

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Antiretroviral Update from the 46th ICAAC

By Joel E. Gallant, M.D., M.P.H.

New data on antiretroviral therapy were sparse at the 46th ICAAC, held in San Francisco in September. A few of the most important studies are discussed below.

More Data Supporting Earlier Initiation of Therapy

The Abbott 720 trial has been following patients treated with lopinavir/ritonavir (LPV/r) for up to 7 years. Prior presentations of the results from this study have demonstrated excellent virologic durability and impressive CD4 increases. Data presented at ICAAC further assessed the immunologic response to therapy with LPV/r, looking specifically at the effect of baseline CD4 count on CD4 response [King MA, et al. Abstract H-1401]. The authors found that those who started with CD4 counts <50 cells/mm³ experienced continued rises in CD4 count throughout the 7-year period, while those who started with higher CD4 counts reached a plateau at 6-7 years. However, those with lower CD4 counts never “caught up” with patients starting at higher counts. Over 7 years, the mean increase in CD4 count from baseline was 532, 476, and 495 cells/mm³ in those with CD4 counts <50, 50-199, and >200 cells/mm³, respectively.

These results are similar to those seen in the Dutch ATHENA cohort [Gras L, et al. 13th CROI, 2006, Denver, Abstract 530] and in the Hopkins cohort [Moore RD, Keruly JC, *Clin Infect Dis* 2007;44:441].



Noe Valley, San Francisco by Joel Meneses

The latter study, a larger observational cohort study, also demonstrated that differences in CD4 response were associated with differences in clinical outcome, despite virologic suppression. Data were also presented from a Canadian cohort of 299 patients, which found that patients who achieved virologic suppression, but failed to attain a CD4 count above 200 cells/mm³, remained at increased risk of clinical events within the first year of therapy (hazard ratio 3.08, p=0.055) and after the first year of therapy (HR=3.94, p=0.08) [Loutfy MR, et al. Abstract H-1403].

Data were also presented from the PISCIS cohort, an ongoing, multicenter

study of HIV-infected adults treated at 10 Spanish hospitals [Jaen A, et al. Abstract H-1059]. Treatment-naïve patients who initiated treatment prior to the diagnosis of AIDS and who remained on HAART for at least 1 month were included in the analysis. The authors found that patients with lower CD4 counts (<200 or 200-350 cells/mm³ compared to >350 cells/mm³) at the time of initiation were more likely to progress to AIDS or death than those with higher CD4 counts after adjusting for lead time. Factors associated with progression after adjustment for sex, age, and time of initiation included

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lower CD4 count, higher viral load, and HCV coinfection. Later initiation of therapy (after 2001) was associated with a decreased risk of progression.

Current treatment guidelines recommend therapy for symptomatic patients or patients with AIDS, and recommend consideration of therapy in patients with CD4 counts <350 cells/mm³ or viral loads >100,000 c/mL, though CD4 threshold is generally given more weight than the viral load threshold. The studies discussed here provide further support for earlier initiation of therapy. There is less enthusiasm now for deferring therapy until the CD4 count

approaches 200 cells/mm³, and accumulating data suggest that initiating HAART at CD4 counts above 350 cells/mm³ may be beneficial. The question of when to start therapy may become more pressing if the CDC recommendations on routine HIV testing [*MMWR Recomm Rep.* 55:No. RR-14; and “Update from the IDSA 44th Annual Meeting in Toronto” on p4 of this issue] become widely implemented. Routine testing should result in earlier diagnosis, with a larger proportion of newly diagnosed patients having CD4 counts above current guidelines criteria for initiation.

Boosting Fosamprenavir with Less Ritonavir

Pharmacokinetic data have supported the use of fosamprenavir boosted by only 100 mg of ritonavir rather than the approved dose of 200 mg/d, but there have been no clinical data supporting this combination. Kimberly Smith presented preliminary 24-week results from the ALERT study, in which 106 treatment-naïve patients were randomized to receive either atazanavir/ritonavir (ATV/r 300/100 mg QD) or fosamprenavir/ritonavir (FPV/r 1400/100 mg QD) along with tenofovir/emtricitabine (TDF/FTC) [Abstract H-1670a]. Virologic results were virtually overlapping, with 83% of ATV/r-treated patients and 79% of FPV/r-treated patients achieving a viral load below 50 c/mL by intention-to-treat (ITT), missing=failure analysis. By observed data analysis, the results were 88% and 84%, respectively. FPV/r was associated with a greater rise in triglyceride levels; there was a similar, modest rise in total and LDL cholesterol in both arms. As expected, hyperbilirubinemia and jaundice were more common in the ATV/r arm. Treatment-emergent resistance was observed in only one patient, who had baseline amprenavir resistance and developed further PI resistance on FPV/r.

This study was not powered to demonstrate non-inferiority of the FPV/r regimen, but the extremely similar results are encouraging. Larger trials with this regimen are in progress.

MK-0518 in Treatment-Experienced Patients

Preliminary 16-week data were presented at CROI earlier this year demonstrating impressive efficacy of Merck’s integrase inhibitor, raltegravir (RAL, MK-0518), in treatment-experienced patients [Grinsztejn B, et al. 13th CROI 2006, Denver; Abstract 159LB]. The 24-week results presented at ICAAC continue to be equally promising [Grinsztejn B, et al. Abstract H-1670b]. A total of 178 highly treatment-experienced patients with 3-class resistance were randomized to receive one of three doses of RAL (200, 400, or 800 mg bid) or placebo in combination with an optimized background regimen (OBR). At baseline, 42-58% had a phenotypic susceptibility score (PSS) of 0, meaning that they had no fully active agents in the background regimen. The PSS for protease inhibitors was 0 in 87-98%. By ITT analysis, viral load was suppressed to <400 c/mL at 24 weeks in approximately 70% and to <50 c/mL in 57-67% of those in the RAL arms compared to 16% and 14% of those on placebo, respectively. Those on RAL achieved a 2 log reduction in viral load—in most cases by 2 weeks—whereas the overall reduction in viral load among placebo recipients was only 0.4 log₁₀ c/mL. Even those with a PPS of 0 had impressive responses, with 54-69% achieving viral suppression to <400 c/mL. Enfuvirtide was used for the first time by approximately one-quarter of the patients and increased efficacy by approximately 20% in both groups. The drug was well tolerated, demonstrating a safety profile that was similar to placebo.

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Further trials of this agent, dosed at 400 mg bid, are in progress in both treatment-experienced and naïve patients, and the drug is now available through an expanded access program (see “*Expanded Drug Access: Etravirine (Formerly TMC-125)*” on p8 of this issue).

Dosing of Boosted Atazanavir with Efavirenz in an NRTI-Sparing Regimen

Gary Thal presented the results of BMS-121, a 48-week, open-label study in which 65 treatment-naïve patients were treated with efavirenz (EFV) plus one of two doses of ritonavir-boosted atazanavir (ATV/r), 300/100 or 400/100 mg qd [Ward D, et al. Abstract H-1057]. Virologic response was similar, with 77% and 87% achieving a viral load <50 c/mL (observed data analysis). However, the small size of the study and the lack of pharmacokinetic data make this study hard to interpret. The primary endpoint of the study was triglyceride elevation: triglycerides levels increased by 48% and 63% in the 300/100 and 400/100 mg arms, respectively. Perhaps the most clinically useful observation was that grade 3-4 bilirubin elevation was observed in 49% of those on the 400/100 mg arm compared to only 13% of those on 300/100 mg, suggesting that when combined with EFV, the lower dose of ATV should be used.

Darunavir Data

More data were presented from the POWER studies, previously reported clinical trials comparing four doses of darunavir/ritonavir (DRV/r, TMC114/r) plus an OBR. A pooled analysis of 924 patients demonstrated no differences in safety and efficacy based on gender, age, and race [Collier A, et al. Abstract H-1396]. A 24-week analysis involving 458 patients found that rates of virologic suppression to <50 c/mL in patients previously treated with LPV/r, FPV/r, and tipranavir/ritonavir

(TPV/r) were 40-44% at 24 weeks, similar to the overall trial population [Lefebvre E, et al. Abstract H-1387].

Among over 56,000 sequences submitted to Virco for resistance testing from 2004-2005, susceptibility was greater to DRV than to tipranavir (TPV) or lopinavir (LPV) among heavily PI-resistant isolates [Picchio G, et al. Abstract H-0999]. Ninety-eight percent of the isolates had no more than 2 DRV-specific mutations and were predicted to be susceptible to DRV. There was some evidence of cross-resistance between DRV and TPV: 3.8% had evidence of resistance to both drugs, 6.4% had evidence of resistance to TPV with susceptibility to DRV, and 1.4% had resistance to DRV with susceptibility to TPV.

Another Induction-Maintenance Failure

The COOL study was a randomized, open-label trial in which 143 patients with viral loads below 50 c/mL on HAART for at least 6 months were randomized to take either three-drug therapy (EFV + TDF + 3TC) vs. two-drug therapy (EFV + TDF) [Girard PM, et al. Abstract H-1383]. The two-drug maintenance arm was clearly inferior to the standard therapy arm: The success rate (viral load <50 c/mL without drug modification at week 48) was 82% vs. 97%, respectively, by ITT analysis and 90% and 100% by as-treated analysis. The rationale for “simplifying” a regimen by discontinuing the best tolerated and least toxic of its components is not obvious. In addition, now that the combination of EFV, TDF, and emtricitabine (FTC) are available as a single tablet, this simplification strategy would involve switching from one to two pills per day.

Coreceptor Tropism and Response to HAART

A study from the Chelsea & Westminster Hospital in London assessed

the impact of coreceptor tropism on rate of CD4 decline before therapy and on response to therapy [Waters LJ, et al. Abstract H-1667]. Of the treatment-naïve patients who started therapy and were included in the analysis, 229 had R5-tropic virus, and 60 had dual or mixed (D/M)-tropic virus at baseline. Pre-HAART CD4 decline during the first 12 months was significantly more rapid in patients with D/M-tropic virus than in those with R5-tropic virus (approximately 40 vs. 15 cells/mm³, p=0.026). However, the magnitude of CD4 increase, the proportion who achieved virologic suppression, and the time to virologic suppression on HAART was no different. These data suggest that while coreceptor tropism is associated with disease progression in untreated patients, tropism is irrelevant once therapy is initiated (provided the therapy doesn't include a coreceptor antagonist).

New Agents

Lalezari presented data from a double-blind, placebo-controlled, dose-ranging trial of **HGS004**, a monoclonal antibody that blocks binding to the CCR5 coreceptor [Abstract H-1668]. The study included 5 dose cohorts with 10 subjects per arm, 8 of whom received a single intravenous infusion of active drug (0.4, 8, 20, and 40 mg/kg) and 2 who received placebo. Antiviral activity was demonstrated for all but the lowest dose, and there was evidence of a prolonged response, with some patients demonstrating continued partial suppression for as long as 56 days. Since this is an IgG molecule, it is thought that it could be administered infrequently. Patients in this study who demonstrated evidence of a tropism shift did not respond to HGS004. There were no severe grade 3-4 adverse

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Update on HIV from the IDSA 44th Annual Meeting in Toronto

By Kristine Johnson, M.D., and Emily Erbeling M.D., M.P.H.

The sessions with HIV content at the meetings of IDSA tend to be designed to provide broad and timely updates on HIV for the infectious disease practitioner, as well as to allow a forum for the presentation of research findings. This article will summarize some IDSA highlights relevant to acute HIV infection, epidemiology and prevention.

A New Operational Paradigm in HIV Testing

Rochelle Walensky [Abstract 712] summarized the central tenets and the key features of the Centers for Disease Control's (CDC) new guidelines for HIV testing released on September 22, 2006 [*MMWR Recomm Rep.* 55:No. RR-14]; for a perspective on the draft version, see Erbeling E, *HHR* 2006;18(6)]. These recommendations represent a major shift in the standard approach to HIV testing in the United States: They promote routine testing of patients ages 13-64 in all health-care settings. For streamlining the testing process, they emphasize a change from the use of specialized written, informed consent for HIV testing to an "opt-out" HIV testing strategy for adolescents, adults and pregnant women. "Opt-out" testing means that the patient is informed that the test will be performed as part of routine healthcare unless s/he decides to "opt-out" and decline the test. Because knowledge of HIV serostatus represents the first step to engaging in HIV care and accruing health benefits, the guidelines are meant to identify and bring to treatment the estimated 250,000 to 300,000 Americans living with undiagnosed HIV infection (roughly 25% of those living with HIV).

These recommendations replace those emphasizing pre-test counseling and written informed consent that have, in some form,

been in effect for two decades. Past guidelines were developed when stigma associated with HIV infection was pervasive and, more importantly, treatment did not offer the same promising outcomes as the HAART regimens of today. Circumstances have changed considerably since then, with new therapeutic options and some lessening of stigma. With this new approach to HIV testing, systems that deliver healthcare are encouraged to use the process of consent for general medical care as the means to obtain consent for HIV testing. Therefore, no separate written, informed consent process would be required. This recommendation may not be compatible with laws in many states in the United States, but the guidelines may serve to catalyze discussions of policy change.

The recommendations also advise that patients identified to be at higher risk for HIV infection (men with same sex contact, injection drug users) be tested annually. For prenatal care, the guidelines also endorse the "opt-out" approach. Repeat screening of pregnant women within high risk populations or in regions of high HIV prevalence is encouraged during the third trimester. HIV testing for individuals pursuing STD care remains the recommended standard.

In a change from prior practice, the need to link counseling by certified counselors to testing is no longer the CDC standard in medical settings. However, the guidelines do emphasize that HIV testing must remain voluntary and that patients should not be tested without their knowledge and assent. For all those testing positive, follow-up care, prevention counseling and social support are vital to manage HIV disease long-term and to prevention transmission. The CDC's recommendations have generated relatively little controversy within the medical

community. This should not be surprising, given the fact that medical providers have reasons to be more confident now than ever before in their ability to treat HIV. They are also the stakeholder group most likely to experience frustration in identifying AIDS-related complications (now nearly entirely preventable) as the first sign of HIV in their patients.

Treatment of Acute HIV Infection

In an oral symposium, Susan Little from UCSD reviewed the balance of factors for and against treating acute HIV infection [Abstract 786]. Despite the collective extensive experience in the treatment of HIV infection garnered over the last 2 and a half decades, the benefits of treating acute HIV infection—defined as the seronegative window period between established HIV infection and formation of antibodies—remains controversial. This remains a challenging area of clinical research for a myriad of reasons: Acute HIV infection is infrequently diagnosed, making it difficult to enroll patients in randomized controlled trials. What we think of as the "gold standard" for evidence based clinical practice guidelines—the controlled trial—is difficult to conduct and will take decades to reach meaningful clinical endpoints. Some have hypothesized, though it remains unproven, that HAART initiated in the stage of acute infection may reverse the massive mucosal CD4 T-cell depletion that occurs early in infection. One small study of three patients treated during with HAART acute infection suggests restoration of gut CD4 cells in jejunal biopsies [Guadalupe M, et al. *J Virol* 2006;80:8236]. However, Mehandru and colleagues performed rectosigmoid biopsies before and during HAART in 8 of 19 HIV-infected subjects identified during acute



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(6/19) or early (2/19) infection [*J Exp Med* 2004;200:761]. These subjects were followed and re-biopsied at 6 months to 5 years after HAART initiation. There was no significant gut CD4 repletion, although peripheral immune reconstitution was noted. These data suggest that treatment during acute HIV infection does not result in a robust reconstitution of a high percentage of the body's total lymphocyte population. As these studies suggest, however, there is no established standard of gut tissue sampling.

During and immediately following acute HIV infection, HIV superinfection remains a concern as well, offering the added possibility of resistant virus transmission and therapy complications due to reduced or inactive drug potency against the predominant viral clone. The high viral loads seen in acute infection probably contribute to greater transmission risk. It may be reasonable to presume that early treatment reduces transmission risk to sexual partners, but the direct and durable benefits to the individual patient remain unclear. Overall, there is evidence to suggest that early treatment is well-tolerated, but there is also an inherent risk of evolution of drug-resistance in non-adherent patients or in patients who acquire a drug-resistant strain and initiate therapy that is only partially active. Large, well-designed prospective controlled trials that use standardized measures to quantify mucosal CD4 cells and that follow treatment outcomes over the long term will be essential before we can formulate guidelines on the management of patients with acute or early HIV infection.

HIV Spread and Methamphetamine

In an oral session, Grant Colfax provided an overview of the growing problem of methamphetamine ("meth") use, particularly among men having sex with men (MSM), its

link to HIV transmission, and the possibilities for effective drug treatment [Abstract 785]. As of 2004, an estimated 1.4 million Americans use meth. Within the MSM population, use of this drug has been linked to greater risk of HIV prevalence and increased STD risk; the use of meth among MSM also appears to be disproportionate to use within other demographic groups. The National HIV Behavioral Surveillance (NHBS) program conducted by the CDC in 17 metropolitan centers show that meth use among HIV-infected MSM in urban centers reflect these trends, though use varied by site. In San Francisco, 21% of the HIV-infected MSM population interviewed admitted to use of meth within the last 12 months, and 6% used weekly or more frequently. In Baltimore, 7% used the drug within the last 12 months, and 3% used it weekly or more often. Casual use of meth among gay men is rare, and the drug is more often associated with abuse and dependence [Shoptaw S, *Top HIV Med* 2006;84:14].

Meth use appears to elevate risk of HIV acquisition independent of other known behavioral risk factors. For example, in the EXPLORE study (a behavioral intervention enrolling HIV-MSM) meth use significantly elevated the risk of new HIV infection (adjusted HR of 1.9, 95% CI 1.4-2.0). While there may be unknown behavioral risk variables associated with meth use that explain this elevated risk (more traumatic sex, partner selection, or differential recall in meth users within the studied population) it is also possible that meth use modifies the host inflammatory response to increase biologic susceptibility to HIV infection. Meth use also clearly adversely influences HAART adherence which can lead to ARV resistance mutations.

In light of the high risks of HIV transmission by HIV-infected MSM and

secondary ARV resistance, promising and creative prevention strategies targeted for the MSM population have been the subject of several clinical trials. These recent studies have explored options for prolonged and effective intervention in meth users. The MATRIX intervention of intensive outpatient cognitive behavioral therapy (CBT) led to reductions in meth use at 6 months of follow-up compared to standard rehabilitation therapy [Rawson RA, et al. *Addiction* 2004;99:708]. CBT versus standard therapy led to greater reductions in unprotected anal intercourse and other sexual risk behaviors. Other strategies include positive reinforcement with vouchers for negative urine toxicology tests, a form of "contingency management," which provides prompt positive feedback when the desired behavior is displayed [Shoptaw S, et al. *BMC Public Health* 2006;6:214; Shoptaw S, et al. *Drug Alcohol Depend* 2005;78:125; Higgins ST, et al. *Am J Psychiatry* 1993;150:763]. Pharmacologic agents have shown some failures (sertraline and dextromethorphan are two examples), but other candidates for pharmacologic therapy, including modafinil, bupropion, mirtazapine, and apripazole are being studied. Given the urgency of need, combination treatment strategies that incorporate behavioral and pharmacologic interventions within a comprehensive program need to be developed and tested.

A Rising Prevalence of Fluoroquinolone Resistance Among Gonococci

The Gonococcal Isolate Surveillance Project (GISP) is a sentinel surveillance program designed to monitor antimicrobial susceptibility of *Neisseria gonorrhoeae* isolates in the United State and to guide treatment recommendations. Weinstock presented data from GISP for 2005 that indicates that

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the days of easy and low-cost therapy with ciprofloxacin (and other fluoroquinolones) are likely to be very limited [Abstract 698]. In 2000, the overall prevalence of quinolone resistant *Neisseria gonorrhoea* (QRNG) among GISP isolates was 0.35%, with all QRNG isolates coming from either Hawaii or the West Coast. By 2005, QRNG represented 9.4% of all GISP isolates; 29% of all isolates from MSM were QRNG, while only 3.9% of isolates from heterosexual men were QRNG. Being heterosexual, Black, or living in Southeastern US were all associated with lower rates of fluoroquinolone resistance. Given these trends, it is unlikely that fluoroquinolones will be reliably useful in the treatment of gonorrhea much longer, leaving clinicians with only a very limited menu of choices. New antibiotic therapies for the treatment of gonorrhea are needed.

HIV RNA Shedding Among Women on HAART

Very low plasma HIV RNA levels are associated with a low risk of HIV transmission among discordant couples, suggesting that achieving virologic control on HAART may prevent sexual transmission of HIV. Susan Cu-Uvin presented data on genital tract HIV RNA from women on HAART followed over time: 45 women with a median CD4 cell count of 415 cells/mm³ were followed over 346 visits [Abstract 694]. Plasma HIV RNA was undetectable in 81% of these visits; 63% of women had at least 1 episode of HIV shedding. With an undetectable plasma viral load, the probability of HIV shedding was 0.03 from the endocervix, 0.02 from the ectocervix, and 0.03 from the vagina. The authors concluded that most HIV-infected women on HAART continue to shed HIV RNA in their genital tract even with good systemic virologic control, which may have implications for the public health benefits of HAART. ▲

U.S. Public Health Service Guideline Changes

By John G. Bartlett, M.D.

There were recent changes in the U.S Public Health Service HIV guidelines. The key changes are summarized below.

Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States - October 12, 2006

The major change is the updated recommendations for the use of antiretroviral drugs in pregnancy:

Nucleosides/tide analog reverse transcriptase inhibitors (NRTIs)

Recommended:	Alternatives:	Inadequate data:	Not recommended:
<ul style="list-style-type: none"> • zidovudine • lamivudine 	<ul style="list-style-type: none"> • didanosine • emtricitabine • stavudine • abacavir 	<ul style="list-style-type: none"> • tenofovir 	<ul style="list-style-type: none"> • zalcitabine

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Recommended:	Not recommended:
nevirapine (use with baseline CD4 >250/mm ³ only if benefit clearly outweighs the risk of hepatotoxicity)	efavirenz (avoid in first trimester; use after 2 nd trimester can be considered if alternatives are not available and adequate contraception can be assured postpartum).

Protease Inhibitors

Recommended:	Alternative agents:	Inadequate data:
<ul style="list-style-type: none"> • lopinavir/ritonavir (Pharmacokinetic studies show low LPV levels in the third trimester. Some experts give standard doses of 2 tabs bid and monitor HIV viremia and drug levels if available; other experts increase dosage from 2-3 tabs bid in the third trimester and return to 2 tabs bid postpartum. Once daily LPV/r is not recommended.) • nelfinavir 	<ul style="list-style-type: none"> • indinavir • ritonavir • saquinavir (Note that saquinavir was previously in the recommended category based on pharmacokinetic studies with <i>Fortovase</i>, which is no longer available) 	<ul style="list-style-type: none"> • atazanavir • fosamprenavir • darunavir • tipranavir

Fusion Inhibitors

Inadequate data: enfuvirtide

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents - October 10, 2006

The major change is recommendations for initial regimens in treatment-naïve patients. Select either an NNRTI or a PI from column A (NRTI or PI) plus one dual-NRTI combination from column B.

	Column A			+	Column B
	NNRTI	OR	PI		Dual-NRTI
Preferred Components in alphabetical order	efavirenz			<ul style="list-style-type: none"> • atazanavir + ritonavir • fosamprenavir + ritonavir (bid) • lopinavir/ritonavir (bid) 	
Alternative to Preferred in alphabetical order	nevirapine	<ul style="list-style-type: none"> • atazanavir(unboosted) • fosamprenavir (unboosted) • fosamprenavir + ritonavir (qd) • lopinavir/ritonavir (qd) 		<ul style="list-style-type: none"> • abacavir/lamivudine • didanosine + (emtricitabine or lamivudine) 	



Drug Profile: Telbivudine (*Tyzeka*)

By Paul A. Pham, Pharm.D. and Chloe Thio M.D.

Manufacturer: Idenix pharmaceuticals

Class: Synthetic thymidine nucleoside analog with activity against HBV but not HIV.

Formulation/Storage: 600 mg tablet/Store at room temperature

Indication: Treatment of chronic hepatitis B (HBeAg pos, irrespective of e-Ag status) with ongoing viral replication and evidence of transaminase elevation or histologically active disease.

Dose: 600 mg once daily with or without food.

Dosing with renal impairment: GFR >50 mL/min: 600 mg once daily; GFR 30-49 mL/min: 600 mg every 48 hr; <30 mL/min (no HD): 600 mg every 72 hr; ESRD (HD): 600 mg every 96 hr (on days of HD, dose post-HD).

Dosing with hepatic impairment: 600 mg once daily

Pregnancy Risk: Category B. Telbivudine was not embryotoxic or teratogenic in animal studies. No human data.

Pharmacokinetics: Telbivudine is well absorbed with a mean C_{max} of 3.69 mcg/mL, AUC 26.1 mcg hr/mL, and C_{min} 0.2-0.3 mcg/mL on 600 mg/d at steady state. Telbivudine is not metabolized, and is primarily excreted via glomerular filtration with a terminal $T_{1/2}$ of 40-49 hours.

Drug Interactions: Telbivudine is not a substrate, inducer, or inhibitor of cytochrome P450 isoenzymes. Interactions with PIs or NNRTIs are unlikely. No antagonism was observed with other NRTIs *in vitro*.

Adverse Drug Reactions: Telbivudine is generally well tolerated with adverse reactions that were similar to lamivudine and adefovir. CK elevation is more common with telbivudine than with lamivudine (9% vs 3%). Cases of reversible myositis have been reported.

Resistance: M204I genotypic substitution accounts for 74%-94% of observed mutations associated with resistance [Bzowej et al. *Gastro* 2006;130:A765; Standring et al. EASL 2006, Vienna]. Additional mutations that have been reported include L80I/V, A181T, L180M, L229W/V. In a two-year follow-up, resistance, defined as breakthrough viremia with mutations, developed in 8.6% and 21.6% of telbivudine-treated patients who were HBeAg-negative and HBeAg-positive, respectively. Although these resistance rates were high, they were present in only 2-4% of a subset of patients with undetectable viral loads at 24 weeks. The clinical implication of this finding is unclear, but some experts have advocated a treatment strategy of using monotherapy for 24 weeks with "intensification" only if viral load remains detectable.

The efficacy of telbivudine against HBV harboring lamivudine and adefovir resistance remains to be determined. *In vitro*, telbivudine is active against lamivudine-resistant virus with the M204V mutation alone, but it was not active against lamivudine-treated virus with the L180M/M204V double mutation or the

M204I mutation. HBV encoding adefovir resistance associated with A181V mutation showed a 3 to 5-fold reduced susceptibility.

Clinical Study Results: The GLOBE study was a randomized, blinded phase III trial comparing telbivudine (600 mg/d) vs lamivudine (100 mg/d) in 1367 treatment-naïve patients with chronic hepatitis B. Patients had HBV DNA >6 log₁₀ c/mL, an ALT 1.3-10x ULN, and compensated liver disease. Therapeutic response was defined as HBV DNA <5 log₁₀ c/mL with HBeAg loss in those with HBeAg-positive disease or ALT normalization. At week 104, therapeutic response was 61% and 74% of HBeAg-positive (n=921) and HBeAg-negative patients (n=446) treated with telbivudine, respectively. These response rates were higher than those observed in lamivudine-treated patients, which were 47% and 62% of HBeAg-positive and HBeAg-negative patients, respectively. However, in the HBeAg-positive group, HBeAg seroconversion was not different between those who received telbivudine and lamivudine, 29% and 24%, respectively. Tolerability was comparable between the treatment groups. Three cases of reversible myositis were reported in the telbivudine group [Lai CL, et al. AASLD 2006, Abstract 91].

In lamivudine-experienced patients, 256 patients with persistent viremia (HBV DNA >3 log₁₀ c/mL) despite 3-12 months of lamivudine treatment were randomized either to switch to telbivudine or to continue therapy with lamivudine. At the preliminary 24 week evaluation, serum HBV DNA level was suppressed to below 5 log₁₀ c/mL in 80% of patients switched to telbivudine compared to 56% in the lamivudine group, and an undetectable HBV DNA was achieved in 41% and 31%, respectively [Gane E, et al. AASLD 2006, Abstract 1007].

In a multicenter, randomized study involving 135 treatment-naïve patients with compensated liver disease, telbivudine, adefovir, and adefovir-telbivudine (adefovir for the first 24 weeks followed by a switch to telbivudine for 28 weeks) were compared. Patients were HBeAg-positive with a HBV DNA >6 log₁₀ c/mL and an ALT 1.3-10x ULN. Compared to adefovir, telbivudine-treated patients had a 1.4 log₁₀ c/mL greater HBV DNA decline at 24 weeks (p<0.001). This benefit was maintained at 52 weeks. In addition, undetectable viral load (HBV DNA <300 log₁₀ c/mL) was achieved in 58% and 39% of telbivudine- and adefovir-treated patients, respectively (p=0.14); however, HBeAg loss and ALT normalization were similar to the two groups. In patients who were switched from adefovir to telbivudine at 24 weeks, an additional 1 log₁₀ c/mL drop in HBV DNA was observed following the switch; HBV viral suppression in these patients was

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Expanded Drug Access: Etravirine (Formerly TMC-125)

By Amanda R. Colquitt, Pharm.D. and Paul A. Pham, Pharm.D.

Manufacturer: Tibotec Pharmaceuticals

Class: Second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI)

Studied Formulations/Storage: 100 mg tablet/store at room temperature

Indication: Treatment of HIV-1 with NNRTI-resistant variants, including those encoding L100I, K103N, Y181C, Y188L, and G190A/S mutations

Expanded access dose: 200 mg twice daily with food (doses up to 1200 mg bid have been evaluated)

Pharmacokinetics:

- **AUC_{12h}:** 7,638 ± 2,254 ng*h/mL; **C_{max}:** 876 ± 233 ng/mL; **C_{min}:** 426 ± 155 ng/mL [Scholler-Gyure M, et al. 46th ICAAC, 2006, Abstract A-371]
- **Estimated elimination T_{1/2}:** 30-40 hrs [Gruzdev B, et al. *AIDS* 2003;17:2487-2494]

Drug Interactions: *In vitro* metabolism of etravirine (ETV) is via CYP3A4 and glucuronidation; however, *in vivo* studies suggest that CYP3A4 is only a minor pathway for etravirine elimination. Etravirine does not induce or inhibit its own metabolism, but appears to be a mild inducer of CYP3A4 [Piscitelli S, et al. 3rd International Workshop on Clinical Pharmacology of HIV Therapy, 2002]. Caution must be used when concomitant use of CYP3A4 substrate medications (see Table on p9).

Clinical data: In an observational study, ten treatment-experienced patients initiating concomitant therapy with DRV/r 600/100 mg bid and ETV 200 mg bid together with two or more NRTIs ± enfuvirtide were evaluated [Boffito M, et al. 46th ICAAC, 2006, Abstract H-1000]. At baseline the median CD4 count was 75 cells/mm³, HIV RNA was 4.67 log₁₀ c/mL, and there was extensive genotypic resistance (7 NRTI mutations, 2 NNRTI mutations, and 4 primary PI mutations). The median viral load decrease was -2.7 log₁₀ c/mL, and the median CD4 increase was

87 cells/mm³. All patients achieved a viral load <400 c/mL; of these, 9 were <40 c/mL. Analysis of a larger prospective, randomized study (DUET) evaluating this combination is in progress.

In a randomized, placebo controlled, partially-blinded study of 199 HIV-infected patients with NNRTI and PI resistance, ETV 400 or 800 mg bid + OBT was compared to the standard of care [Cohen C, et al. 16th International AIDS Conf, 2006, Abstract TUPE0061]. At baseline, patients had a median viral load of 4.7 log₁₀ c/mL and a CD4 count of 100 cells/mm³. The mean change in HIV RNA across treatment groups was -0.88 log₁₀ c/mL to -1.01 log₁₀ c/mL compared to -0.14 log₁₀ c/mL in the placebo group. The mean increase in CD4 count was 58-61 cells/mm³ compared to 13 cells/mm³ with control.


Adverse Drug Reactions: ETV is generally well tolerated and comparable to placebo. The most common reported adverse events included diarrhea, rash (mild to moderate), headache, and nausea. Adverse events categorized as grade 3/4 reported by more than 3 patients were hypertriglyceridemia, CPK elevation, and pancreatitis (unclear association) [Montaner J, et al. 10th European AIDS Conference, 2005 Abstract LBPS3/7B]. Of ETV-treated patients, 9% discontinued therapy due to adverse drug events compared to 3% in the placebo group.

Activity: In a retrospective analysis, ETV maintained activity against NNRTI-resistant virus, including virus expressing K103N and Y181C [Vingerhoets J, et al. International HIV Drug Resistance Workshop, 2006 Abstract 17]. The presence of Y181C in addition to other NNRTI mutations appeared to be associated with higher phenotypic fold-change to ETV; however, there was no significant difference in virologic response at 24 weeks when K103N or Y181C were observed at baseline.

Drug susceptibility assays performed on 2,157 samples revealed 1,081 samples with a ≥10 fold change in EC₅₀ compared to wild-type for at least one of the currently available NNRTIs [Andries K, et al. *Antimicrob Agents Chemother* 2004;48:4680]. Of these, ETV inhibited 98%.

Resistance: *In vitro*, mutations selected by ETV varied [Vingerhoets J, et al. *J Virology* 2005;79:12773-12782]. V179F, Y181C, L214F, and M230L are associated with ETV resistance, especially when present in combination. When ETV is used to treat cells infected with virus expressing the K103N mutation, additional mutations including Y181C/Y with L100I and Y181C with M230M/I were

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Expanded Drug Access: Etravirine (formerly TMC-125)

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Co-administered Drug	Effect of Interaction	Comments/Recommendations
Tipranavir/r (TPV/r)	ETV AUC decreased by 76%. TPV and RTV AUC increased by 18% and 23%, respectively [Scholler M, et al. 13 th CROI, 2006, Denver, Abstract 583]	Avoid co-administration
Darunavir/ritonavir (DRV/r)	ETV AUC decreased by 37% compared to ETV 100 mg bid [Boffito M, et al. 13 th CROI, 2006, Abstract 575C; Kakuda TN, et al. 16 th International AIDS Conf, 2006, Abstract TUPE0086]	No dosage adjustment necessary with ETV 200 mg BID
Fosamprenavir/ritonavir (FPV/r)	APV AUC _{12hr} increased by 69% [Scholler-Gyure M, et al. 46 th ICAAC, 2006, Abstract A-0370]	Dose adjustment of FPV/r may be necessary
Tenofovir (TDF)	ETV AUC increased by 19%; TDF AUC increased by 15% [Scholler-Gyure M, et al. 46 th ICAAC, 2006, Abstract A-371]	No dosage adjustment necessary
Indinavir (IDV)	IDV AUC decreased 46%, ETV AUC increased 51% [Baede P, et al., 42 nd ICAAC, 2002, Abstract A1827]	Dose adjustment of IDV may be necessary
Ritonavir (RTV 600 mg bid)	ETV AUC decreased 46% [Baede P, et al. 42 nd ICAAC, 2002, Abstract A1827]	Co-administration is not recommended with high dose RTV.
Saquinavir/ ritonavir (SQV/r)	ETV AUC decreased 33% [Baede P, et al. 42 nd ICAAC, 2002, Abstract A1827]	No dosage adjustment necessary
Saquinavir/lopinavir/ritonavir (SQV/LPV/r)	Minor AUC change in PIs [Harris M, et al. 13 th CROI, 2006, Abstract 575b]	No dosage adjustment necessary
Lopinavir/ritonavir (LPV/r)	LPV AUC decreased 19%, ETV AUC increased 17% [Piscitelli SC, et al. 42 nd ICAAC, 2002, Abstract A1824]	No dosage adjustment necessary
Didanosine (ddl)	ETV AUC increased 11% [Scholler M, et al. 3 rd IAS, 2005 Abstract 29]	No dosage adjustment necessary
Omperazole	ETV AUC increased 41% [Scholler-Gyure M, et al. 16 th International AIDS Conf, 2006, Abstract TUPE0082]	No dosage adjustment necessary
Ranitidine	ETV AUC decreased 14% [Scholler-Gyure M, et al. 16 th International AIDS Conf, 2006, Abstract TUPE0082]	No dosage adjustment necessary
Methadone ¹³	No change in methadone [Scholler-Gyure M, et al. 7 th International Workshop on Clinical Pharmacology of HIV Therapy, 2006]	No dosage adjustment necessary
Sildenafil	Sildenafil AUC decreased 57% [Scholler-Gyure M, et al. 7 th International Workshop on Clinical Pharmacology of HIV Therapy, 2006 Abstract 45]	Titrate sildenafil to effect

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Drug Profile: Telbivudine (*Tyzeka*)

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similar to that seen in patients who received adefovir for 52 weeks [Bzowej N, et al. AASLD 2006, Abstract 1005].

Comments: In the treatment of chronic hepatitis B, telbivudine offers clinicians a more potent alternative to lamivudine and adefovir. *In vitro*, it is active against lamivudine-resistant strains with the M204V mutation, but the clinical efficacy against this mutant remains to be determined. Although, the resistance rate to telbivudine is lower and slower to develop than with lamivudine, the rate is still high, making it difficult to determine the optimal use for this agent. In contrast to adefovir, lamivudine, and emtricitabine, telbivudine does not have activity against HIV. Head-to-head comparison with more potent agents (e.g. entecavir), combination therapy studies, and studies evaluating sequencing strategies in the treatment of HBV are needed to establish the exact role of telbivudine.

In HIV/HBV co-infected patients who need treatment for both viruses, tenofovir/emtricitabine (*Truvada*) is a better choice than telbivudine since it treats both viruses and is a dual therapy for HBV perhaps reducing rates of resistance. In the co-infected patients who only need HBV therapy, the rates of resistance limit its utility. ▲

Expanded Drug Access: Etravirine (formerly TMC-125)

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selected. Except for M230L, a fold change of >10 for ETV only occurred in the presence of multiple mutations, such as L100I, K103N, and Y181C (fold change 43). The clinical significance of the observed high barrier to resistance seen *in vitro* remains to be determined.

Expanded Access Program (EAP): [http://www.tibotec.com/bgdisplay.jhtml?itemname=EAP2_US, Accessed October 17, 2006; <http://www.clinicaltrials.gov/Identifier:NCT00354627>, Accessed October 11, 2006]

Tibotec Pharmaceuticals has opened its EAP for ETV in the United States. The dose of ETV in this program is 200 mg twice daily with food.

Inclusion Criteria:

- Infected with HIV-1
- ≥18 years old
- Limited or no treatment options due to virological failure or intolerance to multiple ARV regimens
- Unable to use currently approved NNRTIs due to resistance and or intolerance
- Have received licensed oral treatment from each of the 3 major classes of HIV drugs (NRTIs, NNRTIs, PIs)
 - Note for PIs: 2 different PI-based regimens must have been received
 - Note for NNRTI: primary NNRTI resistance can be included if experienced with at least 2 classes of ARVs (PIs, NRTIs) and meet all the other inclusion criteria

Exclusion Criteria:

- Prior or current participation in DUET trials (TMC125-C206 or TMC125-C216)
- Use of concomitant medications prohibited by the protocol
- Use of investigational antiretrovirals (exceptions per protocol)
- Any active, clinically significant disease (i.e. cardiac dysfunction, pancreatitis, acute viral infection) or finding during screening of medical history or physical exam that have not been resolved or stable for ≥30 days before screening phase
- Pregnant or breast-feeding
- Female patient of childbearing potential not using effective non-hormonal birth control
- Patients with specific laboratory abnormalities
- Patients with clinical or laboratory evidence of significantly decreased hepatic function or decompensation ▲

FDA APPROVES ATAZANAVIR (*Reyataz*) 300 MG CAPSULE

On October 16, 2006, the Food and Drug Administration approved a new 300 mg capsule form of atazanavir (*Reyataz*). Atazanavir is now available in 100, 150, 200, and 300 mg capsules.

The new 300 mg capsules allow patients to take one 300 mg capsule in combination with ritonavir (*Norvir*) 100 mg once daily with food. When atazanavir is not combined with ritonavir, the dose is 400 mg (two 200mg capsules) once daily with food.

Courtesy of: Richard Klein, Office of Special Health Issues, Food & Drug Administration ▲



Expanded Access Drug Profile: Raltegravir (RAL, MK-0518)

By Amanda R. Colquitt, Pharm.D. and Paul A. Pham, Pharm.D.

Manufacturer: Merck Pharmaceuticals

Class: Integrase inhibitor

Studied Indications: Treatment-naïve patients or patients with multi-drug resistant HIV-1 infection.

Studied Dose: 100, 200, 400, and 600 mg twice daily

Pharmacology/Drug-drug Interactions: RAL does not require boosting with ritonavir (RTV) to optimize therapeutic concentrations. It is not a potent inhibitor or inducer of CYP3A4; therefore, drug interactions with CYP3A4 substrates are unlikely. It is primarily metabolized by glucuronidation via the enzyme, UDP-glucuronosyltransferase (UGT) 1A1; therefore, inhibitors (atazanavir) and inducers (rifampin, phenobarbital, and phenytoin) of glucuronosyl transferase may increase or decrease RAL concentrations, respectively.

- Ritonavir (100 mg bid) did not affect RAL PK parameters [Iwamoto, et al. ICAAC 2006]
- Efavirenz (EFV) decreased RAL AUC by 36% [Iwamoto, et al. ICAAC 2006]
- Tipranavir/ritonavir decreased RAL C_{min} by 24%, but did not affect AUC [Wenning LA, et al. ICAAC 2006]
- Tenofovir disoproxil fumarate (TDF): no interactions [Wenning LA, et al. ICAAC 2006]

Clinical Studies Results: Treatment-naïve patients: Results of a two-part, Phase II, 48-week, double-blind, randomized trial of treatment-naïve patients were reported at 24-weeks: The dose finding portion of the study demonstrated antiviral activity of RAL as monotherapy at 100, 200, 400, or 600 mg bid for 10 days. Approximately 50%-57% of patients achieved HIV RNA levels <400 c/mL [Morales-Ramirez JO, et al. 10th European AIDS Conference, 2005, Abstract LBPS1/6]. The second part of the study compared RAL or EFV in combination with TDF and lamivudine (3TC) in 198 patients [Markowitz M, et al. International AIDS Conf, 2006, Abstract THLB0214]. Baseline characteristics of the 160 ART-naïve patients randomized to RAL plus TDF and 3TC were: viral load 4.6-4.8 \log_{10} c/mL and CD4 271-314 cells/mm³. Undetectable viral load was achieved in 85% to 100% of patients across all arms. The efficacy was similar in EFV and the RAL arms across all dosages. However, those in the RAL groups achieved virologic suppression to <50 c/mL more rapidly than those in the EFV. After 24 weeks of treatment, the mean increase in CD4 count from baseline ranged from 139 to 175 cells/mm³ in the RAL groups compared to 112 cells/mm³ in the EFV group.

Treatment-experienced patients: In a randomized, double-blind, placebo-controlled trial of patients with multi-drug resistant HIV, doses of RAL of 200, 400, or 600 mg bid were evaluated [Grinsztejn B, et al. 13th CROI, 2006, Abstract 159LB]. All patients were genotypically or phenotypically resistant to at least 1 drug in each of three classes (NNRTI, NRTI, PI). Baseline characteristics of the 124 patients randomized to RAL plus optimal background regimen (OBR) vs OBR alone were: viral load 4.7 \log_{10} c/mL, CD4 226-244 cells/mm³, and 9-11 years of prior ART. The OBR contained a median of 4 antiretrovirals with 45 (36%) receiving enfuvirtide. An undetectable (<50 c/mL) viral load was achieved in 56-72% and 20% of RAL and control patients, respectively.

Adverse Drug Reactions: RAL was generally well tolerated in clinical trials. In one study, pruritis was noted in 2-7%, grade 3/4 transaminase elevation in 2%, and hepatomegaly, tenderness and fever in one patient [Grinsztejn B, et al. 13th CROI, 2006, Abstract 159LB]. In a study comparing RAL with EFV, flatulence was more common in RAL treated patients (6% vs 0%); as expected, headache, dizziness, insomnia, and abnormal dreams were more common in the EFV group [Markowitz M, et al. International AIDS Conf, 2006, Abstract THLB0214].

Expanded Access Program [Merck Pharmaceuticals HIV Investigational Studies website www.benchmark.com. Accessed October 16, 2006.]: EARMRK, Merck Pharmaceuticals' expanded access program (EAP), offers RAL, now in Phase III development, to HIV-infected patients with limited or no treatment options. Patients will receive RAL 400 mg bid in addition to optimized background therapy (OBT).

Inclusion criteria:

- Documented HIV-1 infection
- ≥ 16 years old
- Have limited or no treatment options available due to resistance or intolerance to multiple antiretroviral regimens (resistance or intolerance must be to at least one drug in each of the three major classes of antiretrovirals)
- Not achieving adequate virologic suppression on current regimen
- At risk of clinical or immunologic progression
- Clinically stable

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Antiretroviral Update

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events, but two patients experienced an infusion-associated urticarial rash. A second related compound is showing evidence of greater potency and is being studied further.

Elvucitabine is a novel nucleoside analog from Achillion Pharmaceuticals with a long half-life (approximately 100 hours) that selects for the M184V mutation. Colucci presented results of a 7-day, monotherapy study comparing elvucitabine (10 mg qd) vs placebo [Abstract H-1670d]. Because of its long-half life and the risk of resistance following discontinuation of therapy, subjects took LPV/r alone for 21 days following completion of the monotherapy phase of the study. Patients on the active study drug experienced a $0.85 \log_{10}$ c/mL viral load reduction at day 7, and a $1.72 \log_{10}$ c/mL reduction at day 21, and mean CD4 count increase was 62 cells/mm³ at 7 days. The drug was well tolerated. ▲

Drug Profile: RAL

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Exclusion criteria:

- Prior use of RAL in a clinical trial
- The need for any medications prohibited by the protocol (including phenobarbital, phenytoin, and rifampin)
- Acute hepatitis due to any cause or clinically significant chronic liver disease
- Presence of a condition which investigators deem will interfere with adherence and safety
- Pregnant or breast-feeding

Additional information regarding the RAL EAP is available at www.benchmark.com. This study is registered on www.clinicaltrials.gov under identifier NCT00369941. ▲



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