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.

Pros and cons of fosamprenavir

Two new protease inhibitors have been recently approved by the FDA: atazanavir and fosamprenavir. Another one, tipranavir, will most likely enter the market within the next few months. What can we expect from these new products? Data presented on fosamprenavir at the 9th European Conference on AIDS, which took place last October in Warsaw, Poland, provided new light on the main features of the drug.

Fosamprenavir is the prodrug of amprenavir, a PI already on the market since two years ago. Data are now available from three clinical trials in which the performance of the drug has been examined in different situations.

The NEAT study compared the safety and efficacy of fosamprenavir (1400 mg BID) with respect to nelfinavir (1250 mg BID), both combined with abacavir plus lamivudine, in 249 drug-naive patients with advanced HIV disease. The main results at 48 weeks are recorded below.

The NEAT study

	Fosamprenavir arm (1400 mg BID)	Nelfinavir arm (1250 mg BID)
No.	166	83
Viral load < 400 cop/ml	66%	51%
Viral load < 50 cop/ml	55%	44%
Diarrhea	5%	18%
Hypersensitivity	9%	5%
Rash	7%	2%
Drug resistance		
Protease	8/29 (28%)	8/26 (31%)
RT	16/29 (55%)	20/26 (77%)

The SOLO study examined the efficacy and safety of fosamprenavir boosted with ritonavir once a day (1400 mg/200 mg) compared to nelfinavir (1250 mg BID), both combined with abacavir and lamivudine, in drug-naive patients. The main results are recorded below.

The SOLO study

	Fosamprenavir/r arm	Nelfinavir arm
No.	322	327
Viral load < 400 cop/ml	68%	65%
Viral load < 50 cop/ml	56%	52%
Virologic failures	4%	15%
Adverse events leading to treatment discontinuation	8%	5%
Diarrhea > grade 2	9%	16%
Drug resistance		
protease	0/32	27/54 (50%)
RT	4/32	31/54 (57%)

Finally, the CONTEXT trial examined fosamprenavir boosted with ritonavir in 320 PI-experienced patients with virologic failure. Two different schedules of fosamprenavir (1400 mg QD versus 700 mg BID) along with 200 mg of ritonavir, were compared with Kaletra (lopinavir/ritonavir). These PI's were administered with tenofovir and another nucleoside analog chosen on the basis of HIV genotyping. The virologic results at 48 weeks are recorded below. It should be pointed out that no data are available yet about a potential interaction between tenofovir and fosamprenavir, which might have influenced the results. For atazanavir, the concomitant administration of tenofovir results in 40% reduction of atazanavir plasma levels (26% when atazanavir is boosted with ritonavir).

The CONTEXT trial

	Fosamprenavir/r QD	Fosamprenavir/r BID	Kaletra
No.	105	107	103
Mean viral load drop (log)	1.49	1.53	1.76
Virologic failure	41%	27%	27%
Viral load < 400 cop/ml	50%	58%	61%

Drug resistance to fosamprenavir, as for amprenavir, in PI-naive patients mainly develops as a result of selection of specific changes: I50V; 54M/L; I84V; and V32I plus 47V. Other protease changes frequently seen are 33F or 46I. However, other classical PI-resistance mutations are not selected by the drug, particularly D30N, 54V, 82A/T or 90M.

Considering all these findings, the availability of fosamprenavir represents only a small contribution to the HIV armamentarium. The drug will need to be used with ritonavir as a booster in treatment-experienced patients, and pill burden is only slightly ameliorated.

Pablo Barreiro
Hospital Carlos III
Madrid, Spain

New hopes for saquinavir

Saquinavir (SQV), formulated as hard-gelatin capsule (Invirase), was the first protease inhibitor (PI) available for the treatment of HIV infection. This formulation, however, has low oral bioavailability and mild antiviral activity *in vivo.* Subsequently, SQV became available as soft-gelatin capsule (Fortovase), which has improved bioavailability. However, the high pill burden still represents an important limitation of this drug.

Boosting of SQV with low doses of ritonavir (r) allows reduction of the pill burden. It has been employed for many years, particularly when facing the treatment of heavily pre-treated patients. The doses of SQV and r usually prescribed in this setting varies widely, but the most common are 1000 mg/100 mg BID, 1600 mg/100 mg QD and, more recently, 1000 mg/100 mg plus lopinavir 400 mg BID.

Several studies using SQV/r twice daily (Valer et al. AIDS 2002;16:1964-6; Dragsted, et al. J Infect Dis 2003;188:635-42) or SQV/r once daily (López-Cortés et al. J AIDS 2003;32:240-2; Cardiello et al. J AIDS 2002;29:464-70) have shown a potent antiviral activity as well as safety profile. These SQV/r regimens have the potential to make antiretroviral therapy simpler, more tolerable, and easier to take as well as improving the patients' quality of life. Therefore, SQV is no longer recommended without r boosting.

More recently, 'double boosting' of PI's have been employed in rescue interventions. One of the most popular combinations has been SQV with Kaletra, a fixed combination of lopinavir and low-dose of r. Preliminary results are recorded in the table.

More recently, some studies have demonstrated that the addition of ritonavir leads to significant increase of SQV plasma levels, irrespective of whether the hard or soft formulation is used (Kurowski et al. HIV Med 2003;4:94-100; Cardiello et al. J AIDS 2003;32:375-9). This is important because soft capsules have some disadvantages (larger pill size, increased gastrointestinal disturbances, requirement of refrigeration, and higher cost).

Roche is now developing a 500 mg SQV mesylate tablet that could simplify dosing regimens. The current pill count for SQV/r (1000/100 mg BID) represents 12 pills per day (five SQV capsules plus one r capsule, BID). The new formulation will allow a reduction to half the pill number (two SQV capsules plus one r capsule, BID). The bioavailability of the new SQV formulation in healthy volunteers was reported at the 2nd IAS Conference (Paris, July 2003).

A final improved use of SQV is being examined in combination with atazanavir, a new once-daily PI. Pharmacokinetic data suggest that atazanavir boosts SQV plasma levels up to 5-fold. This combination could be particularly attractive given its favorable lipid profile.

Luisa Valer
Hospital Carlos III
Madrid, Spain

Efficacy of trials with double-boosted SQV/LPV/r regimens in PI-experienced patients

	No.	Efficacy (ITT)
SQV/LPV/r with nucleoside analogs		
Hellinger et al. 9th CROI 2002 [abstract 451-W]	28	42% < 50 HIV-RNA cop/ml at week 24
Ruiz et al. 9th CROI 2002 [abstract 421-W]	24	36% < 80 HIV-RNA cop/ml at week 24
Smith et al. XIV IAC 2002 [abstract TuPeB4547]	35	36% > 0.8 log reduction at week 48
Zala et al. XIV IAC 2002 [abstract TuPeB4492]	23	39% < 500 HIV-RNA cop/ml at week 48
La Porte et al. AIDS 2003;17:1700-2	7	Median HIV-RNA drop of 1.3 log at week 24
SQV/LPV/r alone		
Staszewski et al. 2nd IAS 2003[abstract 583]	52	Median HIV-RNA drop of 3.1 log week 24

Fighting back hypermutation

A new mechanism that cells use to fight infection with HIV-1 is becoming more apparent. The identification of the human gene APOBEC3G (initially referred to as CEM15) as the target of the HIV-1 Vif (viral infectivity factor) in 2002 (Sheehy, et al., 2002) spurred a series of studies aimed towards unraveling the pieces and parts of this host defense mechanism. The long sought-after Vif substrate, APOBEC3G, bears homology with a group of mammalian proteins with RNA editing activity that can lead to the introduction of genetic modifications in mRNA through DNA deamination.

All lentiviruses, with the exception of the equine infectious anemia virus, encode the accessory gene *vif*. These lentiviruses have thereby developed an efficient way to protect their genome from the deleterious effects otherwise associated with cytidine deaminases. Specifically, APOBEC3G causes the deamination of cytosine to uracil in the retroviral minus-strand cDNA, which, in turn, results in G to A mutations in the plus-strand cDNA (Mangeat, et al., 2003). Indeed, the presence of Vif in the producer cell is essential for the generation of HIV-1 particles that can productively infect so-called non-permissive cells (primary CD4+ T-lymphocytes, for example). Conversely, viral particles generated in the presence of ABOBEC3G, but in the absence of Vif, yield proviruses with a high frequency of G to A hypermutations and premature stop codons, providing the explanation for reduced viral infectivity observed for Δ*vif* HIV-1 in non-permissive cells (Lecossier, et al., 2003; Mariani, et al., 2003). Thus, in the absence of Vif, APOBEC3G is incorporated into the newly generated viral particles, and induces G to A hypermutations during the reverse transcription step, which ultimately leads to nonfunctional proviruses.

A number of studies have demonstrated that Vif reduces the level of expression and degrades APOBEC3G in the producer cell by targeting it to the proteosome (Stopak, et al., 2003; Marin, et al., 2003; Sheehy, et al., 2003). Recently, it has been elucidated that a third party, a protein complex similar to Skp1-Cullin F box, is essential and instrumental for this process. Yu, et al. have suggested that Vif interacts with a complex of four cellular proteins (Cul5, Elongin B and C and Rbx 1) that promote APOBEC3G ubiquitination and targeting to the proteosome (Yu, et al. Science 2003).

In summary, the key components of the black box surrounding Vif function have been identified. Targeting proteins to the proteosome pathway is certainly a very efficient way of gene silencing, and lentiviruses took advantage of this pathway to overcome host-cell defense mechanisms. Future studies will reveal whether inhibiting the inactivation of APOBEC3G can result in new antiretroviral treatment strategies.

Viviana Simon
Aaron Diamond AIDS Research Center
The Rockefeller University
New York, USA

A novel HIV-1 inhibitor targeting gp120-CD4 interactions

Investigators from Bristol-Myers Squibb have recently published several manuscripts on a small molecule inhibitor of HIV entry. The compound is called BMS-378806, and represents a new class of HIV inhibitor that binds directly to the HIV-1 envelope gp120, and by this effect, it inhibits the CD4 receptor binding (Ling, et al. PNAS 2003;100:11013-8; Guo, et al. J Virol 2003;77:10528-36).

The recently approved HIV-1 fusion inhibitor enfuvirtide (T-20) demonstrates that viral entry is a valuable target for antiretroviral therapy. Several anti-HIV compounds that block HIV coreceptors (CCR5 and CXCR4) are currently in clinical trials, but BMS-378806 is the first inhibitor to block the gp120-CD4 binding interaction. The compound exhibits inhibitory activity against laboratory-adapted strains of HIV-1 (EC_{50} values vary between 0.9 and 743 nM). The assessment of 53 HIV-1 isolates belonging to clade B showed a median EC_{50} of 40 nM. However, besides being inactive against HIV-2 and SIV, the compound shows decreased activity, or even no activity at all, against HIV-1 subtypes, such as E, F, G and O. Genetic analysis of viruses selected *in vitro* under BMS-378806 exposure shows that resistance develops relatively quickly (in about 20 days), and that several amino acid substitutions, located at or near the gp120/CD4 contact sites, seem to be involved and confer high-level resistance to the drug. This finding indirectly confirms that the CD4 binding pocket of gp120 is indeed the antiviral target of this compound.

BMS-378806 displays many favorable pharmacological traits, such as low protein binding, minimal human serum effects on its anti-HIV activity, good oral availability in dogs, and a good safety profile in animal toxicology studies. It already has entered the clinical development process. Drugs like this prove that the HIV entry process can be effectively targeted with small molecule compounds. This is a promising start for a new class of HIV inhibitors to be added to the current antiretroviral armamentarium.

Dominique Schols
Rega Institute, Katholieke Universiteit
Leuven, Belgium