Hot News

Welcome to "Hot News", a section of AIDS Reviews written by the editors and invited experts which focuses on recently reported information believed to be of both impact and higher interest to the readership.

FDA Issues Labeling Changes for Efavirenz

Efavirenz (EFV) labeling has been revised by the FDA in August 2004. Among the most relevant changes that now appear in the revised labeling are: i) pharmacokinetic data on the interaction with atazanavir or voriconazole; ii) adverse psychiatric experiences; iii) efficacy data through 168 weeks of therapy from Study 006; iv) neurological symptoms; v) risk of immune reconstitution reactions; vi) risk of liver toxicity, and vii) lipid abnormalities.

Given that EFV induces the metabolism of atazanavir when co-administered in treatment-naive patients, the recommended dose of atazanavir should be 300 mg together with ritonavir 100 mg and EFV 600 mg (all once daily). Dosing recommendations for EFV and atazanavir in treatment-experienced patients have not been established yet. EFV should not be administered concurrently with voriconazole, because it significantly decreases voriconazole plasma concentrations.

Study 006 was a randomized, open-label trial that compared EFV + AZT + 3TC (arm A) vs. indinavir + AZT + 3TC (arm B) vs. EFV + indinavir (arm C). New data from week 168 are now available. The proportion of subjects who achieved and maintained plasma HIV-RNA < 400 copies/ml (and < 50 copies/ml) was the following: 48% (43%) in arm A; 29% (23%) in arm B, and 40% (31%) in arm C.

Serious adverse psychiatric experiences have long been reported in patients treated with EFV. In controlled trials of 1,008 patients treated with regimens containing EFV for a mean of 2.1 years, and 635 patients treated with control regimens for a mean of 1.5 years, the rate of specific serious psychiatric events among patients who received EFV or control regimens, respectively, were: severe depression (2.4 vs. 0.9%), suicidal ideation (0.7 vs. 0.3%), non-fatal suicide attempts (0.5 vs. 0%), aggressive behavior (0.4 vs. 0.5%), paranoid reactions (0.4 vs. 0.3%), and manic reactions (0.2 vs. 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with EFV was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increased risk were prior injection-drug use, psychiatric history, and receipt of psychiatric medication at study entry. Patients with serious adverse psychiatric experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of EFV, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Analysis of long-term data from Study 006 has shown that, beyond 24 weeks of therapy, the incidences of new-onset nervous-system symptoms among EFV-treated patients were generally similar to those in the indinavir-containing control arm.

During the initial phase of combination antiretroviral treatment, and particularly in patients with severe immune deficiency, inflammatory responses to indolent or residual opportunistic infections (such as those caused by *Mycobacterium avium* complex, *cytomegalovirus, Pneumocystis carinii*, or *M. tuberculosis*) may develop, and may necessitate further evaluation and treatment. Although the immune reconstitution syndrome was originally linked to protease inhibitor-based regimens, more recently it has also been reported in patients treated with EFV.

Liver function tests should be monitored in patients who initiate EFV-containing regimens and have a history of hepatitis B and/or C. In the long-term dataset from Study 006, 137 patients treated with EFV (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were positive for HBsAg and/or anti-HCV Ab. Among these coinfected patients, elevations in AST to greater than five times the upper limit of normality developed in 13% of patients in the EFV arms and 7% of those in the control arm, and elevations in ALT to greater than five times the upper limit of normality developed in 20% of patients in the EFV arms and 7% of patients in the control arm. Among coinfected patients, 3% of those treated with EFV and 2% in the control arm discontinued from the study because of liver toxicity.

Increases from baseline in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving EFV. In HIV+ patients treated with EFV + AZT + 3TC, increases from baseline in non-fasting total cholesterol and HDL of approximately 20 and 25%, respectively, were observed. In patients treated with EFV + indinavir, increases from baseline in non-fasting cholesterol and HDL of approximately 40 and 35%, respectively, were observed. Non-fasting total cholesterol levels > 240 mg/dl and > 300 mg/dl were reported in 34 and 9%, respectively, of patients treated with EFV + AZT + 3TC; 54 and 20%, respectively, of patients treated with

EFV + indinavir; and 28 and 4%, respectively, of patients treated with indinavir + AZT + 3TC.

All this updated information on the efficacy and safety of EFV are welcome and will help to use the drug more appropriately, and manage more adequately its potential side effects in HIV+ patients.

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Integrase Inhibitors Suppress SHIV Replication in Rhesus Macaques

To date, drugs licensed for treatment of HIV disease belong to the classes of entry inhibitors, nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI and NNRTI), or protease inhibitors (PI). Antiviral resistance in treated and newly infected patients justifies the development of new anti-HIV drugs preferentially targeting alternative steps of the viral replication cycle. Integration of the proviral DNA into the host chromosome through the action of the third viral enzyme, integrase, is an essential step and provides an attractive antiviral target. After binding to the viral DNA, integrase will remove the 3'GT dinucleotides from both long terminal repeat (LTR) ends in the 3' processing reaction; after transport into the nucleus, integrase will insert the trimmed viral DNA into the host DNA during the strand-transfer reaction. Despite a decade of intensive research, few classes of compounds have been identified to inhibit HIV integration in the infected cell. Proof-of-concept was provided by the group of Hazuda, et al. at Merck in 2000, by demonstrating that the inhibition of the strand-transfer step by diketogulonic acid (DKA) was capable of blocking HIV replication (Hazuda, et al. Science 2000;287:646-50). This breakthrough boosted the research effort in developing more potent analogues of these so-called strand transfer inhibitors (INSTIs). S-1360 from Shionogi-GlaxoSmithKline, a diketo analogue in which the carboxylic acid is replaced by a triazole moiety, was the first integrase inhibitor to enter a phase I/II clinical trial. By replacing the labile diketoacid moiety by 8-hydroxy naphthyridine, chemists at Merck developed L-870,810 and L-870,812 that inhibit HIV replication in cell culture at nanomolar concentrations (Zhuang, et al. J Med Chem 2003;46:453-6). L-870,810 entered a Phase I/II clinical trial. The Merck group recently reported that viral resistance against DKA or naphthyridine derivatives in cell culture is primarily associated with different mutations in the integrase gene, although mutation of N155 was associated with cross-resistance (Hazuda, et al. PNAS 2004; 101:11233-8).

While clinical-efficacy data are eagerly awaited, the recent report on suppression of SHIV replication in a rhesus macaque model after oral administration of L-870,812 provides the first evidence for *in vivo* efficacy of integrase inhibitors (Hazuda, et al. Science 2004;305:528-32). Rhesus macaques infected with SHIV89.6P suffer from an accelerated disease, marked by a profound depletion of CD4 cells and a progression from acute viremia to a chronic phase within two weeks. SHIV89.6P is a chimeric virus composed of SIVMAC with an HIV-1 envelope and *tat*, *vpr* and *rev* genes. In the Merck study, one group of animals started treatment 10 days postinfection; another group at day 87. The animals were treated for 77 and 45 days respectively, and monitored for viral load, CD4 cell count, cellular immune response, and antiviral resistance. The oral administration was well tolerated and no clinical signs of toxicity were observed. In the first group, treatment with L-870,812 prevented the decrease in CD4 cell count and in four out of six animals viral load was completely suppressed. The second group of animals was treated starting from day 87 after infection. Although a therapeutic effect was evidenced by a reduction in viral load and an increase in CD4 count, the response was only transient in most animals. In all treated animals that remained viremic, the N155H mutation was detected in the integrase gene. Interestingly, a recombinant virus containing the N155H mutation showed reduced replication fitness, confirming earlier *in vitro* studies (Fikkert, et al. J Virol 2003;21:11459-70) that proposed a considerable genetic barrier to resistance development.

Besides the INSTIs, compounds are under development that specifically target the early steps of HIV-1 integration, the integrase binding inhibitors (INBIs) which interact with the binding of integrase to the proviral DNA. Prototypical compounds of this class are the pyranodipyrimidines (Pannecouque, et al. Current Biol 2002;12:1169-77). For this class of compounds, resistance development in cell culture is slow and no cross-resistance with INSTIs is detected (Witvrouw M., personal communication).

As if on a roller-coaster, the field of integrase research has suffered from moments of belief and disbelief. The recent data from Merck on *in vivo* suppression of SHIV replication, the increasing evidence for a limited mutability of the integrase gene, and the pipeline of novel integrase inhibitors, should convince even the most skeptical to support the development of integrase inhibitors at full speed.

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Light on the Obscure Field of Non-occupational HIV Post-exposure Prophylaxis

Prophylaxis with highly active antiretroviral therapy (HAART) is indicated in the event of healthcare-personnel exposure to blood from HIV-infected patients. However, the assessment and management of incidents with potential for HIV transmission outside this clinical setting is not so well standardized. Experts from 14 European countries have recently released guidelines on how to proceed in case of non-occupational HIV post-exposure prophylaxis (NONOPEP) (Almeda, et al. Eurosurveillance 2004;9:35-40).

Table 1. NONOPEP recommendations after sexual exposure

Sexual exposure	Source person HIV+	Source person Unknown	High-risk factors*
Receptive anal intercourse	R	C	No
	R	R	Yes
Insertive anal, vaginal or receptive oral	C	D	No
(with ejaculation)	R	R/C	Yes
Receptive oral	D	D	No
(without ejaculation)	C	D	Yes

R = recommended; C = considered; D = discouraged

*Source individuals from a group or area with high HIV prevalence (> 15%), rape, menstruation, genital lesions, or sexually transmitted infections. High viral load in the case of HIV+ source individuals.

Table 2. NONOPEP recommendations after blood exposure

Blood exposure	Source person HIV+	Source person Unknown	High-risk factors*
Needle or syringe exchange in IDUs	R	C	–
Other equipment exchange in IDUs	C	D	–
Aggression or	C	D	No
casual stick with needle	R	C	Yes
Non-intact skin, mucosal or bite	C	D	–

R = recommended; C = considered; D = discouraged

*Source individuals from a group or area with high HIV prevalence (> 15%), blood in the syringe, or deep injury. High viral load in the case of HIV+ source individuals.

The rationale for HAART initiation to prevent HIV infection after non-occupational HIV exposure is based on animal models and on the effectiveness of antiretrovirals in reducing vertical HIV transmission. The recommendations are drawn up according to the risk behavior and several cofactors that may increase the probability of HIV transmission. In the case of sexual exposure to persons with known HIV infection, NONOPEP is strongly recommended in the case of anal intercourse, and should be considered for vaginal sex exposures. However, if high-risk factors coexist (i.e. rape, high viral load, menstruation, genital lesions, sexually transmitted infections, etc.), NONOPEP is recommended for any sexual risk behavior, including oral sex. The strength for NONOPEP is similar if the source person has an unknown serostatus, but belongs to any of the recognized risk groups, or comes from areas with a high HIV prevalence (> 15%). Conversely, if these cofactors do not exist, NONOPEP should be offered only in case of anal sex exposure (Table 1).

Blood exposures comprise a higher risk for HIV transmission than sexual intercourse. For this reason, any sharing of injecting equipment among intravenous drug users (IDUs) might justify NONOPEP if one of the partners is known to be HIV+, or the seroprevalence among IDUs in that area is > 15%. Conversely, NONOPEP is not recommended when HIV– individuals comprise the group of IDUs exchanging material. Other needle-related incidents (sticking from abandoned needles or aggression with a needle) in general do not warrant NONOPEP, except for extreme circumstances such as a source individual with HIV infection, high seroprevalence in that area or fresh blood visible in the syringe (Table 2).

Regarding the most convenient drug regimen, a triple combination with two nucs plus a protease inhibitor or efavirenz is suggested for 2-4 weeks. Abacavir and nevirapine are discouraged as they may cause hypersensitivity reactions, as are triple-nuc regimens for their lower potency. In the event of exposure to HIV-infected patients receiving antiretrovirals, the review of medical records may be of help to design regimens avoiding the chance of HIV drug resistance. On the other hand, if the viral load in the source is undetectable, no prophylaxis would be indicated.

This consensus document is welcome as a guide to clinical decisions facing the complexity of non-occupational HIV exposure. However, there are multiple situations in which HIV transmission may occur in daily life, and in which the risks of infection are difficult to ascertain. For this reason, the final decision for NONOPEP should be left to a well-informed patient and experienced physician discussion.

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