

THE HOPKINS HIV REPORT

A bimonthly newsletter for health care providers

Report from Seattle: The 9th Conference on Retroviruses and Opportunistic Infections (CROI)

When to Start HAART: Still a Controversy

By Timothy R. Sterling, M.D.

There were several presentations at the CROI on the controversial issue of when to initiate highly active antiretroviral therapy (HAART) in asymptomatic HIV-infected patients. Although HAART significantly decreases clinical disease progression, currently available drugs are unlikely to eradicate HIV infection. In addition, HAART has been associated with substantial toxicity, such as hyperglycemia, hyperlipidemia, lipodystrophy, and lactic acidosis. Because there have been no prospective, randomized trials to determine the most appropriate time to initiate HAART, we must rely on data from observational cohort studies. A recently-published study by Hogg suggests that HAART could be initiated at CD4 counts substantially lower than 500 cells/mm³, but should be initiated before CD4 counts drop below 200 cells/mm³ [*JAMA* 2001; 286:2568-77]. Two studies from the Johns Hopkins HIV Clinic database have demonstrated that HAART does not have a significant impact on clinical disease progression when initiated at CD4 counts >350 cells/mm³, but that HAART is associated with substantial rates of drug toxicity and non-durable virologic suppression [Sterling TR, et al. *AIDS* 2001;15:2251-57; Sterling TR, et al. *Clin Infect Dis* 2001; 33:1205]. Supporting the claim that HAART can be initiated at relatively low CD4 counts, Philips and colleagues have shown that virologic



suppression is possible even among individuals with a low CD4 count and high viral load prior to starting therapy [*JAMA* 2001;286:2560-7]. Although several studies presented at this conference supported delaying initiation of therapy until the CD4 count is in the 200-350 cells/mm³ range, one study suggested that therapy should be initiated at CD4 counts >350 cells/mm³ [Palella, Abstract 13].

In a study from British Columbia, Wood and colleagues assessed the cumulative mortality rate among a cohort of 1,416 patients who initiated HAART between August 1996 and July 2000 [Abstract 465]. The overall crude mortality rate was 7.8%. The mortality rate was higher among persons with CD4 counts <200 cells/mm³ than among those with >200 cells/mm³ prior to initiating HAART. The mortality rate was also increased among non-adherent patients (defined as patients who received <75% of their medications during their first year of therapy). In addition, the risk of death was increased among patients treated

continued on page 2

Antiretroviral Toxicities Take Center Stage at the 9th CROI

By Gregory M. Lucas, M.D.

As the natural history of HIV disease in developed countries has become synonymous with the natural history of combination drug therapy, clinicians who care for HIV-infected patients are increasingly becoming acquainted with the long-term adverse effects of antiretroviral therapy, which include both subtle and dramatic toxicities. The fact that seven of the nine late breaker presentations at the 9th CROI addressed antiretroviral toxicity is an indication of the growing importance of drug toxicity as a focus of ongoing research efforts.

Epidemiology and Basic Science

- **Atherosclerotic Vascular Disease:** While antiretroviral agents are clearly associated with both short- and long-term toxicities, it's worth reminding ourselves of the big picture. The widespread use of HAART has been associated with a 70% decline in mortality among HIV-infected individuals, a magnitude of effect similar to the introduction of insulin therapy for type I diabetes. Sam Bozzette presented data from 36,766 U.S. veterans treated for HIV between 1993 and 2001 underscoring this point [Abstract LB9]. Antiretroviral use increased from 23.1 to 60.1 years of exposure/100 person-years during this time period, while all-cause mortality fell from 18 to 5/100 person-years. The adverse effects of HAART on atherosclerotic vascular disease

continued on page 4

Inside This Issue

HIV and Hepatitis C5
Treatment of Antiretroviral-Experienced
Patients and Immune-Based Therapy7

New Drugs in Clinical Development and
Treatment of Naïve Patients10

New Drugs:
Attacking Chemokine Receptors12



When to Start HAART: Still a Controversy

continued from page 1

by physicians with less experience in the management of HIV (defined as treating <5 HIV-infected patients). In a multivariate model that adjusted for AIDS at baseline, age, baseline viral load and baseline CD4 count, patients who received >75% of their prescribed medications were 70% less likely to die, and patients whose physicians were more experienced were 33% less likely to die.

This author reported on a study from the Johns Hopkins HIV Clinic, in which 1,130 patients received HAART between July 1996 and June 2001, and clinical disease progression (defined as development of a new opportunistic infection or death) was assessed in patients with durable vs non-durable virologic suppression [Abstract 469]. Durable suppression was defined as more undetectable (<400 c/mL) than detectable viral load measurements. There was no difference in clinical disease progression among patients with durable vs non-durable suppression among those who had baseline CD4 counts >350 cells/mm³, but among patients with baseline CD4 counts <350 cells/mm³, durable virologic suppression was associated with a lower rate of disease progression. However, among patients with baseline CD4 counts <350 cells/mm³ who achieved durable virologic suppression, there was no difference in disease progression among those with baseline CD4 counts <50, 51-200, or 201-350 cells/mm³. The authors concluded that after a relatively short period of follow-up (median 30 months), initiation of therapy at low CD4 counts did not have a negative impact on subsequent disease progression, as long as patients were able to achieve durable virologic suppression. Although this study did not include data on adherence to therapy, other studies have shown that adherence is extremely important for achieving durable virologic suppression. This underscores the importance of addressing issues that would improve adherence (e.g., substance abuse) prior to initiating therapy.

In a study from Abbott Laboratories, the impact of baseline CD4 count and viral load on durable virologic suppression was assessed among patients randomized to receive either lopinavir/ritonavir (LPV/RTV) + d4T + 3TC or nelfinavir + d4T + 3TC [King, et al. Abstract 470]. Patients were followed through 96 weeks.

Low baseline CD4 count and high baseline viral load did not have a substantial impact on the durability of virologic response in persons in the LPV/RTV arm. However, in patients treated with the nelfinavir-based regimen, the durability of virologic response was diminished in persons with lower baseline CD4 counts and higher baseline viral loads. Of note, data on adherence to either regimen were not presented.

In a study from the Swiss HIV Cohort Study, clinical disease progression was assessed among persons who did not achieve virologic suppression while on HAART [Egger, Abstract 471]. They assessed the area under the viral load curve (AUC) as a measure of average viral burden, and assessed its value as a predictor of clinical disease progression on therapy. As one might expect, higher average viral load over time was associated with an increased risk of progression to a new AIDS event or death. The probabilities at 5 years were as follows:

Average Viral Load (per year)	Rate of New AIDS Event or Death
<3.0 log	7.2%
3.0-3.99 log	20.6%
4.0-4.99 log	38.7%
>5.0 log	79.1%

In an HIV clinic-based study of trends in treatment use and virologic suppression, Lampe and colleagues demonstrated that between 1999 and 2001 there was a steady increase in the proportion of patients who were treated with HAART (increasing to 70% by 2001), as well as in the proportion of patients who achieved virologic suppression [Abstract 477]. The proportion of patients with viral load <400 c/mL increased from 71% to 85% among all treated patients, and from 79% to 88% among patients on HAART for >30 weeks.

In another study from the Johns Hopkins HIV Clinic, Perez and colleagues found that HAART had a greater impact on survival in persons >50 years old (n=253) than in those <50 years (n=535) [Abstract 472]. Among patients who did not receive HAART, older patients were significantly more likely to die than younger patients. However, among persons treated with HAART, there was no difference in survival

between older vs younger groups. Stratification by CD4 count <350 cells/mm³ did not change the survival curves. These data emphasize the importance of treating HIV-infected patients >50 years old with HAART and the substantial survival benefit that such therapy provides.

A study presented by Palella suggested that initiation of antiretroviral therapy among patients with baseline CD4 counts >350 cells/mm³ was associated with improved survival [Abstract 13]. This is consistent with data presented at the 8th CROI by Opravil [Abstract LB6], but contradicts the majority of data published in peer-reviewed literature to date. Palella's analysis assessed patients according to whether or not they initiated antiretroviral therapy (not limited to HAART) while within a specific CD4 stratum, or delayed therapy until entering a lower CD4 stratum. The CD4 strata were 501-750, 351-500, and 200-350 cells/mm³. In each of the three strata, more than two thirds of the delayers started therapy at the next lower stratum. For persons with CD4 501-750 cells/mm³, the mortality rate per 100 person-years was 7.5 among those who started in that stratum vs 3.1 in those who delayed (relative risk: 2.38). In the 351-500 cells/mm³ stratum, the rates were 9.6 (initial) and 18.3 (delayed) per 100 person-years (RR: 0.52). In the CD4 350-201 cells/mm³ group, the mortality rate was 18.3 per 100 person-years among those who started in that stratum vs 69.3 among those who delayed therapy (RR: 0.26). A sub-analysis of persons who initiated HAART (instead of just any antiretroviral therapy, as in the baseline analysis) yielded similar results, but there was decreased power due to smaller sample size. Similarly, results were comparable when they assessed AIDS deaths as an endpoint instead of all deaths. The authors concluded that for persons in the 351-500 and 201-350 cells/mm³ CD4 strata, mortality rates were lower among persons who initiated therapy when they first were in those strata vs delaying therapy until they were in a lower CD4 stratum, and therefore, early initiation of therapy is warranted.

Reisler presented data on the incidence of grade 4 toxicity events, AIDS-defining events, and mortality in a large multi-center cohort of patients who were treated with HAART in one of 5 Community Programs



When to Start HAART: Still a Controversy

for Clinical Research on AIDS (CPCRA) HIV treatment studies [Abstract 36]. A total of 3,050 patients were enrolled in the 5 studies. In these five treatment trials there were 316 AIDS events and 663 grade 4 toxicity events. These rates varied according to CD4 count:

Entry CD4	AIDS Events	Grade 4 Toxicity Events
<200	19.7	30.1
200-399	6.1	26
>400	0.9	19.6

At 30 months of follow-up, the cumulative percentage of patients with any

grade 4 event was 27%, while the rate of developing an AIDS-defining illness was 13.4%. The most common grade 4 events were liver toxicity, neutropenia, pancreatitis, and anemia. The authors concluded that in this cohort, surprisingly, the incidence rate of grade 4 toxicity was twice the rate of AIDS events. The risk of death associated with a grade 4 event was similar to the risk of death associated with AIDS; however, the grade 4 events were not found to be attributed to HAART or to any specific HAART regimen. Nonetheless, this report confirms that there is substantial toxicity associated with the treatment of HIV.

Conclusion

The majority of the published data, as well as the data presented at this meeting,

support delaying the initiation of HAART until the CD4 count is in the 200-350 cells/mm³ range, though two studies suggest that it could be beneficial to initiate therapy at CD4 counts >350 cells/mm³. The optimal CD4 count between 200 and 350 at which to initiate HAART remains unknown. The risk of disease progression is lowest among persons who achieve virologic suppression, and suppression is more likely among persons who adhere to therapy. Persons who achieve durable virologic suppression do well, even if they initiate therapy at CD4 levels <200 cells/mm³. Clinician experience in the management of HIV infection also plays an important role in decreasing the risk of disease progression. ▲

THE HOPKINS HIV REPORT

EDITORIAL BOARD

John G. Bartlett, M.D.

*Professor of Medicine;
Director, Division of Infectious Diseases;
Director, The Johns Hopkins University AIDS Service*

Richard E. Chaisson, M.D.

*Professor of Medicine,
Epidemiology and International Health*

Emily J. Erbelding, M.D., M.P.H.

Assistant Professor of Medicine and Pediatric

Joel E. Gallant, M.D., M.P.H.

*Associate Director,
The Johns Hopkins University AIDS Service*

Kelly A. Gebo, M.D., M.P.H.

Assistant Professor of Medicine and Epidemiology

Gregory M. Lucas, M.D.

Assistant Professor of Medicine

CONTRIBUTING EDITORS

Jean R. Anderson, M.D.

Associate Professor of Obstetrics, Gynecology, and Medicine

Joseph Cofrancesco, Jr., M.D., M.P.H.

Assistant Professor of Medicine

James P. Dunn, M.D.

Assistant Professor of Ophthalmology

Charles W. Flexner, M.D.

*Associate Professor of Medicine,
Pharmacology and Molecular Science, and
International Health; Associate Director of Graduate
Training Program in Clinical Investigation*

Rajesh T. Gandhi, M.D.

*Instructor in Medicine Partners AIDS Research Center
Massachusetts General Hospital Boston, MA*

Douglas A. Jabs, M.D.

Professor of Ophthalmology and Medicine

Brooks Jackson, M.D.

*Professor of Pathology; Deputy Director for Clinical Affairs,
Department of Pathology*

Ciro R. Martins, M.D.

Assistant Professor of Dermatology

Justin C. McArthur, M.B., B.S., M.P.H.

Professor of Neurology and Epidemiology

Richard D. Moore, M.D.

Professor of Medicine and Epidemiology

Thomas C. Quinn, M.D.

*Professor of Medicine, International Health,
Molecular Microbiology and Immunology*

Robert Siliciano, M.D., Ph.D.

*Professor of Medicine,
Molecular Biology and Genetics*

Timothy R. Sterling, M.D.

Assistant Professor of Medicine

Glenn J. Treisman, M.D., Ph.D.

Associate Professor of Psychiatry and Medicine

Sharon M. McAvinue

Business Development

Mary Beth Hansen, M.A.

Managing Editor

Lisa Darrah, B.A.

Design and Production

SUPPORT

The Hopkins HIV Report is published six times per year by The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Publication of this newsletter is underwritten by a generous grant from Bristol-Myers Squibb Immunology; we gratefully acknowledge their support.

Visit The Johns Hopkins AIDS Service Website:

<http://www.hopkins-aids.edu>

©2002 The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Permission to use and reproduce portions of this newsletter is hereby granted, provided that author and publication are fully credited and both the copyright and permission notice appear. All other rights reserved.



Antiretroviral Toxicities

continued from page 1

risk factors (increased LDL levels, triglycerides and insulin resistance, and decreased HDL levels) have been well documented. Nevertheless, Bozzette's group observed no trend toward increased cardiovascular or cerebrovascular morbidity or mortality in this large group of veterans. In fact, the rates of hospital admissions or death due to vascular events declined slightly, from 2.0 cases/100 person-years in 1993 to 1.8/100 person-years in 1999. While this does not mean that increased vascular disease risk won't become evident with longer follow-up, it suggests that the added risk is unlikely to be dramatic.

• **Lactic Acidosis** has been correlated with prolonged exposure to nucleoside reverse transcriptase inhibitors (NRTIs), and prior reports have focused attention on d4T and ddI as major culprits. Data presented in Seattle provided additional evidence supporting these associations. A novel presentation of the lactic acidosis syndrome was described by Marcus based on data from the FDA's adverse event reporting system (AERS) [Abstract LB14]. Based on 5 cases of ART-associated lactic acidosis and profound motor weakness, suggestive of the Guillain-Barré syndrome, the FDA searched the AERS and identified 25 cases of combined lactic acidosis and severe motor weakness. Twenty-two of 24 patients were on d4T-containing regimens. Seven patients died, and NRTIs were continued in the face of illness in 18/24 cases, including 6/7 fatal cases. Additionally AERS identified 8 pregnant women who developed pancreatitis and/or lactic acidosis at ≥ 32 weeks gestation. All women were receiving d4T, and 7/8 were on d4T/ddI. The cases resulted in 3 maternal and 3 fetal deaths. While passive surveillance for adverse events may be subject to biases and cannot quantify risk because of the absence of a denominator, the dramatic nature of these presentations and the strong association with d4T (particularly in the pregnant women, in whom AZT is used much more commonly), suggests that the association between d4T and these rare events is real. Clearly the primary message of this report is that nucleoside analog therapy should be stopped promptly with any serious presentation of lactic acidosis.

Lonergeran presented data from UCSD looking at associations between specific NRTIs and symptomatic lactic acidosis in a cohort of 2,144 HIV-infected individuals [Abstract 35]. Lactic acidosis cases were defined as patients taking at least one NRTI who presented with gastrointestinal or

constitutional complaints and a serum lactate elevated above the upper limits of normal. There was a dose-response relationship between the number of NRTIs being taken and lactic acidosis, with each additional NRTI associated with a 2-fold increased risk (95% CI 1.3-3.4). Notably, substantially higher risks were observed for regimens containing d4T and/or ddI (Table 1, below). Five patients, all on d4T-containing regimens, had serum lactate levels >5 mmol/L, and 4/5 died. The main caveat of observational studies such as this one is that there may be a bias in the manner in which patients are evaluated. For example, clinicians at this university-based center may have had a lower threshold for obtaining serum lactate levels on the basis of mild symptoms if patients were taking antiretroviral drugs previously implicated in lactic acidosis. However, the strength of the observed associations and their reproducibility across several large studies suggests that a genuine association is being identified.

Adverse effects of NRTIs, such as neuropathy, pancreatitis, lipoatrophy, and lactic acidosis, have been linked to mitochondrial toxicity. Investigations of pathogenic mechanisms presented at the 9th CROI furthered the hypothesis that there is a hierarchy of toxicity risk among different NRTIs. The ratio of mitochondrial DNA to nuclear DNA (mtDNA/nDNA) was determined in 30 participants in the WATCH Trial [Côté, Abstract 707-T]. In this study, treatment-naïve patients were

Table 1. Association of Specific NRTI Combinations and Lactic Acidosis

Regimen	Incidence Rate (cases/1000 person-years)
Dual NRTI	
AZT/3TC	3.0
d4T/3TC	16.9
d4T/ABC	40.0
d4T/ddI	59.4
Triple NRTI	
AZT/3TC/ABC	12.7
d4T/3TC/ABC	103.4
d4T/3TC/ddI	119.0

[Lonergeran, et al. CROI 2002, Abstract 35]

randomized to receive AZT/3TC/NFV, d4T/ddI/EFV, or to alternate between these two regimens every 3 months. Comparing the mtDNA/nDNA ratio at baseline and 48 weeks may give insight into the relative mitochondrial toxicity of different antiretroviral regimens. For patients treated with AZT/3TC/NFV, the mtDNA/nDNA ratio was 45% of baseline at week 48 compared to 55% of baseline in the alternating group, and just 18% of baseline in the d4T/ddI/EFV group. Similarly, Birkus and colleagues from Gilead evaluated changes in mtDNA in *in vitro* systems of human liver, skeletal muscle, and renal proximal tubule epithelial cells treated with different NRTIs [Abstract 708-T]. They reported the following hierarchy of mitochondrial toxicity: ddC $>$ ddI $>$ d4T $>$ AZT $>$ 3TC = ABC = TDF. While *in vitro* data should never be taken as the final word, these results are consistent with toxicities observed in epidemiologic studies.

Treatment and Switch Studies

• **Lipoatrophy** has been a particularly dreaded long-term complication of HAART because it is so stigmatizing and because there has been no convincing evidence that it is reversible. At CROI, several of abstracts provided a glimmer of hope that switching from d4T to other NRTIs may not only stop fat loss, but begin to reverse the process. Carr and co-workers presented 24-week data from a study in which 111 patients with moderate to severe lipoatrophy were randomized to switch from either d4T (84%) or AZT (16%) to ABC, or to remain on their current regimen [Abstract 32]. The primary outcome was change in limb fat mass, measured by DEXA and CT scanning.

Statistically significant increases in limb fat were observed in the switch group compared to patients remaining on their current regimen. Further supporting the role of d4T in lipoatrophy was the observation that improvements in limb fat were only noted in patients switching from d4T to ABC, and not in those switching from AZT to ABC (although numbers for this comparison were small). However, switching to ABC was not associated with improvements in insulin resistance, serum lipids, or patient-physician perceptions of the severity of lipoatrophy. Although Carr suggested that longer follow-up may lead to clinically meaningful improvements in lipoatrophy, it is disappointing that patients and physicians did not notice the change at 6 months, particularly

continued on page 9



HIV/hepatitis C (HCV) co-infection was a particularly hot topic at the 9th CROI. Cohort studies continued to produce data regarding the long-term complications of HCV infection as well as the interaction of HAART and HCV, and treatment trials with both pegylated and non-pegylated interferon alpha with ribavirin were presented.

Epidemiology—China

Zhang and colleagues used molecular epidemiologic techniques to track HIV and HCV outbreaks in China in the past year [Abstract 16]. Two distinct outbreaks of HIV and HCV occurring in different regions of China were reported: one due to contaminated blood products and blood donation techniques and the other due to injection drug use (IDU). Using molecular epidemiologic tools, they discovered that illegal blood donors and recipients of these blood products had HIV subtype B and HCV genotypes 1 and 2, whereas IDUs had HIV subtype C and HCV genotypes 1, 2, and 3. Zhang concluded that while government officials have made attempts to stop illegal blood donation, transmission is clearly still occurring, and more governmental interventions will be needed to prevent further transmission.

Diagnosis

Carten and colleagues reported data from a study investigating the comparative sensitivity of HCV antibody against qualitative RNA screening for HCV in HIV-infected patients [Abstract 642]. They screened 221 patients in their urban cohort and found 16% positivity by antibody test. Seventy-seven percent of those with positive antibody had positive viremia, but there were no false negatives by antibody. Therefore, they concluded that HCV antibody was a reasonable screening test for the presence of HCV in HIV-infected individuals.

Complications of Hepatitis C: Morbidity, Mortality and Hospitalizations

Several studies were presented that showed worsening morbidity in the HIV/HCV co-infected population, but data on mortality were conflicting. With 10 years of follow-up data from the Atlanta HIV VA cohort, Rimland and colleagues reported a decrease in survival time from the diagnosis of AIDS [Abstract 658]. Controlling for CD4 count at the time of HCV diagnosis, use of antiretroviral therapy, and history of opportunistic infections, the

time from AIDS diagnosis to death was significantly shorter in HCV/HIV co-infected patients (Hazard Ratio 1.48, 95% CI 1.096, 1.985) as was time from HIV diagnosis to death (HR 1.39, 95% CI 1.02, 1.89).

Tedaldi presented approximately 5 years of follow-up data from the three HIV Outpatient Study (HOPS) sites [Abstract 659]. While deaths per 100 person years of follow-up were higher among HIV/HCV co-infected individuals (3.4 vs 1.7 per 100 PY, $p = .008$), after adjustment for baseline CD4 count and number of weeks on HAART, there was no statistically significant difference in survival time between those who were co-infected and those with HIV alone.

This author reported that while hospitalizations decreased between 1995-97 and remained flat between 1998-2000 in HIV-infected but HCV negative patients, there was a significant increase in hospitalizations for HCV/HIV co-infected patients between 1998-2000 [Abstract 660]. The bulk of the increase was due to problems related to liver disease (GI hemorrhage, hepatic encephalopathy, hepatorenal syndrome, hepatocellular carcinoma, hepatitis, chronic liver disease, or necrosis of the liver). IDU related complications remained stable between 1995-2000, while the incidence of opportunistic infections decreased between 1995-97 for both HCV negative and HCV infected patients.

HCV Treatment

Multiple studies were presented on the treatment of HCV/HIV co-infected patients. Sulkowski reported data from a multicenter randomized study of interferon (IFN) alpha 2b plus ribavirin in co-infected patients (HRN-002) [Abstract 651]. This study involved patients who had detectable serum HCV RNA, compensated liver disease, and were on stable HAART regimens. One hundred eighty patients were randomized: 90 to IFN alpha 2b 3 MU qd plus ribavirin 800 mg qd and 90 patients to IFN alpha 2b 3mU three times weekly (tiw) with the same dose of ribavirin. By intent to treat analysis at 12 weeks, daily IFN plus ribavirin was significantly more effective than standard tiw IFN and ribavirin (25.2% vs 9.8%, $p = .01$). However, there were significant side effects, most commonly psychiatric complications and asthenia that led to discontinuation of treatment in 20 patients (10 in each group) prior to 12 weeks. Perez-Olmeda and colleagues reported data from the Spanish HIV Interferon Ribavirin Trial

(SHIRT) that demonstrated similar findings [Abstract 653]. One hundred eleven patients were randomized to receive standard dosing of IFN 3mU tiw for 6 months with ribavirin 800 mg PO bid or induction therapy with IFN 6mU daily for 6 weeks followed by IFN 3mU tiw for 6 months with the same dose of ribavirin. The study population was predominately male (82%); 47% had HCV genotype 1, 38% had genotype 3, and 15% had genotype 4. The combination of IFN and ribavirin was well tolerated, with 12% of patients discontinuing treatment due to side-effects. Sustained viral response was achieved by 22%, with no difference between treatment arms. Of note, 70% of responders had HCV genotype 3. The researchers hypothesized that the relatively low rate of sustained viral response in this trial may be explained by the relatively short duration of therapy (6 months) for patients with genotype 1.

Perez-Olmeda also presented safety and efficacy data from another Spanish study on pegylated IFN plus ribavirin [Abstract 652]. Sixty-five patients, all of whom were naive to IFN were treated with Peg-IFN (Schering-Plough) 150 mg sc once weekly plus ribavirin 400 mg PO bid in an open-label fashion for 6-12 months. Sustained viral response was seen in 33%, but only 10% had genotypes 1 or 4. In addition, adverse events led to discontinuation of drug in 14% of patients. Adverse events included weight loss greater than 10% of pre-study weight in 70% of patients and a significant CD4 drop in 3% of study patients, though no increases in plasma HIV RNA were seen.

Sherman and colleagues reported data from ACTG 5071/5091 on IFN-2a with ribavirin vs pegylated IFN plus ribavirin [Abstract 122]. There were five patients in each arm; one patient had cirrhosis on liver biopsy, and 9/10 of patients had HCV genotype 1. The authors reported that while Peg IFN had a slightly delayed onset of action compared to IFN (9 hrs vs 7.7 hrs), the efficacy was greater (90% vs 65%), and it appeared to increase phase 1 HCV viral clearance (194 days vs 2398 days, $p < .05$). They concluded that by increasing the phase 1 viral clearance, viral clearance predicted by phase II kinetics may also be more rapid.

Chung also presented data from ACTG A5071, in which 133 patients were randomized to receive IFN alpha 2a 6MU tiw for 12 weeks followed by 3MU for 26 weeks

continued on page 6



HIV and Hepatitis C

continued from page 5

versus Peg-IFN alpha 2a 180 mcg per week for 48 weeks [Abstract B15]. Patients in each arm also received ribavirin beginning at 600 mg per day and escalating to a maximum of 1 g per day. By intent-to-treat analysis, Peg-IFN had superior week-24 viral response compared with IFN alpha 2a (44% vs 15% p =.0003). The Peg group experienced more grade 4 toxicity events (17 vs 5, p=.004), but premature discontinuation of the drug was the same in both groups (15% vs 12%). Data on sustained viral response were not presented, but will be especially interesting in this group of patients, as relapse is common.

HIV Treatment With HCV Co-infection

The question of the interaction of HAART and HCV RNA was further

discussed at this meeting. Dietrich and colleagues conducted a retrospective analysis of 1,325 HCV/HIV co-infected patients treated with protease inhibitors for at least 3 months [Abstract 663]. Mean time on PI-containing HAART was 37.8 months. Thirty-nine percent received nelfinavir, 32% indinavir, 17% saquinavir, 13% ritonavir, and 1% amprenavir. Overall, patients had a mean increase in CD4 count of 160 cells/mm³ and a decrease in viral load of 1.12 log₁₀ c/mL. Six percent had grade 3 or 4 elevations in AST, whereas only 3% of those on nelfinavir had this toxicity. The mean increase in CD4 count was higher than with any of the other PIs. In conclusion, nelfinavir was found to be a safe and efficacious treatment for HIV in co-infected patients.

Law reported data from a cohort of Thai HIV-infected patients enrolled in 8 HIV NAT trials [Abstract 661]. All 692 patients had received at least two nucleosides, while 215 received an NNRTI, and 135 received a PI. The prevalence of HCV was 7.7%. Despite longer time to viral suppression, median HIV RNA reductions were approximately 1.5 log₁₀ c/mL regardless of HCV status. In addition, HIV disease progression was similar. They concluded that although it takes longer to achieve viral suppression in co-infected patients than in those without HCV, there are no significant sequelae of this delay.

Hare also presented data on the effect of viral hepatitis in HIV-infected patients treated with HAART [Abstract 662]. A higher incidence of chronically elevated ALT was found in patients co-infected with viral hepatitis, and nevirapine was the only antiretroviral agent associated with increased liver toxicity among co-infected patients in their population. In addition, those with HCV were significantly less likely to receive antiretroviral therapy than those without (AOR 0.35, 95% CI 0.13, 0.92).

Other Treatments: Transplant, Hepatitis A Vaccination, and Abstinence from Alcohol

Two studies regarding transplant in patients with HCV/HIV co-infection were presented. Ragni presented mortality data on 26 liver transplants performed at 5 sites [Abstract 125]. Of the 26 patients, 17 had end-stage liver disease due to HCV, 6 from HBV, and 3 had fulminant liver failure. The primary HIV risk factor was hemophilia in 27%. Seven deaths were reported from HCV: one from post-operative pancreatitis and one from acute liver

rejection. Post-operatively, most patients tolerated HAART well, with the mean VL being <50 c/mL, and an increase in mean CD4 count from 250 to 295 cells/mm³ (p<.01).

Roland presented data on liver and kidney transplantation in HIV-infected patients [Abstract 655]. Eligibility criteria included no history of OI, with a CD4 count >200 cells/mm³ for kidney transplants and >100 cells/mm³ for liver transplants. Other criteria included undetectable viral load or, for liver patients, detectable HIV RNA off HAART with prediction of viral control post-transplant. Eight centers identified 23 eligible subjects (10 liver recipients and 13 kidney recipients). Two deaths occurred: one due to recurrent HCV at 14.5 months, and another due to ischemic bowel 6 months post kidney transplant. All but one graft remained viable. No opportunistic illnesses have been reported in this cohort, though in six comparison patients who did not meet inclusion criteria but were transplanted, two died from PML, and one developed MAC and aspergillosis. These two preliminary studies indicate that in patients with viable HAART options, liver transplant may be feasible for those with end stage liver disease, though further studies regarding transplant in this population will need to be completed.

While pharmacologic treatments dominated most of the hepatitis management discussion, Teshale and colleagues from Atlanta revealed that some of the most effective preventive treatments, such as vaccination for hepatitis A and abstinence from alcohol, are underutilized in this population [Abstract 665]. They conducted a study of 1933 HIV/HCV co-infected patients identified as part of the Adult/Adolescent Spectrum of HIV Disease cohort. Only 6% of the co-infected patients had been vaccinated against hepatitis A, and 20% of co-infected patients were still using alcohol after diagnosis of HCV. These findings suggested that increased efforts should be made by providers to vaccinate against hepatitis A and to instruct patients on the potential interaction of alcohol and HCV.

While optimistic data regarding treatment of both HIV and HCV in co-infected patients were presented at the 9th CROI, long term effects of co-infection, including increased mortality and morbidity, suggest that these patients should be followed carefully. In addition, preventive treatment including abstinence from alcohol and hepatitis A vaccination should be incorporated into routine care. ▲

EDITORIAL POLICY & DISCLAIMER

Organizations providing financial support do not participate in the editorial process or otherwise influence editorial decisions. The information presented in *The Hopkins HIV Report* represents the standards of care of the Johns Hopkins University AIDS Service. Every effort is made to ensure the timeliness and accuracy of information presented in this newsletter, but standards of care change rapidly; therefore, the authors, editors, and publisher will not in any way be held liable for the timeliness of information or for errors, omissions, or inaccuracies in this publication. Readers should review carefully the product information contained in manufacturers' package inserts for any drug mentioned in this publication; mention of products does not constitute endorsement.

THE HOPKINS HIV REPORT IS FREE

Are you reading a copy of the *Hopkins HIV Report* that belongs to someone else? Request your own using one of two easy methods (why not? It's free.):

- The easiest: Go to <http://hopkins-aids.edu>, click on "Publications" (at the top of the screen), look for the *HHR* link, then click on "Subscribe online," fill out the form, and submit.
- The other method: Send your name and complete mailing address to:

The Hopkins HIV Report, Distribution
P.O. Box 651266
Potomac Falls, VA 20165-1266

Change of address? Please let us know by sending a postcard with both your old (very important) and your new address to:

The Hopkins HIV Report, Change of Address
P.O. Box 651266
Potomac Falls, VA 20165-1266

Problems: If you have requested the newsletter and are not receiving it (the *HHR* is published every other month—Jan., Mar., May, June, Sept., Nov.), send a postcard to the address listed above or an e-mail to: hivreport@PMR-printing.com

All other correspondence should be sent to:

Mary Beth Hansen, M.A.
Managing Editor, HHR
JHU ID @ Lighthouse Point
2700 Lighthouse Point, STE 220
Baltimore, Maryland 21224



Treatment of Antiretroviral-Experienced Patients and Immune-Based Therapy

By Gregory M. Lucas, M.D.

The treatment of antiretroviral therapy experienced patients is critically linked to using available data to construct a new regimen with adequate potency and tolerability. This article will review data presented at the 9th CROI on: The efficacy of new drugs in experienced patients, the meaning of “blips” and low level viremia in treatment experienced patients, and the role of immune-based therapies (notably IL-2) and therapeutic vaccines in treating HIV-infected patients.

New Agents in ART Experienced Patients

• **Tenofovir DF (TDF)** is a nucleotide reverse transcriptase inhibitor that was recently approved by the FDA exclusively on the basis of safety and efficacy data in ART experienced patients. Final 48-week data was presented from Study 907, in which heavily experienced HIV-infected individuals were randomized to receive TDF 300 mg qd or placebo in combination with their current antiretroviral regimen for 24 weeks, followed by open label TDF in all participants from week 24 on [Squires, Abstract 413-W]. TDF was as well tolerated as placebo and produced a durable 0.6 log₁₀ reduction in HIV RNA.

The signature resistance mutation selected *in vitro* by TDF, K65R, is rarely seen *in vivo* [Margot, Abstract 414-W]. There has been considerable interest in the association of classic thymidine-associated mutations (TAMs) in predicting the efficacy of TDF, and this was addressed by Miller from Gilead [Abstract 43]. Baseline genotype and phenotype assays were performed in subjects in Studies 902 and 907. There was a dose-response relationship, with greater numbers of TAMs at baseline associated with a poorer response to TDF. More importantly, however, mutations at amino acid residues 41 and 210 were particularly associated with decreased efficacy (Table 1, below).

M. Miller pointed out that there are two minority pathways of TAM development: 67, 70, and 219 or 215, 41, and 210. The former path is associated with a good response to TDF, while the latter is associated with a poor response. Multiple TAMs will clearly prove to be the primary mechanism of resistance to TDF, although high-level resistance is occasionally mediated by the K65R mutation or the T69S double insertion [Abstract 43]. Miller also presented results of a recursive analysis of baseline phenotypic susceptibility to TDF, which suggested two clinically relevant cutoffs. Patients with <1.4-fold change in the 50% inhibitory concentration (IC₅₀) experienced a 0.77 log₁₀ decrease in HIV

Table 1. Response to Tenofovir, According to Specific TAMs Present at Baseline

TAMs Present at Baseline	Average Change in HIV RNA (log ₁₀ c/mL)
0	-0.8
1-2	-0.7
≥3, including 41 or 210	-0.2
≥3, excluding 41 or 210	-0.7

[Miller, et al. CROI 2002, Abstract 43]

RNA; patients with an IC₅₀ between 1.4-fold and 3.8-fold experienced a 0.47 log₁₀ decrease in HIV RNA, while those with an IC₅₀ >3.8-fold demonstrated a 0.24 log₁₀ decrease in HIV RNA, consistent with high level resistance.

• **T-20** is the first in a novel class of anti-retroviral agents, the fusion inhibitors, and is anticipated to play a major role in salvage therapy. Results were presented from an open-label trial in which 71 PI-experienced, NNRTI-naïve participants were randomized to receive a regimen of ABC/RTV/APV/EFV or this regimen plus varying doses of T-20 (50, 75 or 100 mg bid) [Lalezari, Abstract 418-W]. Approximately two-thirds of the subjects had failed ≥2 prior PI-based regimens.

Considering the T-20 recipients in aggregate, 55% achieved HIV RNA <400 c/mL at 48 weeks compared to 37% in the placebo arm, and the corresponding CD4 cell increases were 132 and 90 cells/mm³. Though there was evidence of a dose-response relationship between viral load reduction and T-20 dose, 31% in the highest T-20 dose arm discontinued the study due to adverse effects (particularly local injection site reactions) compared to approximately 6% in the lower dose arms and 15% in the control arm.

Notably, patients in the higher dose T-20 arms had to receive two injections bid (four daily) of the 50 mg/mL formulation. A new 100 mg/mL preparation (which only requires one injection bid) has been determined to be bioequivalent to the 50 mg/mL preparation and hopefully will make the higher T-20 dose more tolerable [Wheat, Abstract 417-W].

• **Atazanavir (ATV)** is a protease inhibitor (PI) in late-stage development at Bristol-Myers Squibb, with a remarkably low propensity for raising lipids that is likely to be the first PI approved for qd administration. Although the potency of ATV has not been striking, and this agent is not anticipated to be a heavy-hitter in PI salvage, results were presented from a trial in which HIV-infected patients with a history of prior virologic failure on a PI were randomized to receive 2 NRTIs plus either ATV 400 mg qd + SQV 1200 mg qd, or ATV 600 mg qd + SQV 1200 mg qd, or RTV 400 mg + SQV 400 mg bid [Haas, Abstract 42]. At baseline, 88% of patients had prior PI exposure, and 30% were NNRTI experienced. Results at 48 weeks are shown in Table 2 (below). By intent-to-treat analysis, only about 40% of patients achieved a 1 log₁₀ reduction in HIV RNA or were <400 c/mL at 48 weeks, and proportions were similar in the three study arms. However, the RTV/SQV arm was plagued by a substantially higher dropout rate due to regimen intolerance (30% compared to approximately 10% in the ATV arms). Notable is the favorable lipid profile with ATV/SQV compared to RTV/SQV, although unconjugated hyper-bilirubinemia was more common with ATV, and was dose-related.

• **Tipranavir (TPV)** is a PI in development at Boehringer Ingelheim that may play an important role in salvage therapy. Forty-one patients who had

continued on page 8

Table 2. Comparison of Saquinavir + Atazanavir or Ritonavir in Salvage Therapy, 48-Week Results

Variable	ATV (400 mg)/ SQV (N=34)	ATV (600 mg)/ SQV (N=28)	RTV/SQV (N=23)
Change in log ₁₀ VL	-1.44	-1.19	-1.66
Change in CD4 count	+109	+55	+149
% Change in LDL cholesterol	-1	-7	+23
% Change in triglycerides	-5	-27	+93
Grade 3/4 hyperbilirubinemia, %	16	33	9

[Haas, et al. CROI 2002, Abstract 42]



Treatment of Antiretroviral-Experienced Patients and Immune-Based Therapy

continued from page 7

failed ≥ 2 prior PIs but were NNRTI naive were treated with EFV 600 mg qd, RTV 100 mg bid, at least one new NRTI, and were randomized to either low- or high-dose TPV [Schwartz, Abstract 562-T]. The results from this study were complicated by the fact that the formulation of TPV was changed mid-way through, from hard-filled capsules (HFC) to the self-emulsifying drug delivery system (SEDDS) [see Gallant, *HHV* 2001,13(5):8]. TPV was associated with durable viral suppression through week 80, regardless of baseline protease resistance mutations (Table 3, below). During therapy, mutations emerged at protease codons 82 and 33 in four of six patients with reduced susceptibility to TPV.

Two- vs Three-Class Salvage in NRTI-Experienced Patients

ACTG 364 was a double-blind, placebo-controlled trial, comparing the efficacy of second line therapy with 2 drug classes vs 3 classes in exclusively NRTI-experienced patients [Albrecht, Abstract 425-W]. One hundred ninety-six subjects with screening HIV RNA >500 c/mL were randomized to 1-2 new NRTIs plus NFV, EFV, or NFV + EFV. By intent-to-treat analysis at 48 weeks, 71% in the triple-class arm, compared to 58% assigned to EFV and 48% receiving NFV achieved HIV RNA <50 c/mL. In pair wise comparisons, subjects in the triple-class arm had a statistically significantly lower risk of experiencing virologic failure (HIV RNA >200 c/mL) during follow-up than subjects in the other two arms. This study is somewhat dated, as patients treated exclusively with non-suppressive NRTI therapy (an inclusion criterion) are substantially less common than they were a few years ago. Additionally, resistance testing would presumably be used in such patients in order to assess the degree of NRTI resistance and the need for triple-class therapy.

Blips and Low-Level Viremia: When to Switch

Now that HIV RNA is routinely measured using ultrasensitive assays in patients on therapy, it is unclear what level of viral activity is

associated with subsequent failure and should trigger a change in therapy. Havlir and colleagues have previously presented data that infrequent “blips,” defined as an HIV RNA >50 c/mL followed by suppression to <50 c/mL, were not associated with subsequent virologic failure in minimally-experienced patients treated with HAART [Havlir, et al. *JAMA* 2001;286:171]. At the 9th CROI, Havlir presented data from a similar analysis conducted on highly-experienced patients treated with salvage therapy in ACTG 398 [Abstract 93]. Approximately 25% of patients who achieved viral suppression in this trial experienced blips, which were not associated with prior antiretroviral exposure, baseline viral load, CD4 cell count, or resistance. Moreover, in this salvage trial, as in naive patients, blips were not associated with subsequent virologic failure.

Using mathematical modeling, Di Mascio and colleagues evaluated blips in 123 naive patients treated with HAART [Abstract 94]. Blips occurred randomly in approximately one out of every 10 viral load measurements in these patients and were independent of treatment duration. A blip was estimated to represent the release of 5×10^8 viral particles, which corresponds to 3×10^5 HIV-infected cells releasing virus. The latter is approximately the same size as the latent reservoir in resting T-cells, making it unlikely that blips represent release of virus from this compartment. The investigators hypothesized that blips were random cycles of viral replication, which are then rapidly cleared in another compartment.

Coakley and colleagues identified a cohort of 39 patients who had low-level viremia (defined as detectable HIV RNA $<1,000$ c/mL) for ≥ 12 months [Abstract 556-T]. Surprisingly, 32 of these 39 patients went on to maintain low-level viremia (non-progressors), compared to 7 who experienced viral rebound $>1,000$ c/mL (progressors) over a mean follow-up time of 22 months. While 90% had antiretroviral resistance by genotype assay, progressors were significantly more likely to have resistance to all agents in their regimen (86%) compared to non-progressors (27%). Progressors also had lower nadir CD4 cell counts (104 vs 278 cells/mm³) and higher peak viral loads ($137,657$ vs $50,527$ c/mL), compared to non-progressors. The interesting finding from this study was that there is a subset of patients who are able to maintain low-level viremia for long periods of time without overt virologic failure. However, this is probably an inherently unstable state, where a tenuous balance is struck among drug pressure, viral resistance, viral fitness and immunologic response.

Immune Based Therapies and Therapeutic Vaccination

• **IL-2:** Extended follow-up data were presented from ANRS 079 [Levy, Abstract 514-M]. In this trial antiretroviral-naive patients were randomized to receive either d4T/3TC/IDV alone (N=58) or HAART + IL-2 (N=58), given in 5-day cycles monthly (3 cycles), then bimonthly (7 cycles). After the formal end of the trial at week 74, 89% of participants agreed to continue in extended follow-up (64 more weeks on average), during which IL-2 was rarely used in either group. At last assessment the proportions maintaining HIV RNA <50 c/mL were similar in the two groups (78% for HAART alone and 76% for HAART + IL-2). The median changes in CD4 cell counts are shown in Table 4 (p. 9). The patients had a median CD4 count of approximately 350 cells/mm³ at enrollment. IL-2 must be administered by subcutaneous injection and is associated with considerable side effects. What remains unproven is whether the boost in CD4 counts mediated by IL-2 is associated with improved AIDS-free survival, or whether IL-2 would be helpful in targeted situations, as in patients with advanced disease who achieve viral suppression on HAART but have a poor immunologic response.

Forty-eight-week data were presented from the HYDRILE trial, in which 69 patients who had failed a PI-containing regimen, but were naive to NNRTIs and ABC were randomized to one of three groups: 1. d4T/ddI/ABC/EFV; 2. HAART + hydroxyurea (HU, 500 mg bid); or 3. HAART + HU + IL-2 [Lafeuillade, Abstract 424-W]. Patients had a mean CD4 count of 386 cells/mm³, a mean viral load of 4.0 log₁₀ c/mL, and had been exposed to a median of 4 NRTIs and 2 PIs. Intent-to-treat data at 48-weeks are shown in Table 5 (p. 9). Use of HU was associated with better viral suppression, and IL-2 mitigated the blunted CD4 response that is seen with HU. However, as has been noted in other trials and observational cohorts, discontinuations due to drug toxicity (pancreatitis, neuropathy, lactic acidosis) were significantly more common in the HU arms.

• **Therapeutic vaccination** has been proposed as a way to boost innate immune responses to HIV during therapy. Data from STI trials have suggested that HIV-specific helper T-cell response correlates with improved immune-mediated control of HIV and a lower viral load setpoint when HAART is stopped. However, this benefit seems to be restricted to patients who initiate HAART shortly following infection with HIV [Lori F, Lisziewicz J, *JAMA* 2001;286:2981].

Table 3. Mean HIV RNA Change (log₁₀ c/mL) From Baseline at Week 80 with Tipranavir, Stratified by Protease Resistance at Enrollment

TPV Dose	≤ 5 protease mutations	>5 protease mutations
Low	-2.1	-1.5
High	-1.9	-1.4

[Schwartz, et al. CROI 2002, Abstract 562-T]



Treatment of Antiretroviral-Experienced Patients and Immune-Based Therapy

continued from page 8

Table 4. Median Changes in CD4 counts (cells/mm³), HAART alone vs HAART plus IL-2

Study Timepoint	CD4 Change HAART alone	CD4 Change HAART + IL-2	CD4 Difference (IL-2 vs HAART alone)
Week 74 (end of trial)	+262	+835	+573
Last assessment (week 138)	+354	+641	+287

[Levy, et al. CROI 2002, Abstract 514-M]

Emilio Emini presented data from Merck's HIV vaccine development program in a plenary talk [Abstract L5]. Emini discussed two vaccine candidates: a plasmid "naked" DNA vector and a replication-defective adenoviral vector. Preliminary data in monkeys suggest that a "prime-boost" scheme, where the plasmid vaccine is followed by the adenoviral vaccine, may be most effective in eliciting SIV-specific cellular immune response. Phase I results from HIV-negative volunteers were also presented, suggesting that both vaccines were well tolerated, and produced durable anti-HIV cellular immune responses in a majority of participants (particularly the adenoviral vaccine). Further development of these vaccines will be required (namely to include a greater variety of HIV antigens), and clinical efficacy remains to be evaluated in both HIV-negative or HIV-positive individuals (i.e., as therapeutic vaccination).

Two abstracts presented at this conference looked at therapeutic vaccination with Remune in patients with established HIV infection. Robbins and colleagues reported that significant increases in HIV-specific CD4 proliferative responses were seen in 5/5 patients on stable HAART treated with Remune compared to 0/4 patients treated with HAART alone [Abstract 315-W]. Bucy presented results from a trial in which patients with viral suppression on HAART were randomized to receive Remune (N=20) or placebo injections (N=8) [Abstract 314-W]. All patients then underwent a treatment interruption. The slope of the initial rise in HIV RNA following therapy interruption was significantly lower in the Remune arm than in the placebo arm, and 5/15

Table 5. 48-Week Results of the HYDRILE Trial

Study Group	HIV RNA <200 c/mL (%)	Change in CD4 Count (cells/mm ³) from Baseline
HAART	25	+118
HAART + HU	59	-27
HAART + HU + IL-2	57	+78

[Lafeuillade, et al. CROI 2002, Abstract 424-W]

evaluable patients in the Remune group had a post-interruption peak HIV RNA <5,000 c/mL, compared to 1/6 in the placebo arm (P=NS). Trials are underway to evaluate Remune as an alternative to STI in recently infected individuals, who are more likely to have clinically meaningful responses, but are much harder to identify.

Conclusions

In summary, the recently approved drug, tenofovir, has modest potency in experienced patients, but is well tolerated and has a durable effect, with slow development of resistance. Data presented at this conference suggest that its role in true salvage will be limited, as TAMs (notably 41 and 210) are associated with lower efficacy. Ironically, this drug, which was approved on the basis of trials in ART-experienced patients, will likely be used more commonly in first line therapy or for intensification in early therapy. T-20 is the first representative of the fusion-inhibitor class likely to be approved, and will be important in salvage therapy, but probably not for early therapy, because it requires subcutaneous dosing.

Tipranavir is a PI in development that appears to retain potency despite extensive baseline PI-resistance. In contrast, ATV appears to be a modestly potent PI that has minimal activity in deep PI salvage situations. However, once daily dosing and a favorable lipid profile make it an attractive candidate for early therapy.

IL-2 causes impressive CD4 gains when combined with HAART; however, the clinical benefits of this injected therapy remain to be proven. Finally, therapeutic vaccination may be a way to have our cake and eat it too, in that HIV-specific immune responses are boosted without the risk of letting HIV out of its cage, as with structured treatment interruptions. Based on STI studies, the likelihood of clinical benefit from therapeutic vaccination is likely to be greater for patients treated with HAART in early HIV infection than in those who initiate treatment in the chronic phase of HIV infection. It remains to be seen whether the promising "prime-boost" vaccine strategy, under study at Merck, will be more effective than STIs in eliciting a clinically meaningful cellular immune response in patients chronically infected with HIV. ▲

Antiretroviral Toxicities

continued from page 4

because the open-label design of this study would be anticipated to bias subjective perceptions in favor of the new therapy.

A similar but smaller study of 40 subjects was presented in the poster session [John, Abstract 700-T], with results that were comparable to those reported by Carr. Additionally, another abstract reported subjective improvements in lipoatrophy in 20-30% of patients who had d4T replaced by either AZT or ABC [McComsey, Abstract 701-T]. However, in this study there was no control group that continued their present regimen.

• **Fat Accumulation:** Rosiglitazone is an antidiabetic agent that has been found to increase subcutaneous fat in patients with type 2 diabetes. Sutinen presented data from a double-blind trial in which 30 HIV-infected patients with lipodystrophy on HAART were randomized to receive either rosiglitazone or placebo [Abstract LB13]. At 24 weeks the rosiglitazone group had decreased insulin resistance compared to placebo. Unfortunately, there were no significant differences between the groups in waist-to-hip ratio, subcutaneous fat, or visceral fat (the latter two outcomes measured by MRI scan and serum leptin concentrations). Additionally, serum cholesterol and triglyceride levels were significantly increased in the rosiglitazone group compared to placebo.

In summary, studies of the toxicity of antiretroviral therapy have come to assume a prominent role in HIV research. Data from a large cohort of U.S. veterans suggested that changes in lipid and glycemic indices, which are associated with HAART, have not translated into a noticeable increase in vascular disease, at least not yet. After the 9th CROI, there can be few lingering doubts that d4T and probably ddI are the NRTIs most strongly associated with mitochondrial toxicity and its manifestations—lactic acidosis, neuropathy, lipoatrophy, and pancreatitis. Additionally, the FDA described a new syndrome of lactic acidosis and profound motor weakness (mimicking the Guillain-Barré syndrome) that also appears to be associated with d4T. However, for the first time, there are some objective data that lipoatrophy may be reversible when d4T is switched to AZT or ABC. Hopefully, these small but statistically significant changes in subcutaneous fat, now detected with sophisticated imaging technology, will eventually translate into clinically meaningful improvements with longer follow-up. ▲



New Drugs in Clinical Development and Treatment of Naïve Patients

By Joel E. Gallant, M.D., M.P.H.

New Drugs

• **TMC 125:** TMC 125 is a second-generation NNRTI from Tibotec-Virco that demonstrates *in vitro* activity against HIV that carries high-level resistance to the three currently available NNRTIs. At ICAAC in December, we heard exciting results from a phase 2 trial in which antiretroviral therapy-naïve patients taking TMC 125 monotherapy experienced an astonishing 1.92 log drop in viral load after only 7 days [Gruzdev, ICAAC 2002, Abstract 1-668]. At the CROI, Joep Lange retrospectively compared these results to those from the ERA trial, in which treatment naïve patients received AZT, 3TC, ABC, NVP, and IDV [Sankatsing, Abstract 5]. Patients on this 5-drug, 3-class regimen had a drop in viral load of 1.76 log₁₀ c/mL, similar to that seen with TMC 125 monotherapy. Although such cross-trial comparisons are always suspect, this is clearly a promising agent.

Of course, the real test for a second generation agent like TMC 125 is its ability to suppress virus resistant to currently available NNRTIs. Brian Gazzard presented data from Tibotec-Virco's C207 trial, in which 16 patients failing therapy with an NNRTI-based regimen were switched to TMC 125 (900 mg bid) for 7 days [Abstract 4]. At baseline, participants had high-level resistance to all available NNRTIs (mean 256-fold decrease in susceptibility to EFV), while susceptibility to TMC 125 was decreased by a mean of 3.2-fold (median 2.2-fold). Three patients had a single NNRTI mutation (103N or 188L); 8 had 2 mutations; 3 had 3 mutations; and one patient had 4 NNRTI mutations. After 7 days on TMC 125, participants experienced a mean decline in viral load of 0.86 log₁₀ c/mL; 44% had a decrease of >1 log. These results demonstrate promising activity against NNRTI-resistant virus. The reason for the more modest change in viral load compared to that seen in the naïve patients described above is unclear. Possible explanations include cross-resistance among the NNRTIs or residual drug interactions between the failing NNRTI and TMC 125. Interestingly, however, there was no relation between serum levels or baseline NNRTI susceptibility and virologic response.

• **DPC 083:** DPC 083 is another second generation NNRTI with impressive activity against NNRTI-resistant virus, though the

data presented at this conference do not clearly establish its future or its role in therapy. In trial 201, naïve patients were treated with EFV or one of three doses of DPC 083 (50, 100, or 200 mg qd) plus two NRTIs [Ruiz, Abstract 7]. Efficacy data were not presented in detail, but the four arms were said to be "highly effective." Patients taking DPC 083 were less likely to experience neuropsychiatric side effects than those taking EFV, but over half of the patients in the DPC 083 200 mg arm had rash, and 14 of 35 discontinued therapy because of rash. The 100 mg dose will be studied in phase III trials in naïve patients, but whether this will be the optimal dose for NNRTI-resistant patients has not been determined.

Ruiz also presented results from the 203 trial involving patients treated with 100 or 200 mg daily of DPC 083 after failing therapy with an NNRTI-based regimen [Abstract 6]. Not surprisingly, virologic response was correlated with the incorporation of new NRTIs in the new combination. However, the poor recruitment, high drop-out, and large number of protocol violations make this an inconclusive study, and one that does not allow dose selection for this patient population.

• **Atazanavir:** Atazanavir (ATV) is a new protease inhibitor from Bristol-Myers Squibb, expected to be the next approved PI and the first to be dosed once daily. Follow-up data from trials previously discussed in *The Hopkins HIV Report* [see Gallant, *HHR* 2002, 14(1):1] were presented, once again pointing out the fact that ATV does not cause the problems with cholesterol and triglyceride elevation that have been observed with all other protease inhibitors [Pillero, Abstract 706-T]. As noted in previous discussions of this drug, potency appears to be equivalent to that of nelfinavir. Follow-up data were also presented from the BMS 009 trial, in which ATV/SQV (400/1200 and 600/1200 mg qd) was compared with RTV/SQV (400/400 mg bid) in PI-experienced patients [Haas, Abstract 42]. After 48 weeks, patients in all three arms had viral load reductions >1 log₁₀ c/mL, though data on percent undetectable were not presented. Not surprisingly, the lipid profile was more favorable in patients treated with ATV/SQV than with RTV/SQV.

• **Tipranavir:** Tipranavir (TPV), an investigational PI from Boehringer Ingelheim, has a unique resistance profile making it an attractive agent for patients with PI-resistant

virus. It is co-administered with ritonavir to improve pharmacokinetics and drug levels, but the optimal dose regimen has not been determined. Trials involving TPV were presented at last year's ICAAC and were discussed in the last issue of *The Hopkins HIV Report*. Schwartz and colleagues looked at development of TPV resistance in patients enrolled in a phase II trial of two TPV/RTV dose regimens after failure of their second PI-based regimen [Abstract 562-T]. They found that TPV resistance was uncommon in this group of highly PI-experienced patients, and that virologic response to TPV was not predicted by the number of baseline PI mutations. Only 14% showed decreased susceptibility to TPV after 104 weeks on the TPV/RTV regimen, associated with a mean of 16 protease mutations. Development of >10-fold resistance occurred infrequently.

• **Tenofovir DF:** By the time tenofovir DF (TDF) made its big debut at ICAAC in December, it had already been approved by the FDA. Nevertheless, we hadn't seen data from naïve patients until CROI. Results were presented from a small trial in which 10 patients with viral loads >10,000 c/mL (mean 4.3 log₁₀ c/mL) were treated with tenofovir monotherapy (300 mg qd) and underwent intensive virologic monitoring [Louie, Abstract 3]. The mean decrease in viral load was 1.5 log₁₀ c/mL by day 21, and mean 1st phase viral load decay was approximately 0.4 log/d. As with the TMC 125 monotherapy trial, these results were retrospectively compared with data from previous studies. Using the combination of LPV/RTV + EFV + 3TC + TDF as a standard (1st phase slope -0.99 log/d), the potency of TDF monotherapy was similar to that of RTV monotherapy (-0.34 log/d). Thus, the efficacy of TDF was comparable to that of a PI, and was approximately 40% of an intensive HAART regimen. Most of the data on TDF's potency come from trials in experienced patients with NRTI resistance, and we are accustomed to thinking of this drug in terms of a modest 0.6 log decline in viral load. This small study hints at greater potency in naïve patients, findings that will need to be confirmed in the Gilead 903 trial, which we can expect to hear about this summer in Barcelona at the World AIDS Conference.

Simplified Antiretroviral Therapy

• **Once-daily Lopinavir/Ritonavir:** The



impressive results seen with lopinavir/ritonavir (Kaletra) in both naïve and experienced patients have been explained primarily by the high drug levels and long half-life of lopinavir when boosted with ritonavir. When given at the standard dose of 3 capsules (400/100 mg) bid, trough levels of lopinavir exceed the IC_{50} for wild-type virus by over 75-fold. These characteristics have made it a logical candidate for once-daily administration. Data were presented from a pilot trial (N=38) comparing bid (3 capsules, or 400/100 bid) with qd (6 capsules, or 800/200 qd) dosing of LPV/RTV [Bertz, et al., Eron, et al. Abstract 409-W]. In an intent-to-treat, missing=failure analysis at 48 weeks, 79% and 74% had viral loads <50 mL, respectively. No increase in gastrointestinal side effects was noted in the qd arm. The median inhibitory quotient was >40 in both groups, and the median trough level was >2.8 ug/mL. There were no differences in AUC_{24} or C_{max} ; however, the C_{min} was approximately 44% of that seen in the bid arm, and trough levels were considerably more variable with the once daily dose. This preliminary report suggests that once daily dosing of LPV/RTV may be possible, especially in patients without pre-existing protease inhibitor resistance. In PI-resistant patients, however, the clear advantage of this drug is its high trough level, an advantage that could be diminished with once daily administration.

• **Stavudine Extended Release Formulation:** A new extended release (XR) formulation of stavudine may be approved soon, joining a growing list of once-daily therapy options. Pharmacokinetic data were presented from a sub-study of BMS 096 involving 16 treatment-naïve patients taking either d4T XR 100 mg qd or standard, immediate-release (IR) d4T 40 mg bid (with dose adjustment for patients weighing less than 60 kg) over 14 days [Abstract 430-W]. Richard Pollard presented preliminary 24-week results from BMS 099, a large, placebo-controlled, randomized, phase 3 trial comparing d4T XR with d4T IR combined with 3TC and efavirenz [Abstract 411-W]. By intent-to-treat analysis, results were similar in the two arms, with 80% and 82% of patients achieving HIV RNA <400 c/mL in the XR and IR groups, respectively, and 55% in each arm achieving <50 c/mL in both arms. Adverse events were similar in both groups, with peripheral neuropathy occurring in 2% of the XR group and 4% of the IR group.

• **Once-Daily Saquinavir/Ritonavir:** Cardiello reported on a trial of once daily saquinavir/ritonavir (SQV/RTV 1600/100 mg qd) plus two NRTIs in 62 patients fully suppressed on saquinavir (soft-gel capsule, 1400 mg bid) plus 2 NRTIs [Abstract 549-T]. Although the trial was uncontrolled, 91% maintained an HIV RNA <50 c/mL after 48 weeks of follow-up. In the FOCUS trial, presented in December at ICAAC [see Gallant, *HHR* 2002, 14(1):1], GI toxicity and drop-out was significantly higher in patients taking SQV/RTV once daily than in those on an EFV-containing arm. Future studies of the SQV/RTV combination as well as combinations of SQV with other PIs will investigate the use of hard-gel SQV (Invirase), which is generally better tolerated than the soft-gel formulation (Fortovase), and which achieves similar or even superior drug levels when combined with RTV [Kurowski, Abstract 432-W].

Treatment Interruption

Perhaps the most dramatic way to simplify therapy is to discontinue it altogether. Bernard Hirschel from Geneva reviewed data on treatment interruption in a symposium entitled “Controversies in Antiretroviral Therapy” [Abstract S18]. In his talk he emphasized the negative results that have been observed with “strategic treatment interruption” (STI) strategies in chronically infected patients, in whom cycles of intermittent therapy do not appear to improve HIV-specific immunity or to blunt virologic rebound. Van Lunzen presented data from an STI trial in chronically infected patients which found that patients who interrupted therapy experienced rapid virologic rebound to baseline without change in virologic set-point despite the presence of HIV-specific CTL [Abstract 538]. The evidence supporting such an approach in patients treated during primary infection is stronger, though these patients are few and far between. The “structured intermittent therapy” (SIT) approach, in which patients go on and off therapy (e.g., 7-days on/7-days off) in order to lessen drug exposure, toxicity, and cost, appears promising, but remains highly experimental given the small numbers of patients who have been studied to date [Dybul M, et al. *PNAS* 2001;98:15161]. Finally, the strategy of “pulse therapy” is beginning to be tested in randomized, controlled clinical trials. In this approach,

patients who have had good immunologic responses to HAART stop therapy periodically, resuming after they have reached a pre-established CD4 count threshold.

At the CROI, Lundgren presented data from the large EuroSIDA cohort on the dangers of what was termed “treatment interruption,” but might be better thought of as good old-fashioned non-adherence [Abstract 48]. The investigators identified patients who had been on HAART for more than 3 months and who then interrupted therapy for any reason for at least 3 months. A total of 5,385 patient initiated therapy (15,312 person-years of follow-up), and 776 interrupted therapy. Of those, 518 reinitiated therapy during the follow-up period. The cumulative probability of treatment interruption was 20% at 60 months. There were a total of 10,637 person-years of follow-up from the start of HAART to a first new AIDS-defining event, death, or the last follow-up. The patients in the cohort had fairly advanced disease: At HAART initiation, the average viral load was 4.4 \log_{10} c/mL, and the average CD4 was 200 cells/mm³ with a nadir of 138 cells/mm³. Almost one-third had had AIDS-defining events. Factors associated with interruption included female gender (OR 1.31, p=0.02), injection drug use (OR 1.51, p<0.001), and higher viral load (OR 1.74, p<0.001). AIDS-defining events or death occurred in 408 patients on HAART (mean CD4 111 cells/mm³, HIV RNA 3.9 \log_{10} c/mL) and 37 patients off HAART (CD4 52 cells/mm³, HIV RNA 5.2 \log_{10} c/mL). Patients who interrupted therapy were at increased risk of AIDS and death compared to those who remained on treatment. However, there was no evidence of increased risk if the CD4 count remained above 200 cells/mm³. This study confirms the importance of CD4 count in determining the risk of complications and emphasizes the importance of continuing HAART in patients with advanced disease. However, it also suggests that treatment interruption may be safe provided CD4 counts are maintained at a high enough level. This appears to have been a group of patients with fairly advanced HIV disease who had strong indications for antiretroviral therapy. As such, they may not be representative of patients who are often considered for treatment interruption: those with earlier stage disease whose CD4 counts are expected to remain well above 200 cells/mm³ off therapy. ▲



New Drugs: Attacking Chemokine Receptors

By Charles Flexner, M.D.

There is concern that the growing list of approved antiretrovirals will discourage pharmaceutical and biotechnology companies from investing in the discovery and development of new drugs. The short list of new investigational agents in the antiretroviral classes at the 9th CROI seems to confirm that fear. However, there were several important advances.

Co-Receptor Blockade: Proof of Concept

In order to infect human cells, HIV must bind to the CD4 receptor plus one of several co-receptors, all of which normally function as receptors for chemokine proteins. The two most common HIV co-receptors are CXCR4, used to infect T-lymphocytes, and CCR5, used to infect macrophages. Three presentations at this conference provided the first evidence that small molecule inhibitors of CXCR4 and CCR5 have activity in HIV-infected patients and could play a role in future treatment.

• **AMD-3100:** Investigators from Johns Hopkins and five other U.S. sites reported the results of the first Phase II trial of AMD-3100, an inhibitor of HIV binding to the CXCR4 chemokine receptor [Hendrix, Abstract 391-T]. In this study, HIV-infected inpatients received a continuous intravenous infusion of AMD3100 and no other antiretroviral drugs for up to 10 days. A total of 40 subjects received infusion rates of 2.5 to 160 µg/kg/hr of drug. At the end of the study, only a single subject (with SI phenotype) receiving the highest dose of AMD-3100 experienced a 1.3-log drop in viral load; no other subjects had a significant change in viral load.

However, when virus from these subjects was examined for co-receptor usage, there was a shift in peripheral virus populations from CXCR4 usage to CCR5 usage, presumably driven by exposure to AMD-3100 [Abstract 2]. Nine of 19 subjects had

a mixed CXCR4-CCR5 usage at baseline, but all 19 had predominately CCR5 virus at the end of the study. Only 2 of 40 patients had predominately CXCR4 usage at the end of the study, and one of these received the lowest possible dose of drug.

High dose AMD-3100 is probably too toxic for chronic use. But based on the results of these studies, the shift in co-receptor usage indicates that CXCR4 blockade could drive a patient's virus population to the more benign CCR5-type. The long-term clinical benefit is unknown, but combining a CXCR4 inhibitor with a CCR5 inhibitor (see below) might be an exciting future approach to anti-HIV therapy.

• **Schering C (SCH C):** For several years, Schering Plough has been developing orally absorbed small molecule inhibitors of the CCR5 chemokine receptor. Two of these, Schering C (SCH C) and Schering D have been in clinical trials in HIV-infected patients. A small Phase II trial of Schering C produced a significant drop in viral loads in patients with NSI phenotype treated with a 25 mg BID dose for 10 days [Reynes, et al. Abstract 1]. The mean viral load drop in 12 patients was 0.6 logs, with a range of 0 to -1.5 logs. Of note, most patients had a small (<0.3 log) increase in viral load in the first 72 hours of treatment, presumably related to CCR5 blockade and a reduction in HIV clearance.

Unfortunately, the drug was associated with cardiac toxicity, producing QT interval prolongation of about one-tenth of a second by Day 10. The long-term safety of this drug is a concern, especially if higher doses need to be used. There were also no data presented on whether SCH C promoted a shift from CCR5 use to CXCR4 use, which would be the anticipated opposite of the AMD-3100 effect. Nonetheless, this study represents proof-of-concept that blocking a chemokine receptor can predictably lower viral load.

New Fusion Inhibitors

Fusion of the HIV virus membrane and the T-cell membrane is mediated by interactions between CD4 and HIV gp160 and is essential for infection. This step in virus entry is blocked by T-20 and related peptide-based fusion inhibitors.

Investigators from Bristol Myers-Squibb reported developing the first small molecule, non-peptidic inhibitor of HIV mediated membrane fusion [Lin, Abstracts 9 and 10]. This molecule, BMS-806, competes with CD4 for HIV envelope binding, and blocks fusion by targeting a part of the HIV envelope also targeted by T-20.

Unfortunately, BMS-806 is HIV-1 selective and has no activity against HIV-2 or SIV. Several clade B isolates of HIV-1 were also resistant to BMS-806 prior to exposure to the drug. Not surprisingly, resistance can develop quickly *in vitro*, with two mutations in the gp41 fusion domain of the HIV envelope conferring >1000-fold resistance. This drug will therefore have to be used as a component of a multi-drug regimen in order to avoid resistance, and its clinical utility remains to be proven.

Integrase Inhibitors

Investigators from Shinogi in Japan reported developing a small molecule HIV integrase inhibitor, S-1360, which is both potent and selective [Yoshinaga, Abstract 8]. This chemical inhibits NRTI-, NNRTI-, and PI-resistant HIV isolates *in vitro*. HIV can become resistant to this drug by mutating its integrase active site. No human studies have been conducted yet. *In vitro* results with S-1360 look similar to an integrase inhibitor developed by Merck. Merck's compound has reportedly been through Phase I trials, but there are still no data on anti-HIV activity in people for any integrase inhibitor. ▲

THE HOPKINS HIV REPORT

The Johns Hopkins University AIDS Service
The Hopkins HIV Report Distribution
P.O. Box 651266
Potomac Falls, VA 20165-1266

ADDRESS SERVICE REQUESTED

Non-Profit Org.
U.S. Postage
PAID
Dulles, VA
Permit No. 056