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.

Nevirapine might reduce the cardiovascular risk of HAART

Cardiovascular (CV) diseases, with coronary heart disease (CHD) being the most common, are the main causes of death in middle-aged and older adults in developed countries (Rosamond *et al.* N Engl J Med 1998; 339: 861-7). An increased blood cholesterol (chol) level, specifically a high LDL-chol, constitutes a significant risk factor for CHD and other CV illnesses. Clinical trials convincingly demonstrate that lowering serum chol, through diet and lipid lowering drugs, substantially reduces the incidence of new CHD events and CHD mortality. There is also a strong inverse association between plasma HDL and the risk of CHD, the ratio total-chol/HDL-chol being a risk predictor of future CHD events.

Dyslipidemia is emerging as an important problem in HIV-infected patients receiving HAART, particularly when using PI. Its long-term consequences are, however, still unknown. On the basis of experience with other diseases in which lipid disturbances are present, it is reasonable to expect a high risk of CV diseases in HIV-infected patients on HAART. There is increasing concern that HAART-related hyperlipidemia will lead to an epidemic of CV disease, mainly because the life expectancy of HIV-positive persons has been markedly improved with the new antiretroviral therapies. Not surprisingly, several reports have highlighted a higher rate of CHD events among HIV+ persons (8th CROI 2001, abstract 655), as well as a higher incidence of myocardial infarction in subjects exposed to PI, compared to the general population (8th CROI 2001, abstract 657). Moreover, a higher prevalence of premature carotid lesions has been noticed in PI-treated individuals (Maggi *et al.* AIDS 2000; 14: 123-8).

In HIV+ subjects under HAART with dyslipidemia, the association with other CV risk factors such as a family history of CV disease, smoking, physical inactivity or overweight, is remarkable (García-Benayas *et al.* Antiviral Therapy 2000; 5 (suppl.5): 27-8). These findings should alert clinicians to the importance of diagnosing and controlling CV risk factors in HIV+ patients under HAART, as a routine part of the total health care needs of these patients.

Results from the Atlantic study reported at the 8th CROI (abstract 654B) have demonstrated that antiretroviral-naive patients randomly assigned to a NVP-containing combination (ddI/d4T backbone) showed a 38% increase in HDL-chol, together with significant increases in large HDL-chol, HDL particle size, LpAI and apoAI, after 24 weeks on treatment (Table 1). A much smaller increase in HDL-chol, LpAI and apoAI, without changes in large HDL-chol or HDL particle size, was noticed in the 3TC arm. These changes were not recognized among patients receiving IDV. The modest increment in LDL-chol in the NVP arm was counterbalanced by a much more relevant reduction of the total-chol/HDL-chol ratio. Replacing PI with NVP may be associated with an improvement in the lipid profile (Martínez *et al.*

Table 1. *Lipid profile outcome at the Atlantic study.*

	NVP arm		
	week 0	week 24	p
HDL-chol (mg/dL)	37.9 ± 9.4	50.4 ± 16.9	<0.0001
total-chol / HDL-chol	4.8 ± 0.3	4.3 ± 0.2	<0.01
LDL-chol (mg/dL)	111.1 ± 33	120.9 ± 34.9	0.0261
Large HDL-chol (mg/dL)	25.9 ± 11.3	37.4 ± 17.9	<0.0001
HDL particle size (nm)	8.9 ± 0.4	9.2 ± 0.6	0.0009
Apo AI (mg/L)	1107 ± 173	1274 ± 223	<0.0001
Lp AI (g/L)	0.4 ± 0.08	0.5 ± 0.14	<0.0001

AIDS 1999; 13: 805-10), whereas switching to EFV does not provide this benefit (Martínez *et al.* Clin Infect Dis 2000; 31: 1266-73).

The need to control viral replication and restore immune depletion must always be paramount, but the control of dyslipidemia and other modifiable CV risk factors in HIV+ patients should be mandatory in order to prevent future CV morbidity. Accordingly, the use of antiretroviral agents less prone to induce dyslipidemia is particularly attractive. NVP represents a valid alternative to PI and EFV in both antiretroviral-naive and in PI-treated individuals, in whom a switching strategy may be recommended. The anti-atherogenic plasma lipid profile of NVP must be considered as an added benefit of the drug when deciding on the prescription of HAART.

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Encouraging progress in HIV vaccine research

Efforts to produce an HIV vaccine are still experiencing major problems related to the tremendous variability of HIV and the ability of the virus to hide inside immune cells. Classical approaches have failed, because the antigens used in candidate vaccines so far either do not cross-neutralize most circulating HIV strains, or do not elicit the proper immune response that protects against established HIV infection.

New approaches are being considered that involve either the use of attenuated replicating strains, or non-protective vaccine approaches. Live attenuated virus as vaccine have been reported to protect against infection during subsequent challenge with SIV in at least some of the monkeys tested (Kumar *et al.* Virology 2000; 269: 268-75), but the danger is that attenuated strains either revert to a more virulent strain or are not entirely benign to immunocompromised persons (such as new-born babies, those on medication after transplantation, or following other diseases). Sally Blower and colleagues estimated the risks and benefits of such a vaccine for humans. The model used predicted that, in countries with high transmission rates, the benefit would outweigh the risk, while in less affected countries, possible complications in immunocompromised vaccinated people would cause a rise in death rates instead of a decline (PNAS USA 2001; 98: 3618-27). Scientists are, therefore, not prepared to take this risk, especially since it is difficult to predict the possible reversion to a more virulent strain.

Recently, another approach achieved a limited success. R. Amara and colleagues from Emory University reported that DNA priming with SIV construct that expresses Gag, Pol, Vif, Vpx, Vpr, Env, Tat and Rev from a single transcript, followed by a boost with a vaccinia virus expressing Gag, Pol and Env, did not protect macaques from infection with a highly pathogenic SHIV (SIV/HIV chimeric virus), but elicited a potent immune response that seemed to contain the virus replication better in vaccinated as compared to control animals. Viral loads were controlled at a level 1000-fold lower than in unvaccinated animals and at 23 weeks post-challenge all control animals had developed AIDS or had died, while all vaccinated animals were healthy, with no signs of immune deterioration. Similar results were reported by GlaxoSmithKline with a vaccine containing a gp120 and a Nef-Tat fusion protein administered with a novel adjuvant (AS02A). All vaccinated monkeys had a functional immune response against a SHIV used for challenge and were perfectly healthy although infected after 18 months, while all control animals developed AIDS.

Both these vaccines do not protect against SHIV infection and it is not known for how long disease can be postponed. Consequently, such an approach cannot be considered a "vaccination" that protects from infection. Vaccinated subjects should, therefore, maintain stringent prevention measures. However, the vaccines are still valuable, since vaccination seems to delay disease progression. Possible applications of this vaccine are thus not only limited to the "vaccination" of uninfected populations but they may also be used as therapeutic vaccine in combination with antiviral therapy in HIV-infected persons.

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Mechanisms of resistance to nucleosides unraveled

Until recently, the selection of distinct, specific mutations at the RT gene was supposed to account for the emergence of resistance to each of the different nucleoside analogues. For instance, 184V resulted in a loss of sensitivity to 3TC, 74V to ddI, and 215Y to AZT. However, the mutations accounting for the lack of sensitivity to d4T remained unknown and mysterious, since 75T was only rarely detected *in vivo*. More recently, it was shown that multi-nucleoside resistant genotypes (151M complex and 69 inserts) represented an additional pathway leading to d4T resistance. But again, these genotypes are selected in less than 5% of subjects failing any d4T-containing combination.

The recognition that classical AZT mutations can be selected in subjects failing d4T has modified our thinking dramatically. Up to 25-33% of subjects failing d4T select the classical AZT

mutations (Pellegrin et al. AIDS 1999; 13: 1705-9; Coakley et al. AIDS 2000; 14: F9-F16; De Mendoza et al. J AIDS 2000; 23: 279-81). Moreover, the influence of these mutations is not limited to AZT and d4T, which are thymidine analogues and therefore cannot be named as TAMs (thymidine-associated mutations), since, to a different extent, they are selected and contribute to causing resistance to abacavir (J Infect Dis 2000; 181: 912-20; AIDS 2000; 14: 163-71) and didanosine as well (J Infect Dis 1995; 172: 1480-5; Antimicrob Agents Chemother 1997; 41: 757-62). Only 3TC escapes its action. Therefore, the term NAMs (nucleoside-associated mutations) would apply more appropriately to this set of mutations (41L, 67N, 70R, 210 W, 215Y and 219Q).

have been incorporated, thus blocking its further extension (Meyer et al. PNAS 1998; 95: 13471-8). Once removed, natural nucleosides can again be incorporated by the RT. This mechanism is markedly different from the competitive inhibition produced by mutations such as 184V or 74V, which modify the steric conformation of the RT, complicating the binding of artificial nucleotides 3TC and ddI, respectively. In summary, the mechanisms of resistance to nucleoside analogues can be grouped in two pathways, one causing an enhanced excision/removal of the chain terminator and the other reducing the affinity of the mutated enzyme for the inhibitors. Other properties distinguishing these two mechanisms (Table 2).

Table 1. *Resistance to nucleoside analogues caused by NAMs*

Genotype	abacavir	ddI	d4T
3 NAMs	no	no	no
+ 44	no	no	yes
+ 44 + 118	no	no	yes
+ 44 + 118 + 184	yes	yes	yes
+ 118 + 69	no	yes	yes
+ 184	yes	no	no
+ 184 + 74	yes	yes	no

At the 5th Workshop on Drug Resistance (Scottdale, Arizona, June 2001), several presentations went deeper into the clinical implications of NAMs. Although NAMs arise using almost all nucleoside analogues (except 3TC), the rate at which they appear, and the loss of sensitivity they produce, varies widely for each drug. Three NAMS plus 184V and/or 74V result in resistance to abacavir. Whereas high-level of resistance to AZT appears with only two NAMs, resistance to ABC, ddI or d4T requires more NAMs plus other mutations (Table 1) (Larder, abstract 47).

The presence of NAMs results in a loss of sensitivity to nucleoside analogues by increasing its removal (pyrophosphorolysis) from the nascent DNA chain in which these artificial compounds

In summary, classical AZT resistance mutations are selected by the rest of the nucleoside analogues (except 3TC) and contribute to causing resistance to them. However, they appear less frequently and reduce their activity to a lesser extent compared with what is seen for AZT.

Table 2. *Mechanisms of resistance to nucleoside analogues*

	↓ binding	↑ removal (NAMs)
Mechanism	Inhibitory competition	pyrophosphorolysis
Specificity	single drugs	broad spectrum
Fitness	Reduced	unchanged
Codons	74, 184	41, 67, 70, 210, 215, 219
Drugs	ddI, 3TC	AZT > d4T > ABC > ddI

Therefore, the presence of NAMs alone should not preclude the use of d4T, abacavir or ddI, since much of the antiviral activity of these compounds can be expected to be maintained. This information is particularly useful when salvage regimens are designed taking into account genotypic drug-resistance testing.

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