

# UPDATE FROM THE 12TH WORLD AIDS CONFERENCE AND 1998 ICAAC

At the San Francisco course, Judith S. Currier, MD, summarized some recent findings in antiretroviral therapy studies reported at the 12th World AIDS Conference (AIDS Conference) and the 1998 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC).

**M**uch recent investigation of antiretroviral therapy has focused on new drugs and novel combinations of available agents. The number of options in initial and subsequent therapy has increased, and some recent findings may help to provide guidance in selection of appropriate treatment. Select studies of regimens containing nucleoside reverse transcriptase inhibitors (nRTIs), nonnucleoside RTIs (NNRTIs), and hydroxyurea without protease inhibitors, protease inhibitor-based regimens, and protease inhibitor combination regimens are reviewed herein. Dr Currier expressed caution about the interpretation of data from trials of potent antiretroviral regimens. Specifically, many of the studies differ in trial design, stage of disease, treatment histories of the study subjects, and methods of analysis. In addition, the open-label or limited nature of many of the trials do not permit assessments of relative efficacies among different potent regimens. Also briefly reviewed are reports of early findings of effects of stopping prophylaxis for *Pneumocystis carinii* pneumonia (PCP).

## Hydroxyurea, nRTI, and NNRTI Regimens

There is considerable interest in protease inhibitor-sparing initial antiretroviral regimens due to (1) concerns over protease inhibitor-associated complications, (2) the desire to preserve therapeutic options in subsequent treatment, (3) the availability of non-protease inhibitor-containing regimens that exhibit efficacy equivalent to

protease inhibitor-based regimens, and (4) favorable dosing requirements of protease inhibitor-sparing regimens.

## Hydroxyurea-Containing Regimens

The 6-month findings of a comparison of didanosine/zidovudine, didanosine/stavudine, didanosine/hydroxyurea, and didanosine/stavudine/hydroxyurea showed that the triple-drug regimen was associated with a significantly greater proportion of patients with plasma HIV-1 RNA level maintained at <400 copies/mL (75%) (Federici et al, AIDS Conference, abstract 12235). Lori and colleagues presented long-term follow-up in a group of patients taking hydroxyurea/didanosine showing continuing decreases in viral load in patients remaining on therapy, from 1847 RNA copies/mL at week 40 to 254 copies/mL at week 122.

## nRTI-Containing Regimens

The 6-month findings in the ALBI study indicate that the combination of didanosine/stavudine was associated with viral suppression (50% of patients at <40 RNA copies/mL) superior to that of zidovudine/lamivudine or didanosine/stavudine for 3 months followed by zidovudine/lamivudine, indicating the utility of this nRTI combination as a backbone of potent antiretroviral therapy (Molina et al, AIDS Conference, abstract 12227). Preliminary 6-month findings of the GW Study CNA 3003 in treatment-naive patients (median HIV RNA of 32,000 copies/mL, median CD4+ cell count of 438/ $\mu$ L) suggest that abacavir/zidovudine/lamivudine is associated with a greater viral suppression than zidovudine/lamivudine (HIV RNA level <400 copies/mL in 60% to 70% vs. 30% to 40%) (Hammer et al, ICAAC, abstract

S-3). Analysis at 16 weeks showed that viral suppression was achieved with the triple-drug regimen in patients with higher viral loads (reduction to <400 HIV RNA copies/mL in 76% with pretreatment viral loads <10,000 copies/mL vs. 67% with >100,000 copies/mL) (Fischl et al, AIDS Conference, abstract 12238). Continued experience indicates that the frequency of abacavir hypersensitivity reaction remains at about 3%. This systemic reaction typically occurs in the first weeks to months of treatment, and is frequently associated with fever (70% of definitive

*Data from the INCAS trial support the importance of nadir viral load in maintaining durable virologic response to treatment*

cases), rash (55%), and nausea (30%) (Hetherington et al, AIDS Conference, abstract 12353); the reaction warrants immediate drug discontinuation and fatal reactions to rechallenge have been observed if the drug is restarted. Therefore, rechallenge should not be attempted.

## NNRTI-Containing Regimens

The recently reported 1-year findings of the INCAS trial indicate the marked superiority of plasma viral suppression with nevirapine/zidovudine/didanosine (approximately 50% of patients had viral load reductions to <20 HIV RNA



copies/mL) compared with zidovudine/didanosine or zidovudine/nevirapine (Montaner et al, *JAMA* 1998;279:930). Data from this trial, in which patients achieving this high level of viral suppression maintained it throughout follow-up, add to the evidence indicating the importance of the nadir viral load achieved in maintaining durable virologic response to treatment and, thus, the importance of initiating therapy with the most potent available regimens. Figure 1 shows time to loss of virologic response according to peak response in study patients.

A small study has shown that 16-weeks of nevirapine/stavudiné/once-daily didanosine is associated with a 1.8-log decrease in HIV RNA level and a 139 cell/ $\mu$ L increase in CD4+ count (Raffi et al, AIDS Conference, abstract 12239). Another study in a small number of patients indicates a reduction in viral load to <500 RNA copies/mL in >90% of patients at 6 months and a large CD4+ cell count increase (>150/ $\mu$ L) with nevirapine/didanosine/lamivudine each given once daily (Haberi et al, AIDS Conference, abstract 22398). Finally, a study of response to protease inhibitor-containing regimens in a small cohort of patients developing high-level nevirapine resistance showed a

median reduction in viral load of 1.54-log HIV RNA copies/mL, with a range of 0.03 to 3.13 log, and a median increase in CD4+ cell count of 96/ $\mu$ L, with a range of -108 to +776/ $\mu$ L (Curry et al, AIDS Conference, abstract 12231); the observation of a wide variation in response provides support for the contention that the best virologic response is achieved with initial therapy and that the ability to switch to maximally suppressive therapy cannot always be assumed.

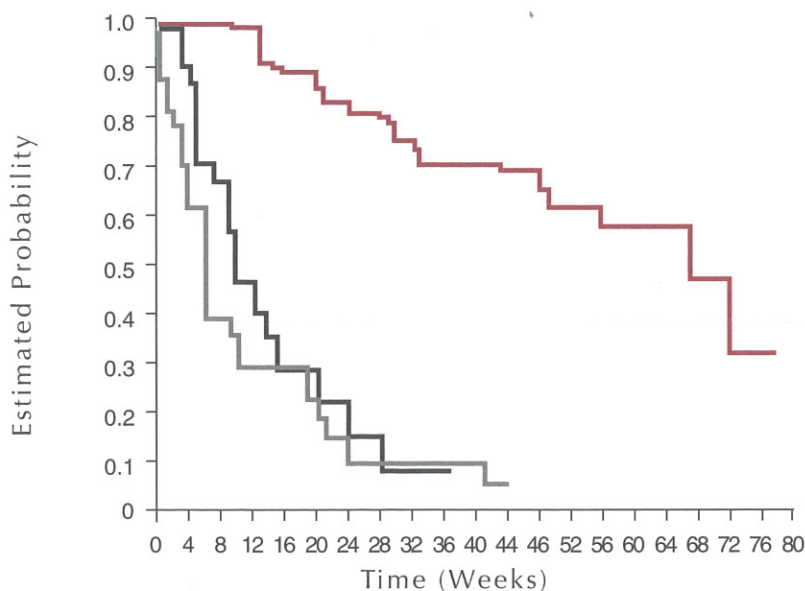
Prior experience with the NNRTI delavirdine generally has been in combination with zidovudine or didanosine in treatment-experienced patients. The 1-year findings in a study comparing delavirdine/zidovudine/lamivudine with delavirdine/zidovudine and zidovudine/lamivudine in treatment-naive patients indicate marked superiority of the triple regimen in viral suppression (approximately 60% of patients with HIV RNA <40 copies/mL) (Para et al, AIDS Conference, abstract 12219).

The NNRTI efavirenz has recently become available. The 36-week outcomes of a trial comparing efavirenz/zidovudine/lamivudine, efavirenz/indinavir, and indinavir/zidovudine/lamivudine provide

some measure of the comparative effectiveness of protease inhibitor-sparing and protease inhibitor-containing regimens (Staszewski et al, AIDS Conference, abstract 22336). Treatment-received analysis indicates that HIV RNA levels were reduced to <50 copies/mL in 88% of patients receiving the efavirenz-containing triple-drug regimen and in 82% of the indinavir-containing triple regimen group (and 67% of the efavirenz/indinavir group). An intent-to-treat analysis using the last-observation-carried-forward method showed that respective proportions of patients achieving this level of suppression in the triple-drug groups were

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66% and 50%, a significant difference favoring the efavirenz-containing regimen (52% in the efavirenz/indinavir group); on intent-to-treat analysis in which patients discontinuing study treatment were counted as treatment failures, viral suppression at this level was observed in 64% and 44% of patients, respectively (43% in the efavirenz/indinavir group). Significantly more patients prematurely terminated treatment with the indinavir-containing triple drug regimen than with the efavirenz-containing triple-drug regimen (30% vs. 25%), with significantly more experiencing adverse events (19% vs. 6%). Another study examining the effects of adding efavirenz to ongoing treatment with zidovudine/lamivudine showed that the resulting antiretroviral effect was transient, with median time to virologic fail-



**Figure 1.** Time from peak virologic response to first loss response, defined as increase in HIV RNA level to within 1 log of baseline, stratified by peak response in HIV RNA. Analysis is of didanosine/zidovudine and nevirapine/didanosine/zidovudine combined. Adapted from Montaner et al, *JAMA* 1998;279:930.

■ PEAK RESPONSE: ≤20 copies/mL ■ PEAK RESPONSE: 21-400 copies/mL ■ PEAK RESPONSE: >400 copies/mL

**Table 1. Protease Inhibitor-Sparing Antiretroviral Regimens: Preliminary Studies**

Regimen	Prior Treatment	Follow Up (Weeks)	Mean Decrease in HIV RNA log copies/mL	Percent of Patients Below Detection (HIV RNA assay)	Assay Detection Limits HIV RNA copies/mL
delavirdine/zidovudine/lamivudine <sup>1</sup>	No delavirdine, lamivudine, ≤6 months zidovudine	52	>2	75	400
stavudine/didanosine/hydroxyurea <sup>2</sup>	None	24	2	75	400
efavirenz/zidovudine/lamivudine <sup>3</sup>	No protease inhibitor, NNRTI, lamivudine	24	Not reported	86	400
abacavir/zidovudine lamivudine <sup>4</sup>	None	16	median 1.7	75	400
stavudine/didanosine nevirapine <sup>5</sup>	None	8	2	85	500

1. Para et al, AIDS Conference, abstract 12219. 2. Federici et al, AIDS Conference, abstract 12235. 3. Staszewski et al, AIDS Conference, abstract 22336. 4. Fischl et al, AIDS Conference, abstract 12230. 5. Raffi et al, AIDS Conference, abstract 12239. Please note that issues such as: trial design (open or randomized enrollment, size or length of the study); stage of disease; patient treatment histories; and methods of analysis and differences in activity of different potent antiretroviral regimens; do not permit assessments of comparative efficacies of different regimens from these data.

ure being 10 weeks (Meyers, AIDS Conference, abstract 22340). Resistance to efavirenz is mediated by single or double reverse transcriptase mutations. The addition of this drug to ongoing nRTI regimens in patients with detectable viral replication is not recommended.

A number of studies have thus shown that there are several protease inhibitor-sparing regimens that exhibit potent antiretroviral activity and have relatively simple dosing requirements. The virologic effects of some of these regimens are summarized in Table 1. Longer-term follow up with these regimens is eagerly awaited.

### Protease Inhibitor-Based Regimens

Notwithstanding the rationale for protease inhibitor-sparing regimens in initial treatment, there are a number of reasons motivating initial treatment with protease

### *Initial protease inhibitor-based therapy continues to be motivated by a number of factors, including proven clinical efficacy and long-term viral suppression*

inhibitor-containing therapy, including proven clinical efficacy and long-term viral suppression, high genetic barrier to resistance to these drugs, the evidence suggesting that the first treatment used should be the most potent, and the limited data on successful sequencing of drugs to support the strategy of reserving protease inhibitor treatment.

Direct comparative data on protease inhibitor-containing regimens have begun to appear. One study in protease inhibitor-naïve patients showed that HIV RNA levels <200 copies/mL were achieved in 82% of nRTI-naïve and 77% of nRTI-experienced patients receiving indinavir, 64% and 77%, respectively, receiving ritonavir, and 95% and 81%, respectively, receiving ritonavir/saquinavir (Pederson et al, AIDS Conference, abstract 12221). The 6-month results of the CHEESE study indicate approximately 2.5-log HIV RNA reductions both with saquinavir soft gel capsule zidovudine/lamivudine and with indinavir/zidovudine/lamivudine (Borleffs et al, AIDS Conference, abstract 12267).

Data on potential alternative protease inhibitor dosing regimens have also begun to appear. A 32-week pilot study comparing standard indinavir tid dosing (800 mg tid) with 1000 mg and 1200 mg bid doses as part of triple-drug regimen



with zidovudine/lamivudine showed no difference in proportions of patients achieving viral suppression to <50 HIV RNA copies/mL. The subsequent larger-scale study was stopped and the bid dosing arm terminated when preliminary data at 24 weeks indicated reduction in HIV RNA levels to <500 copies/mL in 91% of the indinavir tid group vs. 64% of the bid group. Dr Currier noted that for patients who are already responding to indinavir bid, the convenience of the regimen may outweigh the risk of missing doses upon switching to the tid dosing. Pharmacokinetic analysis in a small subset of patients in a study comparing nelfinavir 750 mg tid and 1250 mg bid in combination with lamivudine and stavudine indicated that higher drug levels were achieved with bid dosing throughout the dosing interval. Study results at 48 weeks and 60 weeks indicate that approximately 80% of patients in both bid and tid dosing groups are maintained at HIV RNA levels <400 copies/mL.

Among studies evaluating NNRTI and protease inhibitor combinations, one in largely nRTI-experienced patients with high viral loads (mean, 5.1 log copies/mL; mean CD4+ cell count, 283/ $\mu$ L) showed that efavirenz/indinavir was associated with HIV RNA levels <50 copies/mL in 70% to 80% of patients at 84 weeks and striking CD4+ cell count increases (Havlir et al, ICAAC, abstract I104). Preliminary findings of another study, in which approximately half of the patients were nRTI-experienced (overall, mean HIV RNA of 37,000 copies/mL and CD4+ cell count of 370/ $\mu$ L), indicate that efavirenz/nelfinavir was associated with reductions in HIV RNA levels to <400 copies/mL in 60% to 80% of patients at 24 weeks (Kagan et al, ICAAC, abstract I102).

Some data on the investigational protease inhibitor amprenavir were also reported. Preliminary results in a study in treatment-naive patients (median HIV RNA, 4.6-log copies/mL; median CD4+ cell count, 420/ $\mu$ L) indicate that HIV RNA levels <400 copies/mL were achieved in 59% to 88% of patients taking amprenavir/zidovudine/lamivudine compared with 17% to 19% of those taking

**Table 2. Early Data on Stopping PCP Prophylaxis**

Study	No. of Subjects	CD4+ count (cells/ $\mu$ L)	Follow Up	PCP Cases
Ravaux	40	>300	6 months	0
Reiss	68		34 patient-years	0
Vasquez	34	>200	9 months	0
Furrer	53	>200	5 months	0*
Schneider	50	>200	6 months	0

\* Upper bound 95% confidence interval 13.3 cases/100 patient-years

zidovudine/lamivudine at 16 weeks (Goodgame et al, ICAAC, abstract LB-5).

### Protease Inhibitor Combinations

The use of dual protease inhibitor therapy without inclusion of nRTIs remains controversial, although there are data indicating potent and prolonged virologic response in patients receiving such treatment. Treatment with ritonavir/saquinavir (bid or tid dosing) was associated with reduction of HIV RNA to <200 copies/mL in 90% of patients at 72 weeks, although many patients had taken nRTIs (usually stavudine plus lamivudine) added after 12 weeks (Mellors et al, AIDS Conference, abstract 12295). A study comparing ritonavir/saquinavir/stavudine and ritonavir/saquinavir with an nRTI added at or after week 12 for viral load >400 HIV RNA copies/mL showed that approximately 80% of patients in both arms had viral load <400 copies/mL at week 48, with some patients in the dual protease inhibitor arm having an nRTI added and this level of viral suppression being achieved more rapidly in a higher proportion of patients initially receiving the triple regimen (Gisolf et al, AIDS Conference, abstract 12274); since there appears to be an advantage to achieving maximal viral suppression as rapidly as possible, such findings support the initial

inclusion of an nRTI in the regimen. The 48-week outcomes in another study indicate reductions in plasma HIV RNA to <50 copies/mL in 51% of patients taking saquinavir/nelfinavir/2 nRTIs, 42% receiving nelfinavir/2 nRTIs, 42% receiving saquinavir/2 nRTIs, and 35% receiving saquinavir/nelfinavir (Moyle et al, AIDS Conference, abstract 12222).

Attempts to reduce the total pill burden associated with protease inhibitor therapy and to arrive at optimal doses of protease inhibitors in combination continue. Pharmacokinetic analyses of combined indinavir and nelfinavir indicate that indinavir blood levels at a 1000 mg bid dose were not substantially different from those at 800 mg tid when administered in combination with nelfinavir 1000 mg bid. Studies are under way to determine whether higher doses of these drugs in combination are effective (1200 mg of indinavir, 1250 mg of nelfinavir). Another pharmacokinetic study is comparing indinavir 800 mg bid plus ritonavir 100 mg, 200 mg, or 400 mg bid and indinavir 400 mg plus ritonavir 400 mg bid in the setting of low-fat or high-fat meals. Early findings indicate that this combination is promising with coadministration of the drugs increasing indinavir blood levels substantially. Since sequential use of these two drugs would appear to be contraindicated due to their overlapping resistance patterns, combining them to im-

prove the pharmacokinetics of indinavir warrants further study.

### Stopping PCP Prophylaxis

The use of highly potent antiretroviral therapy has resulted in reduction in the incidence of opportunistic infections, posing the issue of whether PCP prophylaxis can be stopped in patients taking effective antiretroviral therapy. A number of observational studies reported at the 12th

World AIDS Conference have found no occurrences of PCP in short-term follow-up of relatively small groups of patients who decided to stop prophylaxis (Table 2). However, given the short follow-up time, the confidence interval for calculating the number of cases that could occur based on these observational data is very broad; in one study, the upper bound of the 95% confidence interval was a rate of 13.3 cases/100 patient-years. This issue currently is being evaluated in the ACTG 888 study. It is hoped that forthcoming

data will allow determination of risk levels that permit discontinuation of prophylaxis and assessment of the potential impact of discontinuation of PCP prophylaxis on the incidence of other bacterial infections.



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### Resources

Abstracts from the 12th World AIDS Conference; June 28–July 3, 1998; Geneva.

Abstracts from the 38th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 24–27; San Diego.