD. In asymptomatic patients, treatment should be offered to only those with t-scores <-2.5. More research is necessary to further clarify further the optimal screening targets and treatment thresholds in this population. ▲

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