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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.

Liver disease at the 8th CROI

Chronic hepatitis C virus (HCV) infection acts as an opportunistic illness in HIV-positive persons, since both its incidence and the severity of HCV-related liver disease are increased. However, the reverse impact, namely the effect of HCV on HIV disease progression and survival, is less certain. Several groups reported conflicting results at the conference. In a large cohort (n = 1742) followed at the Johns Hopkins in Baltimore (Sulkowski et al. Abstract 34), HCV infection was not associated with a faster CD4 decline or risk of death in a multivariate analysis after considering HAART use. However, a trend was noticed in subjects with low CD4 counts at baseline, and an impaired CD4 recovery on HAART was recognised among HCV-co-infected persons, which is in agreement with data from the Swiss Cohort (Greub *et al.* Lancet 2000; 356: 1800-5). Most HCV/HIV co-infected subjects at the John Hopkins were blacks and active or former iv drugs addicts, and adherence to antiretroviral treatment was low, factors which may be argued have influenced their results. In another study performed in Madrid (Martin *et al.* Abstract 572), which included 902 HIV-positive individuals, both cross-sectional and longitudinal analyses demonstrated a worse immunological and virological HIV outcome among those who were co-infected with hepatitis C, irrespective of the influence of antiretroviral therapy, suggesting that HCV acts as a direct cofactor in HIV disease progression. Therefore, treatment of chronic hepatitis C might indirectly benefit the prognosis of HIV disease.

Chronic HCV infection may worsen the prognosis of HIV disease in another way. The risk of developing hepatotoxicity after beginning antiretroviral drugs is enhanced in subjects with an underlying liver disease (Table 1), and often leads to drug discontinuation. This circumstance may limit the overall benefit of the medication. Several factors are associated with a higher incidence of hepatotoxicity, such as the use of ritonavir and the presence of chronic hepatitis B or C. Although recent warnings have signalled the risk of serious liver toxicity when taking nevirapine (NVP), data pre-

Table 1. *Major studies assessing the risk of severe cytolysis after beginning antiretroviral therapy.*

Author and reference	No.	ART	HCV/HBV	Baseline mean CD4	Incidence	Predictors
Rodríguez-Rosado *et al.* (AIDS 1998; 12: 1256)	187	PI-based	58%	234	26 (13.9%)	HCV
Saves *et al.* (AIDS 1999; 13: F115-21)	748	PI-based	41%	144	67 (9%)	HCV, HBV, prior cytolysis
	1249	2 NRTIs	44%	234	71 (6%)	HCV, HBV, prior cytolysis
Sulkowski *et al.* (JAMA 2000; 283: 74-80)	211	PI-based	51%	109	26 (12%)	HCV, HBV, ↑ CD4, RTV
	87	2 NRTIs	61%	215	5 (6%)	HCV, HBV, ↑ CD4
Den Brinker *et al.* (AIDS 2000; 14: 2895-902)	394	PI-based	22%	150	70 (18%)	HCV, HBV
Saves *et al.* (AAC 2000; 44: 3451-5)	1080	PI-based	30%	290	23 (2%)	HCV, HBV
Núnez *et al.* (J AIDS, in press)	222	HAART (PI, NNRTI)	40%	337	21 (9%)	HCV, age, alcohol

sented at the CROI by different groups permitted more confidence in the safety of the drug when it is adequately used. Sulkowski *et al.* (Abstract 618) assessed the risk of developing severe hepatotoxicity after beginning NNRTI-containing regimens. Its overall incidence was 13.8%. Although it was slightly more frequent when taking NVP than EFZ, the difference did not reach statistical significance (33/202 *vs.* 8/96, respectively).

Until recently, HIV-positive persons have been excluded from transplantation due to concerns about allocating a scarce resource to those with a poor prognosis and to an increased risk of HIV disease progression with immunosuppression. However, HAART-associated improvements in morbidity/mortality have brought a formal evaluation of transplantation to the forefront of the scientific and policy agenda. Two groups at the CROI reported their experience on liver transplantation in HIV-positive persons with end-stage liver disease caused by hepatitis C infection. Boyd *et al.* (Abstract 578) described 4 individuals who underwent liver transplants at the King's College Hospital in London. All survived the immediate post-transplant period, receiving prednisolone and either tacrolimus or cyclosporin as primary immunosuppression. However, all four patients died of complications related to recurrent hepatitis C between 3 and 25 months post-transplant, despite the introduction of interferon plus ribavirin in two of them. Likewise, Rolad *et al.* (Abstract 579) reported one individual who required re-transplantation after hepatitis C re-infection of the first graft lead to rapid liver failure. Therefore, although HIV infection should not be an absolute contraindication for liver transplantation, effective therapy to prevent graft re-infection is warranted.

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Structured treatment interruptions at the 8th CROI

The discontinuation of antiretroviral therapy in patients experiencing a sustained virologic control after being on treatment for long periods of time has become very popular among both patients and doctors in many places. However, data supporting this intervention are scarce and as yet premature. Treatment cessation has been considered for three major reasons: 1) to reduce drug-related toxicities, 2) to boost immune responses in treatment-responders, and 3) to recover drug-sensitive viruses in subjects failing their current therapy.

The interpretation of results obtained after treatment interruption in subjects being on long-term virological control under HAART should be considered separately (Table 2) from the results obtained in heavily pre-treated subjects failing their current therapy.

All these studies indicate that the proportion of subjects attaining a favourable virologic outcome, using any treatment interruption modality, is low and therefore does not favour its widespread use outside clinical trials. So far, STI should be regarded as «supervised» treatment interruptions, as was pointed out by Bruce Walker.

A different consideration came from Dr. Fauci (Abstract Suppl. 16), who described 8 subjects who underwent 22 cycles of 1-week on, 1-week off therapy. Persistence of sustained viral suppression was accompanied in all of them by neither reduction in CD4 cells, nor rebounds in plasma viraemia, nor selection of drug-resistant viruses nor increases in HIV replication in reservoirs (lymph nodes). So far, the advantage of this approach in respect to continued therapy may only be considered in terms of cost reduction, ameliorated toxicity and increased quality of life.

Drug holidays in subjects failing their current therapy represent a distinct group of patients. Deeks *et al.* (Abstract 292) examined 19 subjects failing a PI-containing regimen for at least 6 months who underwent treatment cessation. After a median of 18 weeks, the CD4 count declined on average by 95 cells/μL and plasma HIV-RNA increased 0.74 logs. Virus from 18 subjects became fully susceptible to PI. Six months after re-initiating therapy with 2 NRTI + 1 NNRTI + 2 PI, the CD4 count increased a median of 77 cells/μL and 9/19 (47%) subjects reached HIV-RNA < 50 copies/mL. Persons who were NNRTI-naïve were more likely to reach undetectable vi-

Table 2. *Studies on Treatment Interruption.*

Tx modality after long-term HAART	Time of tx initiation (HIV infection)	Author & Abstract	No. of patients	Success
Cessation	Acute	Markowitz, 288	15	3 (VL <500)
Cycles	Acute	Walker (no abstract)*	14	7 (VL <5000)
Cycles	Chronic	Hermans, 290	13	5 (VL <500)
Cycles	Chronic	García, 289	10	4 (VL <5000)
Cycles	Chronic	Ruiz, 291	12	3 (VL <3000)

*Updated from Rosenberg *et al.* Nature 2000; 407: 523-6.

raemia (7/8), whereas only 2/11 NNRTI-experienced persons reached HIV-RNA < 50 copies/mL at week 24 (p = 0.006). Interestingly, failure of salvage therapy was associated with the emergence of virus exhibiting phenotypic and genotypic characteristics, identical or similar to virus present prior to treatment interruption. This suggests that highly-resistant virus may persist at low levels after drug-susceptible virus emerges in plasma during treatment interruption. Such virus may re-emerge quickly under selective pressure. In favour of this observation, Hance *et al.* (Abstract 294), using cloning as a sensitive tool for the recognition of minority virus populations, showed that 3 months of drug holidays generally did not achieve a complete cleaning of viruses with drug-resistant genotypes. In conclusion, the virologic response seen in heavily pretreated (but NNRTI-naïve) subjects is higher than expected when they undergo drug holidays for 4 months; moreover, most subjects seem to regain CD4 cells lost during that period.

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The euroguidelines initiative has gained momentum

During the 3rd European Symposium on the Clinical Implications of HIV Drug Resistance (23-25 February, Frankfurt, Germany), many resistance data were presented, among which the results and new initiatives from the Euroguidelines group. It consists of representative academic experts from each European country (clinicians and virologists), delegates from industry involved in the development of assays for resistance testing or of new antiviral agents, as well as HIV-community leaders. The panel mission and goal is to develop and update guidelines for the use of resistance testing in the clinical setting for the European HIV population, to generate recommendations related to methodological aspects, quality assurance in the generation and reporting of resistance results in Europe, to assess the cost-effectiveness of resistance testing and to recommend steps to facilitate the implementation of the guidelines as standard of care for all European patients. The group already published 'Clinical and laboratory guidelines for the use of HIV-1 drug resistance testing as part of treatment management -recommendations for the European setting' (Miller *et al.*, AIDS 2001; 15: 309-20), a cost-effectiveness study of resistance testing (Youle *et al.*, Antiviral Therapy 2000; 5: 113-5) and 'Laboratory guidelines for the practical use of HIV drug resistance tests in patient follow-up' (Vandamme *et al.*, Antiviral Ther 2001; 6: 21-40). New initiatives are being started, including the documentation on the epidemiology of transmission of resistance strains in Europe, the establishment of standardisation of genotypic resistance testing in Europe, the documentation of interpretation systems for genotypic resistance data, the assessment of resistance among non-B subtypes, and the comparison of results from different phenotypic assays. The Euroguidelines website (http://www.euroguidelines.org) records the different initiatives from the group. The EuroGuidelines Group has currently obtained charitable status in the UK.

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DHSS panel revises guidelines for therapy initiation

A revision of the United States Department of Health and Human Services (DHSS) guidelines for the use of antiretroviral agents was released with media fanfare during the 8th Conference of Retroviruses and Opportunistic Infections (CROI) held in Chicago this February (www.hivatis.org). Attention was focused on new recommendations to delay therapy in asymptomatic patients until CD4 cell counts reach 350 cells/mm^3 or until HIV RNA levels reach 55,000 copies/mL. The prior guidelines recommended therapy initiation earlier in disease course defined by a higher CD4 (500 cells/mm^3) and a lower HIV RNA threshold (20,000 copies/mL).

The issue of «when to start therapy» has remained a contentious and controversial subject for over a decade. For the tiny proportion of patients identified prior to seroconversion during acute HIV infection, immediate therapy offers the theoretical benefit of preserving HIV specific immunity (Rosenberg *et al.* Nature 2000; 407: 523-6). However, for the majority of patients identified during asymptomatic infections when CD4 cell counts are well above 200 cells/mm^3, there remains uncertainty on the relative risks and benefits of immediate therapy. What has pushed provider and patient alike to initiate therapy later is the recognition that toxicities of currently used

agents are common, unpredictable, and may not be reversible. Glucose intolerance, osteoporosis, lipoatrophy, elevated lipids– these effects may be worse than HIV disease progression itself.

Data presented at the 8th CROI was somewhat reassuring to the argument to delay therapy. Waiting to initiate therapy until patients meet currently recommended CD4 and HIV RNA thresholds did not appear to jeopardize rates of viral suppression or disease course, at least over one to two years (Sterling *et al., Abstract 520*; Kaplan *et al.*). In addition, data from PCP studies demonstrate that immunity to opportunistic infections is reconstituted even in patients who start therapy at very advanced stages of disease (Lopez Bernaldo de Quiros *et al.* NEJM 2001; 344: 159-67; Ledergerber, *et al.*, NEJM 2001; 344: 68-74). And finally, in patients with high CD4 cell counts, HIV related events are rare over the short-term.

The long –term consequences of delaying therapy, however are not known. From a public health standpoint, the new recommendations could potentially increase HIV transmission. In addition, the incentive for early HIV testing–access to treatment– is lost when asymptomatic individuals are counseled that treatments are too toxic. From an individual standpoint, delaying therapy could result in irreversible changes not yet realized. For example, decline in cognitive function due to ongoing HIV replication might not manifest itself for 10 years in individuals who choose to postpone therapy.

For now, though, with the uncertainly surrounding drug toxicities, the current guidelines advocating therapy delay have been embraced if not already implemented by many. It would be difficult to argue that these new recommendations reflect «progress» in the field. In fact, one would only hope that these guidelines merit revision in the near future because advances are made in the understanding or prevention of drug toxicities. It is clear that «progress» in this field will require identification of simpler, more tolerable, affordable therapeutic interventions that tip the balance to favor earlier therapy.

Eradication of HIV does not appear possible with the current generation of therapies due to their limited potency and the pool of long-lived latently infected cells.

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Expanding cell tropism of HIV-1

Although CD4 is still the main receptor for HIV-1, with CD4-positive cells the main target cells, recent results suggest that the cell tropism of HIV-1 is larger than previously appreciated. Saha *et al.* (Nature Medicine 2001; 7: 20-1) reported for the first time the characterisation of a primary isolate with dual tropism, using independently either CD4 or CD8 as receptor. It is not clear which co-receptor is being used by this virus strain, since infection of CD8 cells was independent of CXCR4 or CCR5 co-receptors. The virus had a different envelope sequence than viruses infecting solely CD4 cells, although no clear link with CD8 tropism has been demonstrated yet. Almost simultaneously, Igarishi *et al.* (Proc Natl Acad Sci USA 2001; 98: 658-63) reported on the high replication of SHIV strains (SIV carrying the HIV envelope) in experimentally infected monkeys even after CD4 cells were depleted. In these monkeys, 95% of infected cells were macrophages, suggesting that macrophages are a more important viral reservoir than previously suspected. Both these papers point towards additional viral reservoirs that have to be eliminated if ever an antiviral therapy is intended to eliminate HIV from the body. Antiviral drug design should now also focus on these CD8 cells and macrophages.

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