

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Drug Profile: Darunavir (Prezista, DRV, formerly TMC-114)

By Paul A. Pham, Pharm.D.

Manufacturer: Tibotec
Therapeutics

Class: Protease inhibitor

Formulation/Storage: 300 mg
tablet/Store at room temperature

Price: Wholesale acquisition cost:
\$6.25/tablet

Indication: DRV, co-administered
with ritonavir (RTV), is indicated
for use as part of combination
antiretroviral treatment of HIV-1-
infected adult patients who are
highly treatment-experienced or
have virus resistant to multiple
protease inhibitors.

Dose: DRV 600 mg (two 300 mg
tablets) + RTV 100 mg bid with
food.

Since RTV increases DRV AUC by
approximately 14-fold; RTV co-
administration with DRV is
required in order to achieve the
desired DRV levels.

**Dosing with renal impairment
(with/without dialysis):** Limited
data; usual dose likely.

Dosing with hepatic impairment:
No data; use with close
monitoring.

Pregnancy Risk: Category B: No
human data. Darunavir has shown
no embryotoxicity or
teratogenicity in mice, rats and
rabbits.

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One Pill, Once-a-Day, and Other Charms from Lisbon: Update from the 7th International Workshop on the Clinical Pharmacology of HIV Therapy

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

Lisbon is a European capital visited infrequently by Americans, which is a shame given the physical beauty and charm of this ancient city. In late April, 200 clinical pharmacologists from around the world gathered there for the 7th International Workshop on the Clinical Pharmacology of HIV Therapy. They shared outstanding science, including a number of important reports on the pharmacology of existing and new drugs. Also presented were the first clinical results of studies with the new one pill, once-a-day coformulation of efavirenz (EFV), emtricitabine (FTC), and tenofovir DF (TDF).

One Pill, Once-a-Day

For the past decade, much effort has gone into regimen simplification as a means of improving antiretroviral adherence. This trend has manifested itself most recently with the availability and increasing popularity of the *Truvada* and *Epzicom* coformulations. For several years, investigators from Bristol Myers-Squibb and Gilead have been collaborating to develop a coformulation of three drugs: EFV, TDF, and FTC. This endeavor has been fraught with many problems and setbacks, as the final product had to contain 1,100 mg of drug and very little excipient. Three previous coformulations failed because they produced inadequate EFV concentrations in human subjects. However, it now appears that there is a coformulation with acceptable bioequivalence and manufacturing properties. The first results of clinical studies with this

single tablet regimen (STR) were presented in Lisbon.

Potential advantages of an antiretroviral STR include added convenience and simplicity for the patient. In addition, a single tablet regimen means that the patient will either take all of their drugs or none, perhaps reducing the risk of taking an incomplete regimen and developing resistance. STR regimens should be matched for pharmacokinetic properties (mainly clearance or half-life of the active drug), and must have appropriate chemical compatibility.

Brian Kearney and colleagues from Gilead presented results of a cross-over trial in which 48 healthy volunteers received either the STR or all three individual components as separate tablets, administered in random order 21 days apart. Thirty-five of the subjects were women and 13 were men; 90% were Hispanic. Pharmacokinetic analysis at the end of the study (see Table, p 2) indicated that the new STR met bioequivalence comparisons for all three drugs. Two subjects became pregnant during the study,

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Table. Bioequivalence of the EFV/TDF/FTC Single Tablet Regimen (STR)*

PK Parameter	Efavirenz (% geometric mean ratio and 90% confidence intervals)	Tenofovir	Emtricitabine
C _{max} (STR/individual formulation)	99.9 (93.4, 107)	91.5 (84.6,98.8)	88.8 (84.0, 93.9)
AUC _{0→t} [†]	95.7 (90.5, 101)	99.3 (91.0,108)	98.0 (94.9, 101)
AUC _{0→∞} [†]	95.2 (88.9, 102)	100 (93.2,108)	98.0 (94.9, 101)

* Data from Mathias and coworkers [7th International Workshop on Clinical Pharmacology of HIV, Abstract 82.] Bioequivalence for each pharmacokinetic parameter is defined as 90% confidence intervals falling between 80 and 125%.

[†]The first parameter actually measures AUC to 24 hours only; the second extrapolates AUC to infinity.

but there were no other significant side effects noted.

The size of the new STR tablet is slightly larger than that of the current *Truvada* tablet (see Figure), so this may be a problem for patients who have difficulty swallowing large tablets. However, it is likely that many patients currently taking these three drugs as separate tablets will wish to switch to the single tablet. This may also be an attractive option for treatment-naïve patients desiring a simple regimen that they can take once a day. The true benefits of this new product remain to be determined, but most will see this as a major advance in the quest for unobtrusive, long-term control of HIV infection.



Figure. Comparison of the size of the new EFV/TDF/FTC single tablet regimen (on the right) to current EFV 600 mg tablet and *Truvada* tablet (on the left). Photograph reproduced with the permission of Bristol-Myers-Squibb.

Editor's Note – As this issue of the HHR was going to print the FDA gave approval to this combination of EFV, TDF, and FTC under the brand name Atripla. Full prescribing information may be found on the web at: <http://www.fda.gov/cder/foi/label/2006/021937lbl.pdf>.

Fixed-Dose Formulations: The Down Side

Although providers and patients usually see combined, fixed-dose formulations as a good thing, Raffaella L'homme and colleagues presented a study that emphasized the down side of such tablets [Abstract 2]. This group determined steady-state concentrations of nevirapine (NVP) in 71 Malawian and 56 Zambian children who were receiving the Triomune fixed-dose combination of generic NVP, lamivudine (3TC), and stavudine (d4T). This tablet comes in only one size (200 mg of NVP, 150 mg of 3TC, and 40 mg of d4T, given twice daily). Young children in resource-poor countries are given one-quarter, one-half, or three-quarters of a tablet twice a day depending on body size.

When NVP concentrations were measured in these children (age range 3 months to 16 years), 18% had NVP trough concentrations below the target of 3.0 mg/mL, which is considered subtherapeutic

in some European countries. Most of the underdosed children were small, and were receiving the one-quarter or one-half tablet dose. Children closer to adult size had close to adult concentrations of NVP.

This study makes the point that fixed-dose combinations of some drugs may not be appropriate for pediatric patients. It was also pointed out that children under the age of two years may have a hard time swallowing tablets of any size, and that crushing fixed-dose tablets may not solve the problem because of altered bioavailability of the crushed tablet. This study reminds us that, when it comes to antiretrovirals, one size will never fit all.

A Skin Test for Abacavir Hypersensitivity?

The abacavir (ABC) hypersensitivity reaction (HSR) is an uncommon but life-threatening side effect of an otherwise well-tolerated nucleoside analog. In fact, concern about HSR has led many providers to avoid the *Epzicom* coformulation, which contains ABC and 3TC.

An important problem in managing HSR is the difficulty of distinguishing true hypersensitivity, which often includes fever, abdominal symptoms, and rash, from non-specific symptoms that may be mistaken for HSR. For example, patients started on EFV and *Epzicom* frequently develop rash, which may be mistakenly diagnosed as HSR, although a less serious EFV rash is far more likely. Patients on ABC who develop a fever may also be taken off the drug and labeled as having HSR, even when no other symptoms are present.

Elizabeth Phillips and colleagues in Vancouver have developed a skin test for ABC hypersensitivity. They evaluated this product in 42 patients with a previous diagnosis of HSR [Abstract 33]. Patients were tested with dermal patches containing 0%, 1%, or 10% ABC, and results were read after 24 hours. More than half of these patients (22/42) had negative patch tests.



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Patch test negative patients often did not fit the classic HSR syndrome: they were more likely to have onset of symptoms very early (<3 days) or late (>21 days) after starting ABC, usually had only 1 or 2 symptoms of HSR, and only 9% were HLA B*5701 positive, compared to 100% of patch test positive patients.

The authors concluded that HSR is frequently misdiagnosed, resulting in unnecessary cessation of ABC. Six of the patch test negative patients have now been rechallenged with ABC, and all have done well with no evidence of HSR. The main drawback of this test is that it only has

diagnostic utility in patients already exposed to ABC, since it relies on a delayed-type hypersensitivity (DTH) skin reaction that requires prior exposure to the antigen.

How Protease Inhibitors Increase Tenofovir Concentrations

It has been known for several years that tenofovir concentrations increase by 20-30% in patients receiving some HIV protease inhibitors, including lopinavir/ritonavir (LPV/r) and atazanavir (ATV). The mechanism for this interaction has been a mystery, since tenofovir is entirely excreted through the kidney. LPV and

ATV inhibit hepatic drug metabolizing enzymes like cytochrome P450 3A4 but are not known to alter the renal excretion of other drugs.

Investigators from Gilead carried out a series of *in vitro* experiments to examine the potential role for drug transport proteins in this interaction [AS Ray, et al. Abstract 39]. They determined that TDF uptake into renal tubular cells *in vitro* is mediated by two transport proteins called organic anion transporters-1 and -3 (OAT1 and OAT3).

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The Hopkins HIV Report is published six times per year by The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Publication of this newsletter is underwritten by a generous grant from Boehringer Ingelheim; we gratefully acknowledge their support.

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Efflux of TDF out of the renal tubular cell and into the urine is mediated by multidrug resistance protein-4 (MRP-4). LPV and ritonavir (RTV) inhibit tenofovir uptake mediated by OAT3 and could therefore reduce renal excretion of this drug. The PIs had no effect on MRP-4, so they would not be expected to increase tenofovir accumulation in renal tubular cells, which might cause greater nephrotoxicity.

A second study examined the transport of tenofovir across intestinal epithelial (CaCo) cells [AS Ray, et al. Abstract 49]. The tenofovir prodrug TDF was found to be a substrate for the intestinal efflux transporter p-glycoprotein (P-gp). ATV,

LPV, and RTV all inhibited P-gp mediated efflux of TDF. If P-gp plays an important role in limiting absorption of TDF (by effluxing the drug back into the intestinal lumen), then P-gp inhibition by PIs could improve systemic bioavailability of tenofovir by allowing more drug to enter the circulation. This is consistent with clinical data showing that the main effect of PIs is on tenofovir bioavailability, not clearance.

Although these data are strictly from experimental cell lines, this model better explains the interaction between TDF and PIs than any other previously proposed.

No Interaction Between Tipranavir and Maraviroc

An important effect of the new HIV protease inhibitor tipranavir (TPV) is induction of the clearance of other drugs and a decrease in their concentrations. Specifically, TPV reduces LPV, amprenavir (APV), and saquinavir (SQV) concentrations by more than 50%, even when boosted with RTV, so TPV cannot be coadministered with these PIs. It has been assumed that this interaction mainly reflects induction of hepatic cytochrome P450 3A4 (CYP3A4), but TPV's effect on other antiretrovirals that are CYP3A4 substrates has not been examined.

Maraviroc is a promising new CCR5 antagonist (reviewed by Shepherd J and Quinn T, *HHR* 2004; 16[4]:1). It is also a CYP3A4 substrate. Investigators from Pfizer examined what would happen to maraviroc concentrations if this drug was combined with tipranavir, as might occur in heavily treatment-experienced patients [S Abel, et al. Abstract 77]. Twelve healthy volunteers received maraviroc at the standard dose of 150 mg bid and added TPV/r at the standard dose of 500 mg/200 mg bid for 14 days. At the end of the combination period, maraviroc concentrations were unchanged except for a slight increase in trough concentrations.

This study indicates that TPV will not inevitably reduce the concentrations of all coadministered CYP3A4 substrates. This is good news for the future use of TPV/r in combination with drugs like maraviroc. The explanation for the lack of interaction is that TPV/r acts principally as an inducer of intestinal p-glycoprotein (P-gp) but as an inhibitor of CYP3A4. The bioavailability of PIs that are P-gp substrates, like SQV, APV, and possibly RTV, is therefore greatly reduced in the presence of TPV, because P-gp prevents absorption of the PIs. However, concentrations of drugs that are CYP3A4 substrates but not P-gp substrates, as presumably would be the case for maraviroc, would be unaffected or increased by TPV/r.

Pharmacology of HIV Integrase Inhibitors: Peak, Trough, or AUC?

HIV integrase inhibitors are perhaps the most promising new class of antiretroviral agents, given the potent suppression of viral load seen with the three agents tested thus far in monotherapy studies. One of these agents, GS-9137, which is being developed by Gilead, was the subject of a detailed pharmacokinetic/pharmacodynamic (PK/PD) analysis designed to determine which PK properties drive the antiviral benefit.

Brian Kearney and colleagues presented data from 40 treatment-naïve and treatment-experienced patients treated with GS-9137 alone for 10 days [Abstract 73]. These subjects received one of five different regimens that produced very different peak and trough concentrations: 800 mg qd; 200, 400 or 800 mg bid; or 50 mg qd with 100 mg of ritonavir (data taken from a study discussed in detail by Flexner C, *HHR* 2006; 18[2]:10).

When a variety of pharmacokinetic parameters were compared to the degree of viral suppression in individual patients, it appeared that virologic response was driven by the trough concentration, with greater suppression associated with the higher troughs [Abstract 73]. Peak concentration

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Please note: The *HHR* is published every *other* month— January, March, May, July, September, and November.



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and area-under the concentration-time curve (AUC) were not strongly correlated with efficacy.

This is an important finding, because it indicates that the greatest long-term benefit from this drug is likely to derive from regimens producing high troughs at the end of a dosing interval. This would favor ritonavir-boosting of this drug, which is a CYP3A4 substrate, or more frequent administration of unboosted drug (bid rather than qd). Results of this analysis were used by Gilead to choose regimens for their Phase 2 studies.

This study confirms what many pharmacologists have believed about the dosing of antiretroviral drugs: that it is more important to maintain the highest possible concentration of a drug in the plasma for the longest period of time, and that higher peak concentrations may increase the risk of toxicity but do not contribute to antiviral benefit [Flexner and Piscitelli, *AIDS* 2002; 6 (Suppl 1): S1-S3]. This also provides a concrete example of the value of PK/PD analysis early in antiretroviral drug development.

Differences in Drug Toxicity, Adherence and Drug Interactions in the Developing World

Gary Maartens from Cape Town University presented a comprehensive review outlining the main differences in antiretroviral-induced toxicities, management of drug interactions, and adherence in the developed and developing world. He started by noting that although there has been a massive expansion of antiretroviral access in resource-poor settings, only a limited number of drugs are available in the majority of these places. This limitation complicates patient management, as there are few alternatives to overcome common occurrences such as drug-induced toxicity.

For example, the combination of d4T, 3TC, and NVP is one of the first line regimens recommended by the WHO for the treatment of patients with AIDS in

resource-poor settings. However, a recent study in South Africa suggested that toxicity-driven regimen changes were most commonly caused by d4T-induced adverse events [Boulle A, et al. CROI 2006, Abstract 66]. Even more concerning was the report of higher rates of symptomatic hyperlactatemia and lactic acidosis in that study population compared to rates previously described in developed countries. The authors reported that rates of hyperlactatemia and lactic acidosis were as high as 70% in women above 75 kg, which is of concern, since 70% of patients starting antiretroviral therapy in this setting are women. The reasons for higher rates of d4T-induced toxicity are unknown but could be driven by a number of factors, including genetic polymorphisms and the surprisingly high prevalence of obesity among urban South African women. These findings reinforce the importance of conducting studies in resource-poor settings, to continue to assess safety and efficacy of antiretroviral therapy, and to strengthen pharmacovigilance in these populations. It remains to be seen whether these findings will influence public policy and lead to changes in the current WHO recommendations for first line regimens.

Dr. Maartens reminded us that drug scarcity in resource-poor settings is not confined to antiretroviral therapy, but also extends to agents used in the treatment of AIDS-associated co-morbidities. For instance, anticonvulsants such as phenytoin and carbamazepine are commonly available but are potent inducers of cytochrome P450 3A4 (CYP3A4), the main metabolic pathway shared by most PIs and NNRTIs. Co-administration of these drugs with PIs and NNRTIs can significantly lower antiretroviral plasma concentrations and potentially lead to resistance and treatment failure. There are new anticonvulsant drugs that bypass the CYP450 metabolic pathway, but these drugs are costly and not readily available in resource-poor settings.

Treatment of tuberculosis also represents a challenge. Rifampin is a potent CYP3A4 inducer and thus not recommended for concomitant use with most PIs and NNRTIs. Rifabutin, a rifamycin with less potent inducing effects, is not available or affordable in most resource-limited settings, leaving clinicians to cope with significant drug interactions. There are a number of other agents, such as antimalarials, antifungals, antibiotics and traditional medications, that can also affect the metabolism of antiretroviral drugs.

Finally, Dr. Maartens briefly reviewed topics relevant to adherence to antiretroviral therapy in resource-poor settings. He described the results of a recent study conducted in South Africa showing an association between higher adherence rates and improved survival [Nachega J, et al. 2006, in press]. The authors also reported that adherence rates between 95-100% were associated with a higher proportion of patients having undetectable viral loads (<400 c/mL). These results are similar to what has been described in the developed world and reinforce the need for randomized clinical trials to study practical interventions for improving and maintaining adherence in these settings.

Significant progress has been made in the availability of antiretroviral drugs for resource-poor countries. Now that HIV treatment is available in many of these countries, it is important to understand population differences that could affect the safety and efficacy of these drugs. It is also crucial that clinicians understand the basic principles of drug metabolism, since a number of drugs available in these settings share metabolic pathways with PIs and NNRTIs. Finally, the importance of adherence must be reinforced in resource-poor settings, where antiretroviral availability is limited and durability of the first regimen is crucial for prolonged viral suppression. ▲



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Pharmacokinetics: With RTV co-administration, DRV is well absorbed with an absolute bioavailability of 82%. Food (a light snack or a full meal) increases DRV AUC by 30%. At steady-state, the geometric mean DRV AUC and C_{min} was 62.35 mcg/mL-hr and 3.54 mcg/mL, respectively. DRV trough was 6-fold higher than the EC_{50} for resistant virus and 18-fold higher than the EC_{90} for wild type virus. DRV undergoes extensive oxidative metabolism via CYP3A4 to weakly active oxidative metabolites that are primarily excreted in the feces with a terminal half-life of 15 hours.

Drug Interactions: DRV is a substrate and inhibitor of CYP3A4. With RTV co-administration, the net effect of DRV/r on CYP3A4 is generally inhibitory. Drugs that inhibit or induce CYP3A4 may increase or decrease DRV serum concentrations, respectively.

- **Contraindicated with DRV:** terfenadine, astemizole, cisapride, ergot alkaloid, midazolam, triazolam, and pimozide.
- **Avoid co-administration:** simvastatin, lovastatin due to increased statin concentrations
- **Avoid co-administration:** rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's Wort due to decreased DRV concentration.
- **Avoid or use with dose adjustment and close monitoring:** DRV/r may significantly increase the serum concentrations of these CYP3A4 substrate drugs: amiodarone, bepridil, quinidine, lidocaine, propafenone, trazodone, itraconazole, rifabutin (dose adjust to 150 mg qod), calcium channel blockers (felodipine, nifedipine, and nifedipine), fluticasone, prednisone, cyclosporine, tacrolimus, sirolimus, PDE-5 inhibitors (sildenafil, tadalafil, and vardenafil).
- **Use with caution:** DRV/r may decrease voriconazole, warfarin, methadone, and ethinyl estradiol/norethindrone serum concentration.
- The following table summarizes established drug interaction data to date:

Co-administered Drug	Effect of Interaction	Comments/Recommendations
Atazanavir	No interactions	Dose: ATV 300 mg qd plus DRV/r 600/100 mg bid
Efavirenz	DRV C_{min} decreased by 31%. EFV AUC and C_{min} increased 21% and 17%, respectively.	Dose not established. Consider: DRV/r 600/100 mg bid plus EFV 600 mg qd
Enfuvirtide	No interactions	Use standard dose
Indinavir	IDV AUC and C_{min} increased 23% and 125%, respectively. DRV AUC and C_{min} increased 24% and 44%, respectively.	Dose not established. May increase risk of nephrolithiasis.
Lopinavir/r	DRV AUC and C_{min} decreased 53% and 65%, respectively. LPV AUC and C_{min} increased 37% and 72%, respectively.	Avoid co-administration
Nevirapine	No significant change in DRV AUC and C_{min} . NVP AUC and C_{min} increased 27% and 47%, respectively.	Limited data (historical control comparison). Consider: DRV/r 600/100 mg bid plus NVP 200 mg bid
Saquinavir	DRV AUC and C_{min} decreased 25% and 42%, respectively. No change in SQV serum concentration.	Avoid co-administration
Tenofovir DF	DRV: no change. TDF AUC and C_{min} increased 22% and 37% respectively.	Use standard dose
Acid reducing agents (PPIs, H-2 blocker)	No interactions	Use standard dose
Atorvastatin	Increased atorvastatin exposure by approximately 4-fold.	Dose: Start with atorvastatin 10 mg qd and titrate slowly
Clarithromycin	DRV: no change. Clarithromycin AUC increased 57%.	Dose: clarithromycin with renal impairment. CrCl 30-60 mL/min=250 mg bid, CrCl <30 mL/min = 250 mg qd. Avoid with QTc prolongation
Ketoconazole	DRV AUC increased 42%. Ketoconazole AUC increased 212%.	Do not exceed ketoconazole 200 mg qd or use alternative agent
Paroxetine	Paroxetine AUC decreased by 39%. DRV: no change	Titrate paroxetine to therapeutic effect



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Co-administered Drug	Effect of Interaction	Comments/Recommendations
Pravastatin	Pravastatin AUC increased 81%	Dose: Start with 10 mg qd and titrate slowly
Sertraline	Sertraline AUC decreased by 49%. DRV: no change	Titrate sertraline to therapeutic effect
Sildenafil	No significant change in sildenafil AUC.	Use with caution. Do not exceed 25 mg in 48h

Clinical Studies Results: The approval of DRV/r is based on the 24-week pooled analyses of two ongoing randomized trials (POWER 1 and 2) involving highly treatment-experienced patients. All patients were 3-class (NRTI, NNRTI, PI) treatment-experienced and had at least one primary PI mutation at screening. Baseline characteristics of the 131 patients randomized to DRV/r plus OBR were: VL= 4.52 log₁₀ c/mL, CD4= 153, 8 IAS PI mutations associated with resistance (with ≥3 primary mutations in 54%), and phenotypic resistance to all approved PIs (with the exception of TPV/r due to availability) in 64% of patients. After the initial dose finding part of the study, patients were randomized to receive an optimized background regimen (2 or more NRTIs +/- enfuvirtide [ENF]) with DRV/r 600/100 mg bid OR investigator choice of PIs, including boosted or dual-boosted PIs (control group). The primary efficacy endpoint was defined as a decrease in plasma HIV RNA of ≥1 log₁₀ c/mL versus baseline. In an ITT analysis, 69.5% of DRV/r-treated patients and 21% of control patients achieved at least a 1 log₁₀ c/mL reduction in HIV RNA through week 24. An undetectable (<50 c/mL) viral load was achieved in 45% and 12% of DRV/r and control patients, respectively. Virologic response was strongly associated with a DRV phenotypic FC of less than 10-fold, less than 10 IAS PI mutations, and a good baseline phenotypic susceptibility score of the background regimen [Vangeneugden T, et al. XV International HIV Drug Resistance Workshop, 2006, Abstract 31 and De Meyer, et al. XV International HIV Drug Resistance Workshop, 2006, Abstract 73]. Adverse events were comparable between groups.

Adverse Drug Reactions: Adverse reactions were comparable between DRV/r and comparator PIs in the POWER studies. Rates of discontinuation of therapy due to adverse events were 9% and 5% in the DRV/r and comparator PI treated groups, respectively. The most commonly reported adverse reactions were GI intolerance (nausea, vomiting, and/or diarrhea) in approximately 20%, headache in 15%, and nasopharyngitis in 14%. Other PI class adverse effects, including lipodystrophy, hyperglycemia, hyperlipidemia, and transaminase elevation, were comparable between groups. DRV contains a sulfonamide isostere moiety and should be used with caution in patients with severe sulfa allergy. Rash was observed in 7% of subjects with a 0.3% discontinuation rate.

Resistance: Baseline phenotypic DRV fold-change (FC) was the strongest predictor of virologic response. At week 24, 50%, 25%, and 13% of patients with FC ≤10, 10-40, and >40, respectively, achieved HIV RNA <50 c/mL. FCs of ≤10, 10-40, and >40 were associated with <10, 10 or 11, and ≥12 IAS PI mutations. However, the following mutations were more predictive of virologic outcome than IAS PI mutations: 11I, 32I, 33F, 47V, 50V, 54L/M, 73S, 76V, 84V, and 89V [De Meyer, et al. XV International HIV Drug Resistance Workshop, 2006, Abstract 73]. With 0-2, 3, or ≥4 of these mutations at baseline, the virologic response (VL <50 c/mL at Week 24) was 50%, 22%, and 10% respectively.

In vitro, the pathway to DRV resistance appears to be different from other PIs. Among amino acid substitutions during virologic failure (patients with virologic rebound or never suppressed) in the POWER studies, the most common substitutions developed at position V32 (in 30% of isolates), I54 (in 20% isolates), and I15, L33, I47, G73, and L89 (in 10-20% of isolates). In these isolates, the median DRV phenotypic FC increased from 21-fold at baseline to 94-fold at failure.

In vitro, 77% and 70% of clinical isolates (n=2682) that have decreased susceptibility to LPV and TPV, respectively, were susceptible (FC <10) to DRV [De Meyer, et al. XV International HIV Drug Resistance Workshop, 2006, Abstract 73]. Using Virco's lower DRV FC cutoff of 3.4, other investigators reported higher cross-resistance rates. Analyses of over 50,000 isolates found that only 42% and 28% of isolates with resistance to LPV and TPV will have predicted response to DRV [Staes M, et al. International HIV Drug Resistance Workshop, 2006, Abstract 28]. On the other hand, clinical isolates (n=586) that have decrease susceptibility to DRV retained susceptibility to LPV and TPV in only 0.5% and 53% of the cases, respectively [De Meyer, et al. XV International HIV Drug Resistance Workshop, 2006, Abstract 73].

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Making HIV Testing Routine: New CDC Guidelines to Diminish Barriers to Diagnosis

By Emily J. Erbelding, M.D., M.P.H.

A draft version of new counseling and testing guidelines was released for public comment in March, 2006, by the Centers for Disease Control and Prevention (CDC). This document, *Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health Care Settings*, promotes testing procedures that would make HIV testing a routine part of medical care for all teenagers and adults in the United States. Full integration of these recommendations will enhance HIV case finding, but may also represent a major operational shift in the approach to testing in some clinic sites. This article will discuss the history behind some barriers to HIV testing and the rationale for making testing more routine.

Why Promote Expanded Screening for HIV?

Screening for HIV in the general population meets many of the criteria for an effective preventive practice intervention: HIV serologic tests are reliable and inexpensive; untreated infection has serious health consequences; highly effective treatment for HIV is now available; and the average person will gain years of productivity and health if treatment is initiated prior to development of AIDS-related symptoms. Recent cost-effectiveness analyses have demonstrated that HIV screening is as cost-effective as screening interventions for other chronic diseases, even when prevalence rates in the screened population are less than 0.1% [Paltiel AD, et al. *N Engl J Med* 2005;352:586]. If early detection of HIV leads to behavior modification that reduces rate of secondary spread to others, more aggressive screening may have even greater public health benefit not accounted for in these cost effectiveness models.

HIV Testing—The Historical Approach

Serologic testing for HIV first became available in March, 1985, when AIDS/HIV

was an untreatable and nearly universally fatal condition. The diagnosis was shrouded in stigma, and the knowledge of an HIV diagnosis could cause an enormous change in one's life and outlook, even when clinically asymptomatic. Therefore, HIV testing without specific consent procedures represented a violation of an individual's right to self-determination in a much greater way than other blood tests done for diagnostic purposes. Written informed consent for HIV testing was mandated by statute in most states.

Prevention of HIV spread was also solely linked to changing the behavior of those with HIV infection and those deemed to be at risk for HIV infection: injection drug users, men having sex with other men, and sexual partners of those in these specific groups. Therefore, there was an emphasis on behavioral risk assessment at the time that testing occurred. Organizations that received federal money for HIV counseling and testing were required to collect data on the behavioral risks of those tested. These federally supported counseling and testing sites also had to demonstrate that counselors had competency in "prevention counseling"—training in the assessment of deficits in HIV knowledge and in altering risk behaviors based upon theory-based models of behavior change. Certification was deemed particularly important when counseling and testing centers employed non-professional counselors who were "peers" (i.e., recovering addicts or gay men) in order to make their community outreach more successful. In peer-based models of HIV service delivery, counselors may lack a background in biomedical science or health education but may be more equipped to reach and motivate the targeted community. Thus, unlike other medical diagnostic tests, risk reduction counseling by a certified counselor became tightly linked to HIV testing.

To meet the data collection requirements and requirements of written informed consent, the testing process involved at least 20-30 minutes of time beyond phlebotomy. These practices created barriers in busy practice settings that served patients with a risk of HIV infection who might have presented for other health concerns. For example, given the relatively high prevalence of HIV infection among emergency department (ED) patients, EDs were identified as ideal sites for HIV case finding. However, given other pressing services needs in emergency departments, providing traditional HIV counseling prior to testing (written informed consent and behavior change counseling by a certified counselor) proved operationally difficult, and opportunities for case finding were often missed. Similarly, in STD clinics, where high risk patients presented for STD care and often had blood drawn for routine syphilis testing, HIV testing often required a separate visit with a certified counselor in order to meet standards required for federal funding. Although these additional steps had a valid purpose, they also added operational barriers that led to missed opportunities for diagnosis.

New Considerations

In pregnant women, a streamlined approach to the HIV counseling and consent process, making it a routine part of prenatal care (opt-out), results in a greater proportion of pregnant women getting tested [*MMWR Morb Mortal Wkly Rep* 2003;51:1013] compared to an opt-in approach. While patients with traditional HIV risk behaviors are most likely to be tested if it is recommended by their medical provider [*MMWR Morb Mortal Wkly Rep* 2005;54:597], targeted testing in many clinic settings based upon declared behavioral risk factors fails to identify those



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at highest risk for HIV [Chen Z, *Sex Transm Dis* 1998;25:539]. Also, although some of the special requirements surrounding HIV testing arose due to its stigma, a series of risk assessment questions leading to the recommendation of HIV testing may paradoxically reinforce stigma and lead to lower rates of testing acceptance. Making HIV serology a routine test, rather than an exceptional one, may actually serve to minimize stigma. The use of the risk assessment to identify those in need of testing is also problematic because of the changing epidemiology of HIV in the United States: With increasing HIV prevalence among heterosexual men and women and higher cases rates among non-urban populations, it is likely that targeted testing based upon traditional risk factors will become even less effective over time.

The new proposed guidelines from the CDC recommend testing for all adolescents and adults (age 13-64 years) as a routine part of medical care. Those with elevated behavioral risks (drug use, men with same sex contact, etc.) should be tested annually. The CDC guidelines for medical providers also emphasize elimination of regulatory barriers to testing, such as legally mandated requirements for informed written consent and the linkage of testing to prevention counseling. Key changes in the guidelines from the past version released in 2001 are summarized in the Table.

Testing Guidelines for Pregnant Women

Universal HIV screening for pregnant women as early as possible in the pregnancy is unchanged from the last set of CDC guidelines [*MMWR Recomm Rep* 2001; 50(RR-19):63]. The new draft CDC guidelines reiterate that all pregnant women should be screened for HIV infection as early in the pregnancy as possible, but further emphasize the need to minimize other procedures and documentation that may serve as a barrier to universal testing, such as informed written consent. It is

recommended that the discussion of HIV testing should occur after a pregnant woman is informed that HIV testing will be part of the routine prenatal care test package unless she declines it (the “opt-out” approach). To further reduce the risk of perinatal transmission should HIV infection occur during pregnancy, the new guidelines also endorse repeat HIV testing during the third trimester (ideally before 36 weeks) for all women. Re-testing is particularly recommended for those who reside in areas of increased HIV prevalence among women (Table) and in healthcare facilities serving women with an increased HIV prevalence among women of childbearing age. Repeat

testing during the third trimester should also be a priority for those with identifiable risk behaviors during pregnancy (Table).

Concerns Over Streamlined Testing

There is now a strong consensus that decreasing the barriers to HIV diagnosis represents a social good. However, getting tested for HIV is not the same as getting a complete blood count or a serum cholesterol test. Most of the barriers to HIV testing were initially conceived as a means to protect vulnerable groups and have, to some extent, served as an important safeguard. Although

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Table. Summary of Key Changes in HIV Testing Guidelines from Prior Version

Changes in New Guidelines:
<ul style="list-style-type: none"> • Make HIV tests routine screening measure in all adolescents and adults age 13-64 yrs unless they specifically decline (“Opt-out”) • Eliminate separate written consent procedures • Make prevention counseling optional for those tested • Re-screen annually in those with high-risk behaviors identified • Give HIV test results in same manner as results of other medical tests
Unchanged in New Guidelines:
<ul style="list-style-type: none"> • HIV testing is voluntary • Access to clinical care and social support services remain a priority for those with a HIV-positive test result • Testing recommended for all diagnosed with tuberculosis or seeking STD care • Prevention counseling remains a priority for those with high risk behaviors
Specific to Pregnant Women:
<ul style="list-style-type: none"> • Women should be notified that HIV testing is routine part of prenatal laboratory testing and that she will receive test unless she declines (“Opt-Out”) • Re-screening during 3rd trimester (before 36 weeks) should be considered for all pregnant woman; 3rd trimester re-screening should be considered a priority in pregnant women residing in geographic areas* with an elevated HIV prevalence among women or at healthcare facilities where HIV is not uncommonly identified among pregnant women and in pregnant women with behavioral risks for HIV exposure‡

* Alabama, Connecticut, Delaware, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Mississippi, New Jersey, Nevada, New York, North Carolina, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington DC.

† At least 17 newly diagnosed HIV cases per 100,000 women screened during pregnancy.

‡ Injection drug users or their sex partners, commercial sex workers, those with known HIV+ sex partners, those with multiple sex partners during pregnancy.



Summary of Changes: DHHS Guidelines for Use of Antiretroviral Agents

May 4, 2006

By John G. Bartlett, M.D.

The following is a summary of changes contained in the May 4, 2006 edition of the “DHHS Guidelines for the Use of Antiviral Agents in HIV-infected Adults and Adolescents.”

1. Genotypic resistance testing is now recommended prior to initiation of antiretroviral therapy, and the results should influence the selection of the agents. An option is to obtain the resistance test earlier in the course of the infection for later use when treatment is to be started. The previous version of the guidelines recommended resistance testing only in patients who had been treated and had virologic failure. The change was prompted by three observations: First, there are reports that transmitted strains with resistant mutations persist for more prolonged periods than resistant strains that have evolved on non-suppressive therapy [Little SJ, et al. 11th CROI 2004, San Francisco, Abstract 36LB; Novak RM, et al. *Clin Infect Dis* 2005 40:468]. For this reason, baseline testing in chronically infected persons may yield important information, although it is uncertain how long transmitted resistance persists. Second, some studies also show that patients with baseline resistance respond less well to initial treatment [Weinstock HS, et al. *J Infect Dis* 2004;189:2174-80; Wensing Am, et al. *J infect Dis* 2005;192:958-66; Cane P, et al. *BMJ* 2005;331:1368; Saag MS, et al. *JAMA* 2004;292:180-90; Gallant JE, *N Engl J Med* 2006;354:251-60]. Further, recent studies indicate that up to 16% of treatment-naïve patients have resistance mutations. Finally, there are also studies showing that baseline testing is cost-effective [Sax PE, et al. *Clin Infect Dis* 2005;41:1316-23]. This recommendation received a score of BIII meaning moderate priority (B) but no randomized controlled trials to support the recommendation (III).
2. The section on treatment interruption now states that treatment should be interrupted when it cannot be avoided, such as for surgery or serious adverse drug reactions. The prior document suggested that CD4-driven treatment interruption was an option, but recent clinical trials now indicate this strategy could be dangerous and needs more study. The Trivacan ANRS 1269 trial found that severe morbidity was significantly higher in the treatment interruption arm than in the continuous therapy arm at 24 months (17.6/100 patient-years vs. 6.7/100 patient-years; $p=0.001$) [Danel C, et al. *Lancet* 2006;367:1981]. The SMART trial, which was reviewed by Joel Gallant [*HHR* 2006;18(2):1], found that treatment interruption was associated with a statistically significant increase in HIV-related events, drug toxicities and deaths. Both trials used a study design that permitted drug discontinuation when the CD4 was $>350/\text{mm}^3$ and re-initiation when the CD4 count was $<250/\text{mm}^3$.
3. The section on hepatitis B co-infection has been rewritten to state that: a) lamivudine (3TC), tenofovir (TDF) and emtricitabine (FTC) have activity against hepatitis B virus (HBV), and discontinuation of these drugs may cause a HBV flare; b) HBV resistance is about 40% when 3TC is used as a single agent against HBV; c) immune reconstitution may be associated with an increase in hepatic transaminases; d) patients with immune reconstitution may have loss of HBV early antigen (HBeAg) that is associated with a hepatitis flare; and e) administration of PIs and NNRTIs are associated with high rates of transaminase elevations in coinfecting patients. The cause of the transaminase elevation is unclear, since they may decrease with continued therapy. Nevertheless, the common recommendation is to stop the implicated drug when the increase in AST or ALT is $>5-10$ times the upper limit of normal. For management of HIV/HBV-co-infected persons:
 - All should: a) be advised to avoid alcohol; b) be vaccinated against hepatitis A vaccine if non-immune; and c) be advised on methods to prevent HBV transmission.
 - The treatment regimen for HIV but not HBV should include a NRTI backbone of TDF/FTC or TDF/3TC (You have to treat HBV anyway unless you can avoid 3TC and FTC).
 - When the goal of therapy is either to treat HIV or both HIV and HBV, the treatment regimen should include TDF/FTC or TDF/3TC. Another option is entecavir alone for HBV).

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the “opt-out” approach does not change the voluntary nature of HIV testing in theory, provider communication surrounding the testing event may be less clear in a busy clinic setting when written consent is not a legal requirement. Skipping the basic counseling points on HIV transmission and on individual risk reduction may also serve to perpetuate ignorance in populations with low health literacy.

Summary

The approach to HIV serologic testing in the future will focus on normalizing the HIV test and minimizing barriers to testing. As systems of care move this CDC guideline to full implementation, medical providers should remain committed to ensure that patients know when an HIV test is being ordered and understand that it is voluntary. ▲

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Summary of Changes: DHHS Guidelines for Use of Antiretroviral Agents May 4, 2006

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- When the goal of therapy is to treat HBV without treating HIV, interferon alpha is recommended; another option is entecavir.
 - Liver enzymes need to be monitored if is necessary to discontinue 3TC, TDF or FTC; consider substituting adefovir or entecavir to prevent flares.
4. Discontinuation of NNRTIs was addressed, since persistence of nevirapine (NVP) or efavirenz (EFV) after discontinuation may result in relative monotherapy due to the long half-lives of these drugs. The period of relative monotherapy in such cases varies based on genetic difference, and appears to differ among races. One approach to preventing resistance is to discontinue the NNRTI before stopping the NRTIs, but the optimal interval is unknown, and there could be substantial individual variation. Discontinuing NVP four or seven days before stopping NRTIs substantially reduced the risk of NVP-resistance in a MTCT study [McIntyre JA, et al. 3rd IAS Conference on HIV Pathogenesis and Treatment; 2005, Rio de Janeiro, Abstract TuFo0204]. An alternative is to discontinue the NNRTI and substitute a ritonavir-boosted PI, which is then continued along with NRTIs for up to four weeks. (There are no data to support this strategy.)

The latest version of all DHHS Guidelines may be found on the web at <http://www.aidsinfo.nih.gov>. ▲

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