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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.

Structured Treatment Interruptions Hope or Hype?

There is great interest in the use of structured treatment interruptions (STI) for the management of HIV disease, in large part due to the concerns of drug related toxicity associated with continuous, long-term therapy. STIs are being evaluated in several different settings. When antiretroviral therapy is initiated with acute HIV or SIV infection, subsequent treatment interruptions stimulate immune responses, enhancing control of viral replication (Rosenberg et al., Nature 2000;407: 523-6). In theory, HIV could then be managed with less intensive drug regimens because of augmented host responses. At the opposite end of the spectrum -patients with chronic infection and multidrug resistant HIV-, a period of treatment interruption permits re-population of drug sensitive virus that may be more responsive to new therapy (Deeks, et al., N Engl J Med 2001; 344:472-80).

STIs are also being evaluated in patients with chronic infection who have achieved viral suppression with antiretroviral therapy. One of the first approaches in this population was to try to stimulate HIV immune responses, similar to acute HIV infection. While some small studies suggested that immune responses could be augmented, a recent update by Hirschel (9th CROI, Seattle 2002, abstract 528) of the largest study to date, suggested otherwise. After repeated treatment interruptions, viral load stayed below 5,000 HIV-RNA copies/ml in only 11% of patients. Hirschel concluded that these data do not support the auto-vaccination hypothesis in chronic infection, perhaps due to deletion of key HIV responses early in the course of disease.

Another approach to treatment interruptions for patients with chronic HIV infection is aimed at reducing drug exposure and toxicity without jeopardizing virologic control. The results recently published by Fauci's group (Dybul, et al. PNAS 2001;98:15161-6) were encouraging. In this pilot study, 10 individuals who had achieved virologic suppression on a variety of regimens were put on a 7 day on, 7 day off schedule of "structured intermittent therapy." using indinavir, ritonavir, d4T and 3TC. There was no viral rebound in the 8 patients who adhered to the schedule followed for up to 68 weeks. Lipid profiles of the patients improved. This "proof-of principle" study provides the rationale to proceed to randomized studies of STI to determine whether these intriguing results will hold up in larger studies and other populations. Reduction of drug burden may not only reduce toxicity, but could also potentially increase access to therapy where drug costs are a limiting factor.

Despite the lack of controlled studies, many patients with chronic HIV infection opt for treatment interruptions. Other patients must stop therapy for toxicity or adherence reasons. When Lundgren examined outcomes of 3610 patients in the EuroSIDA data base, the risk of an AIDS event or death was 2.4 fold higher in patients with treatment interruptions (9th CROI, Seattle 2002, abstract 48). With all the limitations of this analysis, one must be cautious about the interpretation. Nevertheless, these results remind us that there are detrimental consequences of treatment interruptions. While there are data to provide hope that treatment interruptions may play a role in treatment strategies in the future, for now the emphasis should be placed on determining the utility of STIs in carefully conducted studies in a research setting.

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Mutations at codon 215: the silent threat

Changes at codon 215 in the reverse transcriptase gene were the first to be reported to confer resistance to the first antiretroviral drug, AZT (Larder, et al. Science 1989;246:1155-8). The selection of two nucleotide changes at codon 215 drives the substitution of Threonine (T) by Tyrosine (Y), which reduces 16-fold the suscepti-

bility to AZT. The mechanism why T215Y results in AZT resistance seems to involve an enhanced excision of the terminator nucleoside in the growing cDNA chain (pyrophosphorolysis). More recently, this mechanism of resistance has been postulated to produce wide cross-resistance within the nucleoside family, and likewise results in resistance to d4T, ddI, and abacavir. Thus, more appropriately, T215Y may be considered a broad multi-nucleoside resistant mutation.

Transmission of AZT-resistant viruses was described for the first time in 1993 (Erice, et al. N Engl J Med 1993;328:1163-5). Several studies in the United States and Europe show that currently 5% to 10% of new HIV-1 infections are produced by viruses carrying T215Y. More recently, a report from the Center for Diseases Control & Prevention (García-Lerma et al. Proc Natl Acad Sci USA 2001;98:13907-12) has highlighted that ~3% of newly-diagnosed persons with HIV, having no previous exposure to antiretrovirals, may harbor viruses with amino acids substitutions distinct of T or Y. This unique set of mutations includes 215D/C/S. They differ from 215Y by one nucleotide, and most likely represent revertants of 215Y in the absence of drug pressure. By themselves, these mutations do not confer reduced susceptibility to either AZT or d4T, but were found to increase the ability of the virus to select 215Y *in vitro* under drug pressure, likely reflecting the need for only one nucleotide change to evolve to 215Y.

The risk that viruses with 215D/C/S may evolve rapidly *in vivo* to 215Y and become AZT- or d4T - resistant may have clinical implications. As is well known, AZT and d4T almost always are part of any first-line, triple-combination antiretroviral therapy.

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Initiating HAART at the DHHS Guidelines (February 4, 2002): Just do it, but much later!

In February, a new version of the US DHHS Guidelines for the use of antiretroviral agents in adults was released. Little changes were introduced regarding the use of viral load and CD4+ cell counts for the monitoring of HAART. In patients under antiretroviral therapy, optimal virus suppression should be considered only when viral load is below 50 HIV-RNA copies/ml, and the definition of virological success should require at least six months on therapy. With respect to criteria for initiating HAART in asymptomatic individuals, a trend towards a more conservative approach is given. The big figures remain the same: thresholds of 350 cells/µl for CD4+ T lymphocytes and of 55,000 copies/ml for plasma HIV-RNA. However, a second look at the MACS cohort (Mellors J et al. Ann Intern Med 1997;126: 946-54) suggests that subjects with CD4+ counts between 200 and 350 cells/ml and viral load below 20,000 HIV-RNA copies/ml, are still at low risk for AIDS progression if they remain untreated (4.1% in 3 years). Therefore, why to treat them?

It can be argued that very few antiretroviral-naive patients will show CD4 counts between 200 and 350 cells/ml in the absence of high viral load; however, the Panel steps a little further in its conservative view. According to another study (Egger M, et al. 41st ICAAC, Chicago 2001, abstract LB-18), the benefit of HAART in preventing AIDS-defining events in subjects with plasma HIV-RNA below 100,000 copies/ml was significant at 3 years only in subjects having fewer than 200 CD4+ cells/ml. In such cases, the risk was placed at 9%. In contrast, when considering being below or above 350 CD4+ cells/ml, AIDS progression under HAART occurred in 4.7% versus 3.4%, respectively. In conclusion, it seems that HAART initiation could be delayed beyond 350 CD4+ cells/ml in naive subjects harboring "not high" viral loads.

Discontinuation of treatment has been the subject of study for the last two years. The Panel leaves this strategy for investigational purposes, except for drug holidaying, which is not recommended due to significant CD4+ cells loss and poor virological benefits in most instances. However, the question regarding stopping indefinitely all drugs in subjects with good virological and immunological status, for the sake of quality of life improvement, is left unanswered. The many patients who began HAART with old-fashioned treatment criteria need to be identified as the primary population for such a strategy to be explored in randomized trials.

Drug resistance testing has found its place in routine clinical practice, as in multiple studies it improves the management of failing patients. Genotyping and phenotyping offer complementary information, particularly in multi-experienced, failing patients. If virus suppression is suboptimal shortly after a new regimen is initiated, the DHHS Panel points out that resistance testing should be requested to identify the culprit drug. The detection of early mutations affecting one compound may allow its selective replacement, while preserving the rest of the regimen. Apart from failure, genotypic testing should be performed in the context of acute HIV infection, due to the possibility of drug-resistant HIV strains being transmitted. In contrast to other guidelines, neither chronic HIV infection, nor pregnant women are the subjects for resistance assessment before initiating treatment.

In summary, the new DHHS guidelines are more conservative in considering when to begin

HAART, although strong efforts are encouraged in order to achieve and maintain virus suppression once therapy is started.

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HP68, a new target for HIV drug therapy?

Virus assembly is an event in the viral life cycle that so far has been somewhat neglected in antiviral drug design, in part because it is not fully understood, and suitable assays for drug screening are not available. It was known before that an ATP-dependent factor was required for HIV capsid formation (Lingappa, et al. J Cell Biol 1997;136:567-81). Now Zimmerman, et al. (Nature, 2002;415:88-92) have identified the protein involved, HP68, also known as RNase L inhibitor.

Human HP68 seems to be essential for post-translational events in HIV-1 capsid formation, by acting as a molecular chaperone during the capsid assembly. HP68 binds to the viral Gag/Gag-Pol and Vif proteins. Gag is the main component of viral capsids, while Vif is known to be essential for virion infectivity. The HP68 inhibitory activity of RNase L may also be beneficial for the virus. Therefore, it is not surprising that HIV infection upregulates HP68 transcription (Martinand, et al. J Virol 1999;73:290-6). Zimmerman and colleagues developed a cell-free capsid assembly assay, in which HP68 was found to be an essential ingredient. Evidence for the post-translational mechanism of HP68-dependant capsid assembly comes from genetic (dominant negative), biochemical (depletion-reconstitution) and morphological (electron microscopy) data. This better understanding of virus capsid formation, and the availability of a cell-free assay, may promote the search for new antiviral drugs, directed to block virus assembly.

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From TAM to NAM

A set of six mutations in the reverse transcriptase of HIV-1 including M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E originally described as zidovudine (ZDV)-resistance mutations are now being widely recognized as having a role in resistance to stavudine (d4T). Because both ZDV and d4T are thymidine analogs, these mutations have been referred to as thymidine analog mutations or TAM. However, more recent data suggest that TAM may confer broader cross resistance to many nucleoside analogs and may, therefore, be more appropriately called nucleoside analog mutations or NAM.

Whitcomb, et al. presented data at the 9th Conference on Retroviruses and Opportunistic Infections (Feb 24-28, 2002, Seattle, WA, USA; abstract 569) on the effect of NAMs and the M184V mutation on susceptibility to all the NRTI class of drugs. By evaluating NRTI susceptibilities from a large number of HIV-1 samples with matched phenotypic and genotypic measurements, this work showed that an increasing number of NAM was associated with decreased susceptibilities to all NRTI, however the degree of cross-resistance was modulated by the M184V mutation. Two NRTI cross-resistance groups were defined based on the effect of M184V: group 1 (ZDV, d4T, tenofovir) and group 2 (ddI, ddC, abacavir, 3TC). The M184V mutation generally increased susceptibility to group 1 and decreased susceptibility to group 2 NRTIs. According to this study, broad cross-resistance among all NRTIs is far more common than previously appreciated. The magnitude of NRTI cross-resistance was found to be highly correlated with the number of NAM, and is modulated by M184V. These *in vitro* observations may have important implications for the selection of effective drug regimens following initial NAM-associated virologic failures.

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Learning more about Nevirapine

Antiretroviral therapy should nowadays be considered as a life-long proposition. As a consequence, previously unexpected, long-term adverse events, and particularly a greater risk of cardiovascular complications, have become a major concern among HIV-infected persons. This fear is particularly apparent among consumers of protease inhibitors (PI). A large number of uncontrolled studies have compared different PI-sparing regimens in order to assess their relative toxicity and complexity. However, a direct comparison between nevirapine (NVP)- and efavirenz (EFV)-containing regimens was still lacking. Two Spanish studies have recently addressed this issue.

In the first study (Negredo, et al. CID 2002; 34:456-62), 77 patients naive for non-nucleosides were randomized to switch from a successful, long lasting PI regimen to NVP, EFV, or to continue the same PI combination. No significant changes between the three arms were found at 12 months regarding viral load, CD4 cell count increases, and adverse events. Relevant differences, however, were noted in the lipid profile.

Total cholesterol, LDL-cholesterol, and triglycerides diminished in the NVP arm, whereas there were no significant changes among subjects under EFV or PI (see table bellow).

Drug	NVP	EFV	PI
Number of pts	26	25	26
% undetectable VL	96	92	92
CD4 cell count	↑	↑	↑
Total chol mg/dl	199±38*	218±52	229±42
LDL chol mg/dl	Not shown*		
Tg mg/dl	160±94*	218±214	229±158

*p<0.05 compared with baseline values

In the second study, the NEFA trial (Martínez, et al. Seattle, 9th CROI, abstract LB-17), a total of 460 patients under PI regimens with undetectable viral load during the last 6 months, were randomly assigned to switch to NVP, EFV or ABC. The proportion of patients with undetectable viremia at 12 months was significantly lower in the ABC arm. However, fewer subjects with cholesterolemia above 240 mg/dl at 12 months were seen in the ABC arm as compared with the NVP and EFV arms. A sub-study conducted on 93 patients showed a significant rise in HDL-cholesterol in both NVP and EFV arms and a significant decrease in triglycerides only in the NVP arm.

The NEFA trial.

Drug	NVP	EFV	ABC
Number of pts	155	156	149
% undetectable VL	94	94	87
CD4 cell count	↑	↑	↑
% pts chol >240 mg/dl	24	22	9
Sub-study			
Number of pts	32	32	29
HDL-chol	↑*	↑*	↓*
Tg	↓*	=	=

*p<0.05 compared with baseline value

Therefore, the NVP recipients were those showing a better lipid profile (see table above).

In conclusion, these two studies confirm the benefit to the lipid profile of switching to NVP- in respect to EFV- and/or PI-containing regimens. Given that avoidance of cardiovascular toxicity has become one of the primary goals when considering antiretroviral regimens, the availability of drugs with a favorable lipid profile is very valuable, and will help in the future design of less toxic antiretroviral combinations.

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