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# INFECTIOUS DISEASE ALERT®

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## Summaries from the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy: Part III

CONFERENCE COVERAGE

***Note:*** *The following summaries represent a selection of papers from those presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held September 24-27, 1998, in San Diego, CA. It is important to recognize that many of these summaries are extracted only from the published abstracts, and it is possible that some of the material may have differed at the time of presentation. Parts I and II, which summarized presentations not related to HIV, were published in the previous two issues of Infectious Disease Alert. —Stan Deresinski, MD, FACP*

### HIV Infection and Its Complications

#### Epidemiology

A 20-year-old HIV-infected man in Chautauqua, N. Y., recently achieved notoriety in the national news media for having infected a number of sexual partners. The completed investigation, confirmed by genetic analysis of viral isolates, found that he had, in fact, infected 13 (31%) of 42 female sexuals partners whose ages ranged from 13-21 years. The median number of their sexual contacts with him had been only four, with some infected women having had only a single contact. No secondary cases were identified. *(Abstract S-85.)* This miniepidemic is consistent with the notion that, similar to observations in HBV infection, certain individuals represent a disproportionate risk in the transmission of HIV-1 infection.

Because of the increased risk of HIV transmission in the presence of other sexually transmitted diseases, one potential approach to HIV control is the aggressive identification and treatment of all STDs. However, in a large randomized study in Uganda, there was no effect on reduction of new HIV infections (despite the successful reduction in the incidence of other STDs)

other than bacterial vaginosis. This failure may have been related to the enormous baseline prevalence of HIV infection of 16%. *(Abstract S-86.)*

## Antiretroviral Therapy

### Resistance

The potential for varying antiretroviral resistance patterns in different body compartments was addressed. No differences in RT and protease sequences were found between 42 paired viral samples obtained from plasma and lymph node of 28 patients. *(Abstract I-122.)* Drug resistance was infrequently detected in virus isolated from the genital tract of women when compared to paired virus isolated from their plasma. *(Abstract I-124.)*

A consensus is emerging that current methodologies for detecting in vitro resistance of HIV-1 to antiretroviral agents may be useful in predicting which drugs will be ineffective, but that the methodologies are insufficiently sensitive to minority viral populations to be reliably predictive of drug success.

There is, in addition, a continuing battle among varying technologies for determining genotypic and phenotypic resistance. Three methods of genotyping were compared: gene chip hybridization-based sequencing (Affymetrix), direct solid phase sequencing (Applied Biosystems), and point mutation probe assay (Murex). A panel of nine RT plasmids and 28 clinical isolates were examined. While gene sequencing detected the most mutations, the other two methods also performed well. *(Abstract I-114.)*

Polymorphic changes in the HIV-1 gene pool not associated with drug resistance consistently developed prior to the appearance of mutations associated with drug resistance. This suggests that their detection may serve as an early warning system. *(Abstract I-76.)*

An evaluation of treatment-experienced patients given ritonavir and saquinavir in combination found, by multivariate analysis, that both baseline genotype (by VircoGENTM sequence analysis) and phenotype (by Antivirogram TM) antiretroviral susceptibility tests were highly predictive of response to this combination. Patients with baseline phenotypically susceptible virus were 12-fold (95% CI 1.2-111; $P < 0.05$) more likely to respond (HIV RNA < 500 copies/mL) than those with non-susceptible patterns. Virologic response was four-fold (95% CI 1.0-13; $P < 0.05$) more likely in those with genotypic susceptibility. Nonetheless, only approximately one-half of patients with in vitro evidence of drug susceptibility responded to the salvage regimen with a reduction in viral load below the limits of detection. *(Abstract I-78.)* This is consistent with the emerging consensus noted above, that genotypic and phenotypic tests are useful in predicting treatment failure, but not success.

One potential mechanism of resistance not detectable by current assays is reduced phosphorylation of nucleoside analogs. The thymidine kinase content of peripheral blood mononuclear cells is decreased in patients with high viral load and/or low CD4 count, theoretically leading to decreased phosphorylation of some NRTIs and resultant reduced antiretroviral activity. *(Abstract A-70.)*

Multinucleoside analog resistance (MNR) has previously been associated with the accumulation of multiple mutations, as well as with the codon 151 multidrug resistance cluster. MNR has also been found in association with insertions in the RT gene at or near codon 69, most commonly 69S (-S-S). While this alteration alone does not cause significant resistance, its presence together with ZDV resistance mutations is associated with cross-resistance to d4T, ddI, and ddC. *(Sunday, Abstract LB-4.)*

The ZDV-associated resistance mutations, M41L and M41L + K70R, are associated with reduced viral fitness. *(Abstract I-111.)*

The complete protease genes of HIV-1 isolates from 58 PI naïve patients were sequenced prior to the initia-

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tion of therapy, which included a PI to determine if the presence of polymorphisms predict failure of response to treatment. No mutations known to be associated with PI resistance were detected, but differences from the subtype B consensus sequence were detected at 29 individual codons, with a median number of differences per isolate of four. There was no correlation between the number of amino acid substitutions and response to therapy, indicating that these natural polymorphisms are not relevant to PI treatment outcome. *(Abstract I-112.)*

Failure of ritonavir therapy is initially associated with increased drug resistance and reduced viral replicative capacity (fitness). At this stage, the viral protease demonstrates an increased protease Ki to ritonavir, consistent with resistance to this drug; the reduced fitness is associated with diminished catalytic efficiency of the protease. With continued drug administration (and, thus, continued selective pressure), however, a quadruple mutant (36I-54V-71V-82T) that has increased replicative efficiency may subsequently arise. Evolution of this increased viral fitness is associated with an increased catalytic efficiency of the protease compared to wild type viral protease, while the ritonavir Ki remains stable. The unfortunate consequence is a drug-resistant virus with increased replicative capacity. *(Abstract I-118.)*

## Protease Inhibitors

If cure of HIV infection is to be accomplished, it will require the elimination of proviral DNA. The kinetics of HIV-1 DNA clearance were assessed in 11 protease inhibitor naïve patients at the time of initiation of highly active antiretroviral therapy. When adjusted for number of CD4 T cells, a 71% decline was seen at one month, with an additional 50% decline through six months. *(Abstract I-250.)*

**Pharmacodynamics.** Many HIV-1 protease inhibitors bind avidly to alpha-1 acid glycoprotein, a normal constituent of plasma that is an acute phase reactant. Binding reduces the activity of drugs because it is only the unbound fraction that is active. The increase in mean serum concentrations of alpha-1 acid glycoprotein seen in the presence of acute infections is associated with a reduction in activity of protease inhibitors against some strains of HIV-1. Indinavir appears to be the least affected, while amprenavir, ritonavir, and nelfinavir are the most affected. *(Abstract A-42.)* This suggests that intercurrent infection may impair the antiretroviral activity of these drugs in vivo.

**BID Dosing.** Evaluation of bid dosing of indinavir in regimens in which it is the only protease inhibitor used in combination with NRTIs has been abandoned because of the results of a 24-week interim analysis of data that showed that the tid regimen was more effective than the twice-daily regimen in reducing levels of viral RNA to less than 400 copies/mL in patients initiating therapy. At week 24, 91% of patients on the approved dosing regimen had achieved viral levels below 400 copies/mL, compared to 64% of patients on the twice-daily regimen.

Trials examining bid dosing of indinavir in combination with another protease inhibitor or an NNRTI, however, continue. Thirty-seven antiretroviral naïve patients with viral loads less than 35,000 copies/mL and a median CD4 count of 247/$mm^3$ (range, 4-616/$mm^3$) were treated with the following, with all drugs given bid: two NRTIs, indinavir (400 mg per dose), and ritonavir (400 mg per dose). Twelve of 12 patients who reached 16 weeks of treatment had plasma HIV RNA less than 500 copies/mL. *(Abstract I-213.)* This bid regimen allows indinavir to be taken without regard to food intake.

Twice daily dosing of nelfinavir (1250 mg bid) appears to be as effective as thrice daily dosing (750 mg tid), in patients with less than six months prior NRTI experience (most of whom were 3TC-naïve) when it is given together with d4T and 3TC for as long as 48 weeks. Diarrhea occurred with equal frequency in both groups. *(Abstracts I-216, I-218.)*

**Metabolic and Other Adverse Effects.** Comparison of HgbA1c and fasting lipid profiles found no differences between patients receiving and not receiving protease inhibitor therapy. *(Abstract I-72.)* Endocrinologic investigation of six diabetic HIV-infected patients receiving protease inhibitor therapy provided evidence of insulin resistance with relative insulin deficiency as well as hyperglucagonemia. *(Abstract I-90.)* Eight protease inhibitor treated men (median HIV RNA, 13,200 copies/mL) with hypertriglyceridemia (median, 1803 mg/dL) were given gemfibrozil at a dose of 200 mg qd for a median of 175 days. The median triglyceride level decreased 83% to 300 mg/dL (P = 0.012) after institution of gemfibrozil therapy. There was, however, no change in cholesterol or HDL cholesterol. Triglycerides increased significantly in three gemfibrozil recipients whose protease inhibitor was changed to nelfinavir, suggesting an interaction between these two drugs. *(Abstract I-88.)*

The cumulative probability of developing lipodystrophy during protease inhibitor therapy was 3.2% at six months, 10.7% at 12 months, 29.1% at 18 months, 62.5% at 24 months, and 75% at 30 months. The risk was not affected by the individual or combination protease inhibitor used (nelfinavir was not used in these patients). *(Abstract I-92.)* On the other hand, a separate retrospective study found that the greatest relative risk

for development of hypercholesterolemia was associated with ritonavir use. *(Abstract I-95.)*

A retrospective study found that ritonavir use was associated with a six-fold greater risk of severe hepatotoxicity (ALT or AST > 5 × ULN or > 3.6 × abnormal baseline) than other PIs. The relative risk was 4.8 for ritonavir recipients (P = 0.001) and 32% for ritonavir + saquinavir recipients (P = 0.001). HCV infection did not appear to predispose to protease inhibitor associated severe hepatotoxicity. *(Abstract H-116.)* The latter finding was confirmed in a separate study. *(Abstract H-118.)* The occurrence of adverse side effects correlates closely with the plasma concentration of ritonavir. *(Abstract A-75.)*

Three men, ages 41-49 years, receiving protease inhibitor-based therapy developed aseptic necrosis of the hip. Two of the three had a history of alcohol abuse. *(Abstract I-71.)*

### RTIs: Adefovir and Abacavir

**Adefovir.** One hundred sixty-four antiretroviral naïve patients with a CD4 count of greater than 100/mm$^3$ and HIV RNA more than 5000 copies/mL were randomized to receive either adefovir dipivoxil + indinavir + either ZDV, 3TC, d4T, or ZDV and 3TC; or indinavir + 3TC + ZDV. At 20 weeks, the proportion of patients whose viral load had decreased to less than 400 copies/mL was similar in each group, as were the absolute increases in CD4+ T cell counts. However, almost 40% of patients in the four drug arm had dropped out. *(Abstract I-107.)*

Four hundred forty-two patients with HIV RNA greater than 2500 copies/mL (bDNA) and CD4 count of more than 200 cells/mm$^3$ were randomized to have either adefovir dipivoxil or placebo added to their standard antiretroviral regimen (all were also given (L-carnitine). Close to 40% of patients altered their background therapy during the study, somewhat confounding interpretation of the results. At 24 weeks, there was a mean decrease of plasma HIV RNA of 0.4 log$^{10}$ in those assigned adefovir (P < 0.001 vs placebo result); this result was also sustained through 48 weeks. There was no significant change in CD4 cell count. Administration of this nucleotide analog prodrug was associated with an unexplained mean decrease in body weight of 5.3 pounds vs. no change in placebo recipients (P < 0.001). Vomiting or diarrhea occurred more frequently in the adefovir group. Abnormalities of proximal renal tubular function occurred in 1% of adefovir recipients at 24 weeks; after an additional, 24-week open label phase, the incidence had increased to 39.1% in those who had received adefovir dipivoxil for 48 weeks. *(Abstract I-108.)*

Three-fourths of a group of highly NRTI experienced patients who were entered into a trial in which adefovir or placebo were added to their existing regimens had the 3TC-associated M184V mutation at baseline, and one-half had multiple mutations associated with ZDV resistance. Despite these findings, the mean decrease in plasma HIV RNA at 24 weeks in adefovir dipivoxil recipients in the group overall was 0.39 $\log_{10}$ and was 0.53 $\log_{10}$ (P < 0.0001 when compared to placebo response) in a subset of patients undergoing intense virological studies. A significant decrease in viral load was also noted in those with 3TC-resistant or high-level ZDV/3TC resistant virus at baseline (-0.94 $\log_{10}$), but not in those with only high-level ZDV resistance (-0.5 $\log_{10}$). Furthermore, the decrease in viral load at 24 weeks in patients whose virus developed new NRTI-associated resistance mutation during adefovir dipivoxil was a mean of 0.64 $\log_{10}$ (P = 0.0003) when compared to placebo response). *(Abstract I-84.)* The latter finding is consistent with data indicating increased susceptibility of virus with the 3TC-associated M184V mutation to adefovir .

**Abacavir.** Seventy patients receiving one or more NRTIs for at least eight weeks, with plasma HIV RNA of more than 50,000 copies/mL and CD4 count of more than 50 cells/mm$^3$, were started on Combivir plus abacavir (patients on ZDV at the time of study were excluded). Fifty percent of patients had plasma HIV RNA less than 50 copies/mL at eight weeks, while 78% had values less than 400 copies/mL. This combination appears to provide us with a potent NNRTI- and PI-sparing regimen. *(Abstract I-98.)*

The AUC of abacavir is increased 41% by coadministration of ethanol. *(Abstract A-67.)*

## NNRTI: Efavirenz

Nelfinavir (750 mg tid) plus efavirenz (600 mg qd) were administered to 32 antiretroviral naïve and 30 NRTI experienced (but PI and NNRTI naïve) patients with HIV RNA more than 10,000/mL and CD4 more than 50 cells/mm$^3$. At 24 weeks, in an intent-to-treat analysis, 64% of naïve and 41% of NRTI experienced patients had a viral load less than 50 copies/mL. *(Abstract I-102.)*

Of 59 patients receiving efavirenz + indinavir, at 84 weeks, 74% had viral loads of less than 50 copies/mL and a mean increase of 350 CD4+ T cells/mm$^3$ at the time of their last assay. Contrary to results from other studies, for some inexplicable reason, no CNS toxicity was observed by these investigators. *(Abstract I-104.)*

Four hundred fifty PI, NNRTI, and 3TC naïve

patients (85% were completely antiretroviral naïve) with viral loads of more than 10,000 copies/mL and CD4 counts more than 50/mm$^3$ were randomized to receive one of three regimens: efavirenz + indinavir, efavirenz + ZDV + 3TC, or indinavir + ZDV + 3TC. The somewhat startling 24-week results reported in Geneva continued to hold at the 36-week analysis. In the intent-to-treat analysis, the proportions of patients whose plasma HIV RNA was reduced to less than 50 copies/mL were, respectively, 43%, 64%, and 44%. Rashes and, especially, CNS side-effects (mostly insomnia, anxiety, and dysphoria) were commonly attributed to efavirenz. Only 22% discontinued the drug as a consequence, however. This study demonstrates that efavirenz + ZDV + 3TC is a potent regimen in a largely antiretroviral naïve patient population. The apparent superiority over the comparable indinavir-based regimen is puzzling and is confounded by the high, premature discontinuation rate in this group (41% vs 25-30%) and by the discrepancy with the much better results obtained with this regimen in other studies. *(Abstract I-103.)*

**GM-CSF**

One hundred twenty-five Brazilian patients with CD4 count less than 300/mm$^3$ were randomized to receive GM-CSF (sargramostim) or placebo in addition to their standard antiretroviral therapy, which consisted of ZDV alone or with a second NRTI. The GM-CSF was administered subcutaneously in a dose of only 125 mg/m$^2$ twice weekly. At six months, the median changes in viral load were -0.51 $\log_{10}$ in the GM-CSF recipients and -0.01 $\log_{10}$ in those assigned placebo (P = 0.02). In addition, 80% of GM-CSF recipients had a more than 30% increase in CD4 count, compared to only 58% in the placebo group (P = 0.027). The incidence of opportunistic infections in the former group was 40% and 63% in the placebo group; this difference was not, however, statistically significant. *(Abstract I-243.)* Coadministration of GM-CSF does not affect indinavir pharmacokinetics. *(Abstract A-72.)* The significant reduction in viral load associated with GM-CSF administration is consistent with a recent finding that this cytokine reduces CCR-5 expression and HIV-1 (R5 strain) infectivity of macrophages in vitro (*AIDS Res Hum Retroviruses* 1998;14:129).

**Interferon alpha-n3**

The antiretroviral activity of interferon alpha-n3, derived from human leukocytes, had a modest antiretroviral effect, comparable to that of ZDV, in patients with baseline CD4 count of more than 400/mm$^3$. *(Abstract I-100.)*

**Management of Antiretroviral Treatment Failure**

The combination of abacavir, efavirenz, and adefovir dipivoxil (plus L-carnitine) was administered to four heavily pretreated patients with viral loads of more than 100,000 copies/mL. All had previously received ZDV, d4T, 3TC, nevirapine, saquinavir, indinavir, nelfinavir, and ritonavir. None, however, had detectable mutations at the 103, 106, or 181 positions of the RT gene associated with NNRTI resistance. The mean log reduction at two months was 0.7 $\log_{10}$. *(Abstract I-200.)*

In contrast to the more dismal experience of others, 49% of 29 saquinavir hard gel experienced patients (for a median of 20 months), whose therapy was changed to indinavir plus at least one new NRTI, experienced a reduction of viral load to less than 50 copies/mL at six months. Neither the number of preexisting PI mutations, the viral load at baseline, nor the duration of exposure to saquinavir correlated significantly with virologic response. Baseline resistance to 3TC was, however, a predictor of a poor virologic response. *(Abstract I-82.)*

**Arguments for Early Aggressive Treatment**

In the opening symposium, the importance of the role of HIV-specific CD4 T cell response to the immunologic control of HIV infection was discussed. A study of a small number of patients with acute HIV infection found that early treatment was associated with restoration or improvement in the CD4 response to antigens of HIV.

Treatment of primary HIV-1 infection with ZDV + 3TC + indinavir was associated with acceleration of the appearance of specific neutralizing antibodies directed at autologous virus when compared to a cohort of untreated patients. *(Abstract I-190.)*

In a study using an assay with a lower limit of detection of 5 copies/mL, results were found that further support the value of early treatment. Eight of 10 subjects with primary infection who were given ZDV, 3TC, and indinavir achieved a negative result with this assay, while none of those with chronic infection and CD4 count below 500/$mm^3$ did so. While approximately one-half of those with chronic infection and CD4 cell count above 500/$mm^3$ did reach a viral load of less than 5 copies/mL, none were able to maintain this level of viral suppression. *(Abstract S-102.)*

An analysis of the INCAS study at the Geneva conference demonstrated that, at least with nevirapine-based regimens, it is necessary to achieve viral load suppression below the limits of detection of ultrasensitive assay (< 20 copies/mL) in order to achieve long-term viral suppression.

These findings, taken together, provide a strong argument for not delaying the institution of antiretroviral therapy. Early treatment may also prevent the viral divergence and emergence of SI strain predominance associated with subsequent disease progression. *(Abstract S100.)*

## Opportunistic, Intercurrent Infections and Malignancies

### PCP

In a study that also has relevance to antiretroviral therapy, the efficacy of education in improving adherence to PCP prophylaxis was evaluated in patients at an inner city institution by randomization to usual care or to nurse-based directed interviews at the end of each scheduled clinic visit. Although the intervention group was demonstrated to have improved knowledge of PCP, there was no difference in adherence to prophylaxis as determined by use of the Medication Monitoring Systems (MEMS) device. In addition, although 96% of the patients could read their medication label, 22% were unable to interpret it correctly. *(Abstract I-178.)*

Accumulating data suggest that it may be safe to discontinue PCP prophylaxis in some patients who have had significant responses to HAART. PCP prophylaxis was discontinued in 45 patients whose CD4 count had risen above 200/$mm^3$ after institution of highly active antiretroviral therapy. The mean CD4 count at the time of discontinuation was 335/$mm^3$ (range, 200-963/$mm^3$) and the mean viral load was 3.35 $\log_{10}$/mL (range, undetected to 5 $\log_{10}$/mL). No cases of PCP have occurred after a mean prophylaxis follow-up of 329 days (range, 46-1334 days). *(Abstract I-204.)* Separately, PCP prophylaxis was discontinued in 26 patients under similar circumstances. No cases of PCP occurred after a mean follow-up of 291 days. *(Abstract I-206.)* No cases of PCP occurred in 21 patients followed for a mean of 8.5 months whose primary prophylaxis was discontinued. *(Abstract I-262.)* Finally, no cases occurred after a mean follow-up of 12.5 months in 60 Dutch patients whose primary prophylaxis was discontinued or, after a mean follow-up of 6.6 months, in 13 whose secondary prophylaxis was discontinued. *(Abstract I-269.)*

### Mycobacterial Infections

Immune response disease is sometimes seen in patients in the months after introduction of successful HAART. Six of 10 cases of MAC infection in patients receiving highly active antiretroviral therapy were localized rather than disseminated. Two each had osteomyelitis, mesenteric lymphadenitis, and mediastinal adenopathy with bronchial compression. Four of these patients had received treatment for MAC and had plasma HIV RNA of less than 200 copies/mL. *(Abstract I-105.)* These manifestations are likely the result of a newly developed inflammatory response to an infection that was present prior to the institution of HAART.

Mycobacterial lymphadenitis, which presents within 12 weeks of initiating effective antiretroviral therapy, is usually due to MAC and is not part of a disseminated infection. *(Abstract I-264.)*

Coadministration of clarithromycin increases the amprenavir AUC by 18%; 14-hydroxylation of clarithromycin is inhibited. *(Abstract A-73.)* A decrease in concentrations of the latter may impair the usefulness of this drug in the treatment of *Haemophilus influenzae* infections.

### CMV

CMV viremia (by PCR) became undetectable in 16 of 16 patients following the institution of highly active antiretroviral therapy after a median interval of 13.5 weeks. All but two remained CMV negative by PCR for a median of eight months. *(Abstract I-268.)*

A retrospective comparison of 14 patients given HAART following a diagnosis of CMV retinitis to a control group of 14 with CMV not given HAART, found that survival in the former group at two years was 75%, while it was only 3% in the latter group ($P < 0.00001$). Similarly, HAART was associated with a reduction in the proportion of patients whose retinitis

relapsed from 100% to 36%, with all relapses in the latter group occurring during the first five months of HAART. The downside of this success is that of inflammatory ocular responses resulting from immune reconstitution. Thus, inflammatory vitritis was frequently seen in HAART recipients, but not in the group not receiving HAART. *(Abstract I-270.)*

Anterior uveitis may occur during cidofovir therapy of CMV retinitis. The investigators believe it to possibly be the result of intraocular accumulation of the drug. *(Abstract H-112.)*

**Malignancies**

HAART is associated with improved survival of patients with non-CNS non-Hodgkin's lymphoma. Compared to a median survival of six months, a previously reported cohort given HAART had a median survival of approximately two years. *(Abstract I-265.)*

Administration of either foscarnet or ganciclovir has no effect on circulating HHV-8 (KSHV) DNA load. *(Abstract H-113.)*

**PML**

HAART was instituted in 11 patients with progressive multifocal leukoencephalopathy and their outcomes were compared to those of 23 patients previously treated with Ara-C. The median time to survival was approximately two months in each cohort, suggesting no benefit from HAART. *(Abstract I-273.)*

**Hepatitis Viruses**

The clinical course of acute HAV infection does not appear to be more severe in HIV-infected patients than in non-HIV infected patients. *(Abstract H-114.)*

In patients coinfected with HBV whose HBV is responding to 3TC, hepatitis may worsen if the 3TC is discontinued. *(Abstract H-119.)*

HIV-infected patients are commonly coinfected with HCV, with by far the highest rates of coinfection in injection drug users. Successful HAART does not lead to reduced plasma HCV RNA levels. *(Abstract H-111.)* In fact, institution of HAART may be associated with a transient increase in HCV levels.

**Q Fever**

Acute Q fever in 10 HIV-infected patients appeared to be of comparable severity to that encountered in non-HIV infected individuals. *(Abstract I-131.)* ❖

## *Did You Know....*

The Aspergillus Web Site, **http://www.aspergillus.man.ac.uk**, is designed to provide information on pathogenic *Aspergillus* species for clinicians and scientific researchers. The site includes DNA sequence data, a comprehensive bibliographic database, laboratory protocols, treatment information (including management algorithms), and discussion groups. ❖

## *CME Questions*

**28. Which of the following is *incorrect*?**

a. Currently used phenotypic and genotypic methods of HIV-1 susceptibility testing appear to be useful in predicting drug treatment failure.
b. Currently used phenotypic and genotypic methods of HIV-1 susceptibility testing appear to be insufficiently sensitive to minority viral populations to reliably predict drug treatment success.
c. Institution of successful HAART is associated with evidence of reduction in proviral HIV-1 DNA.
d. Acute intercurrent infection causes a reduction in serum alpha-1-acid glycoprotein and a resultant increased antiretroviral activity of HIV-1 protease inhibitors.

**29. Which of the following is *incorrect*?**

a. Gemfibrozil administration is associated with a reduction of serum hypertriglyceridemia in HIV infected patients receiving HIV-1 protease inhibitor therapy.
b. Gemfibrozil administration is associated with a reduction of serum hypercholesterolemia in HIV infected patients receiving HIV-1 protease inhibitor therapy.
c. Abnormalities of proximal renal tubular function commonly occur in patients receiving abacavir.
d. The susceptibility of HIV-1 to adefovir is increased in the presence of the 3TC (lamivudine) resistance-associated M184V mutation.

**30. Which of the following is *incorrect*?**

a. GM-CSF administration to HIV-1 infected patients is reported to be associated with a reduction in viral load and increase in CD4+ T lymphocyte count.
b. HAART administration is associated with an increased risk of inflammatory vitritis in patients with CMV retinitis.
c. The incidence of adefovir-related adverse reactions involving the kidneys is significantly increased after six months of treatment with this drug.
d. Ritonavir appears to protect against hepatotoxicity in HIV-1 infected individuals.

## In Future Issues:

Controlling Antibiotic Resistance: One Small Victory?

# UPDATES

By Carol A. Kemper, MD

## Antenatal HIV Screening in Ireland

**Source:** Birchard K. *Lancet* 1998; 352:796.

This news brief from the *Lancet* describes Ireland's recent success in the care of HIV-infected pregnant women. Ireland provides antenatal antiretroviral therapy, presently using combinations of antiretroviral agents, to all known HIV-positive women. Since the program started in 1994, none of the children born to known HIV-positive women have been HIV infected. Based on this accomplishment, the Irish Department of Public Health is preparing draft guidelines for screening all pregnant women for HIV infection, much the same as that recently proposed for the United States. The head of the National Pediatric AIDS Program, Karina Butler, MD, acknowledged, however, that, as a result of the success of their program, some HIV-positive women are choosing to have more children. ■

## Another Bad Cat Tale. . .

**Source:** Zanusso G, et al. *Lancet* 1998;352:1116-1117.

Neurologists at the university of Verona report on the simultaneous occurrence of clinically similar spongiform encephalopathies in a 60-year-old man and his 7-year-old previously healthy cat. The cat usually ate canned cat food (which can contain cattle remains) and slept with her owner in the same bed. The man was not known to have any unusual dietary habits—although pensioners have been known to eat pet food because it's cheap.

The man presented with visual complaints, cerebellar ataxia, and myoclonic jerks; he rapidly deteriorated and died within two months. The cat presented with similar symptoms, and required euthanization one week after her owner's death. This rapid disease progression differs from other reports of feline spongiform encephalopathy.

Although there is considerable controversy whether differing strains of prion-protein complexes (e.g., from differing origins) can be distinguished based on their size and morphology, examination of the brain tissue from both the man and his cat showed similar histopathological changes, as well as similar prion-protein constellations—which Zanusso and colleagues believed were similar to those observed in cases of sporadic Creutzfeldt-Jakob disease, but differed from those associated with Bovine-spongiform encephalopathy (BSE).

While it is not clear whether these two cases represent a common source of infection (e.g., the cat food) or possible horizontal transmission (in either direction), Zanusso et al believed that, based on the genetic strain typing and the similar clinical presentation, the two cases appear to be causally related but inconsistent with BSE. ■

## Malarone for Malaria Prevention

**Source:** Shanks GD, et al. *Clin Infect Dis* 1998;27:494-499.

Current prophylactic regimens for malaria are limited by a lack of universal efficacy, convenience, and tolerance. The combination of atovaquone and proguanil (Malarone) has proven safe and effective in the treatment of drug-resistant *Plasmodium falciparum* and is being used with increasingly frequency in England and Europe. Although the mechanism is not well understood, atovaquone and proguanil (A/P) act synergistically against blood parasites (schizonticides).

Shanks and associates examined the safety and effectiveness of A/P as a chemoprophylactic agent in Lwak, Kenya, an area of intense disease activity in the spring and summer, when this study was conducted. Following a course of four tablets of atovaquone (250 mg) plus proguanil (100 mg) per day for three days (a regimen designed to eradicate any pre-existing infection), adult volunteers were randomized to one of three regimens for 10 weeks: two tablets daily, one tablet daily, or placebo.

None of the patients receiving either of the two treatment regimens developed *P. falciparum* infection, whereas more than one-half (52%) of the patients in the placebo group developed disease ($P = 0.001$). The frequency of side effects were comparable for all three groups, and none of the treated patients experienced dose-limiting side effects (one patient required hospitalization for repeated vomiting during the initial 3-day treatment course). Daily A/P was well tolerated and was 100% successful in preventing malaria during this 10-week trial in Kenyans at high risk for chloroquine-resistant malaria. Similarly, A/P was highly effective and well-tolerated when administered as prophylaxis to children in Gabon (Lell B, et al. *Lancet* 1998;351:709-713).

Malarone will be a valuable chemoprophylactic alternative to mefloquine in the United States once approved by the FDA and can safely be administered to children. The cost of a Malarone tablet in countries outside the United States is reportedly about $7, which is not cheap, but it is comparable to the cost of mefloquine in our area ($8.43 per tablet). ■