Providing Evidence-based Clinical Information for 23 Years

INFECTIOUS DISEASE ALERT®

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Antivirals and the SARS Coronavirus

ABSTRACT & COMMENTARY

Synopsis: *Interferon α-n1 (Wellferon), interferon α-n3 (Alferon), and interferon β-1b (Betaferon) were each found to have in vitro activity against a strain of the SARS coronavirus.*

Source: Tan ELC, et al. Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. *Emerg Infect Dis*. 2004;10:581-586.

TAN AND COLLEAGUES TESTED THE ACTIVITY OF A VARIETY OF antiviral agents against a Singapore strain of SARS coronavirus grown in Vero cells. No inhibition of cytopathic effect was found when the following drugs were used: acyclovir, ganciclovir, indinavir, nelfinavir, saquinavir, lamivudine zidovudine, oseltamivir, zanamivir, amantadine, foscarnet, interferon α-2a, interferon α-2b, and interferon β-1a. Complete inhibition of cytopathic effects was noted with interferon α-n1 (Wellferon), interferon a-n3 (Alferon), and interferon β-1b (Betaferon). Ribavirin exerted an effect only at concentrations that produced direct cytotoxicity.

COMMENT BY STAN DERESINSKI, MD, FACP

Many patients with SARS have been treated with a combination of ribavirin and corticosteroids. However, this and previous studies have failed to demonstrate clinically useful activity of ribavirin as a single agent in vitro. Neither agent has been demonstrated to be effective in clinical trials, and both have potential toxicities.

This study indicates that certain interferon preparations may have potential as therapeutic agents in patients with SARS. However, some of the results conflict with those previously reported. For instance, investigators at Fort Detrick found that recombinant interferon β-1a inhibited SARS coronavirus replication in vitro.[1] Consistent with the finding of in vitro activity with the non-pegylated form of this molecule,[2] pegylated interferon α, given prophylactically, significantly reduced viral replication and excretion, as well as pulmonary damage, in experimentally infected macaques.[3]

VOLUME 23 • NUMBER 9 • JUNE 2004 • PAGES 97-108

The combination of corticosteroids and interferon alfacon-1 (Infergen) has been reported to improve out-comes relative to patients given corticosteroids alone in an open-label study.[4] This consensus interferon was not evaluated by Tan et al. It differs from interferon α-2a and interferon α-2b by 18-19 amino acids, with changes at 2 of 3 interferon-binding sites.

Immunological approaches to treatment and prevention of SARS are also under investigation. A human monoclonal antibody to the S1 domain of the spike protein involved in binding to cellular receptors is an effective inhibitor of SARS coronavirus cell entry.[5] This finding also suggests that a vaccine that elicits antibody that binds to this site may potentially be protective against SARS. In fact, a DNA vaccine encoding the viral-spike glycoprotein induces neutralizing antibody and protective immunity in mice.[6] An adenoviral-based vaccine eliciting a response to the spike protein also has been demonstrated to elicit neutralizing antibody in rhesus macaques.[7] ■

Infectious Disease Alert, ISSN 0739-7348, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Christie Messina Petrone.

GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Infectious Disease Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

THOMSON
AMERICAN HEALTH CONSULTANTS

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail Address: customerservice@ahcpub.com
E-Mail Address: christie.petrone@thomson.com
World-Wide Web: www.thomson.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $249
(Student/Resident rate: $125).
Multiple Copies
1-9 additional copies: $224; 10 or more copies: $199.
Canada
Add 7% GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 36 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.
AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.
This CME activity was planned and produced in accordance with the ACCME Essentials.
This CME activity is intended for the infectious disease specialist. It is in effect for 36 months from the date of the publication.

Questions & Comments

Christie Messina Petrone,
Senior Copy Editor, at (404) 262-5416, or e-mail to christie.petrone@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, we disclose that Dr. Deresinski serves on the speaker's bureau of Merck, GlaxoSmithKline, Ortho, Bayer, and Pfizer. Dr. John is a consultant for Cubist, Roche, and BioMerieux, is on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Bayer, and Wyeth, and does research for Merck. Dr. Kemper serves on the speaker's bureau of Virologic, GlaxoSmithKline, Pfizer, and Agouron and is involved in research with Chiron, Merck, Agouron, and Virologic. Dr. Schleis is on the speaker's bureau for Aventis and Bayer and is a consultant for FFF Enterprises, Aventis, and Bayer. Dr. Muder does research for Aventis, and Pharmacia. Dr. Tice is a consultant for Roche, Merck, and ZLB and is on the speaker's bureau of Roche, Ortho, GlaxoSmithKline, and Pharmacia, and does research for Elan, Roche, Merck, Pharmacia, and Becton-Dickinson. Dr. Jenson is on the speaker's bureau of Merck. Dr. Donnelly is a consultant for OrthBioTech, and does research for Janssen, Merck, Novartis, Numico, Pharmacia, and Pfizer. Dr. Smilack reports no speaker's bureau, research, stockholder, or consulting relationships having ties to this field of study.
Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

References

1. Hensley LE, et al. Interferon-beta 1a and SARS coronavirus replication. *Emerg Infect Dis*. 2004;10:317-319.
2. Stroher U, et al. Severe acute respiratory syndrome-related coronavirus is inhibited by interferon-alpha. *J Infect Dis*. 2004;189:1164-1167.
3. Haagmans BL, et al. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. *Nat Med*. 2004;10:290-293.
4. Loutfy MR, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: A preliminary study. *JAMA*. 2003;290:3222-3228.
5. Sui J, et al. Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. *Proc Natl Acad Sci USA*. 2004;101(8):2536-2541.
6. Yang ZY, et al. A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. *Nature*. 2004;428:561-564.
7. Gao W, et al. Effects of a SARS-associated coronavirus vaccine in monkeys. *Lancet*. 2003;362:1895-1896.

Melioidosis in Australia

ABSTRACT & COMMENTARY

Synopsis: *Melioidosis is endemic in parts of Australia that may be visited by tourists.*

Source: Melioidosis—Australia (Northern Territory). ProMED-Mail Archives. March 22, 2004.

ALLEN CHENG REPORTED THAT, AS OF MARCH 20, 15 patients with melioidosis had been seen at the Royal Darwin Hospital during the 2003-2004 rainy season. The Royal Darwin is the referral center for the "Top End" region of the Northern Territory of Australia.

■ COMMENT BY STAN DERESINSKI, MD, FACP

Melioidosis, first described in homeless morphine addicts in Rangoon in 1932, is caused by the soil and water organism *Burkholderia pseudomallei*. It is endemic in tropical areas, particularly in Southeast Asia. Cases are also seen in Africa, India, the Middle East, the South Pacific, and northern Australia.[1] Isolated cases have occurred in tropical areas of the Western Hemisphere, as well as in Hawaii and Georgia. Infection is believed to be acquired by inhalation of contaminated dust, ingestion of water containing the organism, and by contact with conta-

minated soil. The latter is facilitated by the presence of abrasions or more severe breaks in epidermal continuity. Person-to-person transmission by contact with body fluids is described, including 2 cases of sexual transmission.

Melioidosis in Australia is not restricted to the Northern Territory, also being reported from Queensland in association with heavy rains. Between November 1, 2001, and October 31, 2002, 47 cases were identified in the Northern Territory and Queensland. While the average annual incidence per 100,000 population was 58 overall, it was 25.5 among indigenous Australians.[2] Eighty-seven percent of cases occurred during the wet season. The mortality rate was 21%. In an earlier series of 252 cases in northern Australia over 10 years, 46% of patients were bacteremic, and the overall mortality was 19%.[3]

The incubation period may be as short as 2 days and as long as years. This means that patients may present after many years in a nonendemic area. After the Vietnam war, this knowledge led to concern of a "ticking time bomb" of disease emerging in veterans well after the war. Fortunately, this event never materialized to any extent.

Infection may be inapparent. Clinical disease may result from an acute localized infection, such as a local cutaneous infection at the site of inoculation, which may, however, lead to bacteremia. Pulmonary infection may range from a relatively mild bronchitis to severe progressive pneumonia, and acute bloodstream infection may present as septic shock. Chronic infection may affect any body organ. One-third of affected Thai children present with acute uppurative parotitis.

B pseudomallei grows readily on a number of media. It may be suspected when an oxidase-positive Gram-negative bacillus is found to be resistant to gentamicin and colistin but susceptible to amoxicillin/clavulanate—a quite unusual antibiotic susceptibility pattern.

Patient with comorbidities such as diabetes mellitus and chronic lung disease are at increased risk of infection. An adult with cystic fibrosis who had returned from vacation in northern Australia was recently seen by the Infectious Disease Service at Stanford with an exacerbation of pulmonary infection due to *B pseudomallei*. The association with cystic fibrosis has previously been reported a number of times. The combination may be lethal.

A variety of antimicrobials have been used in the treatment of melioidosis. A randomized trial in Thailand involving 214 culture-confirmed cases found no difference in mortality between patients randomized to either ceftazidime or imipenem, although failure after 48 hours of therapy was observed more frequently in the cephalosporin recipients.[4] Meropenem is used at the Royal Darwin Hospital where, in fact, all patients admitted to their ICU with sepsis during the wet season receive this carbapenem as initial therapy until culture results exclude melioidosis. This same group has also reported that adjunctive therapy with G-CSF improved survival in a cohort analysis with comparison to a historical control.[5] ■

References

1. White NJ. Melioidosis. *Lancet*. 2003;361:1715-1722.
2. Cheng AC, et al. Melioidosis in northern Australia, 2001-02. *Commun Dis Intell*. 2003;27:272-277.
3. Currie BJ, et al. Endemic melioidosis in tropical northern Australia: A 10-year prospective study and review of the literature. *Clin Infect Dis*. 2000;31:981-986.
4. Simpson AJ, et al. Comparison of imipenem and ceftazidime as therapy for severe melioidosis. *Clin Infect Dis*. 1999;29:381-387.
5. Cheng AC, et al. Adjunctive granulocyte colony-stimulating factor for treatment of septic shock due to melioidosis. *Clin Infect Dis*. 2004;38:32-37.

An Aspirin A Day Keeps the Biofilm at Bay

ABSTRACT & COMMENTARY

Synopsis: *Aspirin possesses potent activity against the formation of biofilms formed by* Candida albicans *and could be useful in combination for managing biofilm-associated infections.*

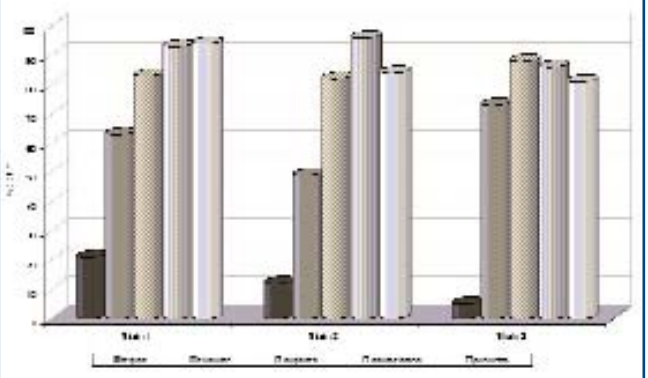
Source: Alem MAS. Effects of aspirin and other nonsteroidal anti-inflammatory drugs on biofilms and planktonic cells of *Candida albicans*. *Antimicrob Ag Chemother*. 2004;48:41-47.

PATHOGENIC FUNGI INCLUDING THE YEAST *Candida albicans* produce prostaglandins that may modulate host immune responses but also assist virulence by enhancing germ-tube formation. Inhibitors of cyclooxygenase (COX) isoenzymes (eg, ibuprofen) also inhibit fungal prostaglandin synthesis. This is manifest in *C albicans* by loss of biofilm production and less hyphae formation. Alem and colleagues explored this phenomenon further by exposing 3 strains of C albicans to aspirin and a variety of other NSAIDS (diclofenac, ibuprofen, indomethacin, meloxicam, piroxicam, etodolac, celecoxib, and nimesulide) and showed aspirin to be very effective in preventing biofilm formation at concentrations of 100 μM or more (= 18 mg/L)—more so than the other NSAIDs (see Figure)—and at concentrations that are attainable in blood after a regular dose of 500-1000 mg.

Aspirin did not simply inhibit biofilm formation since it

Figure

The Effect of Aspirin and Other NSAIDS on Biofilm Formation of *Candida albicans*



had little effect on adhesion but inhibited the metabolic activity of yeasts already embedded in established biofilm. The effect could be reversed by adding prostaglandin E2. Aspirin also drastically reduced the viability of the biofilm to 1%, whereas other COX inhibitors were much less effective, with indomethacin having no effect at all. The cell surfaces of the yeast appeared wrinkled after exposure to aspirin, but not the other drugs, indicating that aspirin exerts damage in several different ways. The NSAIDs could be divided into 2 groups in terms of their effect on biofilm. Both yeast cells and hyphal forms were apparent after exposure to piroxicam and aspirin, whereas exposure to etodolac and indomethacin resulted in biofilms consisting almost entirely of yeast cells. The effect of each drug on germ-tube formation was examined specifically and showed that aspirin had almost no effect, while ibuprofen, indomethacin, and celecoxib resulted in 80% fewer germ tubes when compared with untreated controls. Alem et al concluded that the effects of NSAIDS on the development of biofilms and morphogenesis of C albicans suggest that these processes involve COX-dependent synthesis of fungal prostaglandins, opening up therapeutic possibilities for managing biofilm-associated infections, particularly with aspirin.

COMMENT BY J. PETER DONNELLY, PhD

Biofilms are now accepted as the typical mode of growth for many, if not most, bacteria and yeasts associated with infections on natural and artificial surfaces, be it mucous membranes or catheters and implants. Unlike planktonic cells, cells in biofilm consortia are more resistant to biocides, antiseptics, and antibiotics, making prevention and treatment difficult, if not impossible. The recalcitrant nature of implant infections with *C albicans* such as those affecting central venous catheters in patients for whom they are fairly essential is frustrating, with removal of the device being the only effective option. This makes the observations reported in this article all the more interesting, especially as the NSAIDS are readily available and familiar drugs. Exploring aspirin further for its efficacy in preventing colonization of devices is an obvious point of departure. This might be achieved by instillation or using the so-called "lock" technique whereby the drug is left in contact with the lumen surfaces of the device for several minutes as has been done with antibiotics. The apparent activity of aspirin against bacteria like the staphylococci commonly involved in these infections makes this even more attractive. Just as interesting is the observation that other NSAIDS like ibuprofen, indomethacin, and celecoxib inhibit germ-tube formation, which is a prelude to infection on body surfaces including the oral cavity and vagina. This may open up alternative avenues for patients suffering chronic infections of these sites. Most intriguingly of all, these apparently off-beat laboratory studies serve to remind us to look beyond the obvious and explore the effects of agents that are not primarily antimicrobial but nonetheless influence the physiology of pathogenic microorganisms and help shift the balance in favor of the host. ■

Suggested Reading

1. Bouza E, et al. Catheter-related infections: Diagnosis and intravascular treatment. *Clin Microbiol Infect*. 2002;8:265-274.

Misidentification of *Candida* Species by Clinical Laboratories—Not a Good Thing!

ABSTRACTS & COMMENTARY

Synopsis: *Almost 1 in 20* Candida *species isolated were misidentified by clinical laboratories; these errors have potential for engendering adverse clinical outcomes.* C glabrata *was the species most frequently misidentified.*

Sources: Coignard C, et al. Resolution of discrepant results for Candida species identification by using DNA probes. *J Clin Microbiol*. 2004;42:858-861; Hajjeh RA, et al. Incidence of bloodstream infections due to *Candida* species and in vitro susceptibilities of isolates from 1998 to 2000 in a population-based active surveillance program. *J Clin Microbiol*. 2004;42:1519-1527.

COIGNARD AND COLLEAGUES AT THE CDC EXAMINED 935 Candida bloodstream isolates from 51 institu-

tions in Connecticut and the city and county of Baltimore. They used a DNA probe-based species identification system (PCR-EIA) in order to resolve discrepancies in phenotypic identification by more classical methods between the referring institutions and CDC.

Twenty-three (54%) of the referring institutions used germ-tube formation tests to identify *Candida albicans,* and 80% used one or another carbon assimilation biochemical panels to identify non-albicans species. The CDC used the CHROMagar, API 20C AUX (also used by 39% of referring sites) or RaPID Yeast Plus system, and microscopic morphology on cornmeal-Tween 80 plates.

CDC's phenotypic identification of all but one isolate was confirmed by PCR-EIA, but identification discrepancies between CDC and the referring institutions were observed with 43 (4.6%) of the isolates (*see Table*). *C albicans* comprised 45% of isolates, *C glabrata* 24%, and *C parapsilosis* 13%. *C glabrata* was the organism that had most frequently been misidentified, accounting for 37% of discrepancies, followed by *C parapsilosis* (35%). Seven percent of *C glabrata* and 12% of *C parapsilosis* were misidentified. Of the 16 *C glabrata* isolated and for which a discrepancy was observed, 7 (44%) were misidentified as *C albicans*. Six *C parapsilosis* were misidentified as *C albicans*, as was one *C lusitaniae*.

Hajjeh and colleagues at the CDC, Yale, and Johns Hopkins examined the susceptibility of this group of isolates to antifungal agents by NCCLS broth microdilution, except for amphotericin B, for which the E test was used. High-level resistance (MIC > 64 µg/mL) to fluconazole was detected in only 1.2% of *C albicans* and in 5.9% of non-albicans isolates. While all *C parapsilosis* isolates were susceptible, 7% of *C glabrata* and 6% of *C tropicalis* were resistant. Only 35% of *C krusei* isolates were considered resistant. Except for *C albicans*, the frequencies of itraconazole resistance were somewhat higher. The amphotericin B MIC was > 1 µg/mL for 1.7% of all isolates and was > 1 µg/mL for only 0.4%. The amphotericin B MIC90 for the 15 *C lusitaniae* isolates was 0.25 µg/mL, identical to that for *C glabrata*, while the MIC90 for *C krusei* was 2.0 µg/mL. Flucytosine performed well, with only 2.4% of all isolates resistant.

TABLE

Identification Discrepancies

Organism	Total #	# Discrepant	% Discrepant	% of Total Discrepant	% Flu res.*
C glabrata	226	16	7%	37%	7.1%
C parapsilosis	123	15	12%	35%	0%
C tropicalis	118	7	6%	16%	7%
*C albicans***	423	3	0.7%	7%	1.2%
C lusitaniae	15	2		5%	0%

* MIC > 64 µg/mL.

**Does not include 9 identified as *C dubliniensis*.

COMMENT BY STAN DERESINSKI, MD, FACP

While the overall identification error rate of 4.6% does not seem terrible, severe consequences could potentially result from some of these misidentifications. Because antifungal susceptibility testing is not readily available to many clinicians (susceptibility testing was performed at the referring institution on only 10% of isolates) and, even when it is, the results are often not available for a week or more, there is a frequent reliance upon species identification in predicting likely antifungal susceptibility patterns and antifungal therapy. Thus, an identification of an isolate as *C albicans* usually implies to the clinician a relatively high likelihood of susceptibility to azole antifungal agents. Initial identification by the laboratory of "*Candida*, non-albicans" in contrast, raises increased concern about azole resistance.

Species identification of some non-albicans isolates may further increase that concern. For example, *C krusei* is considered invariably resistant to high concentrations of fluconazole (although this was not found with the isolates studied here). *C glabrata*, which is being isolated with increasing frequency from the bloodstream while the incidence of *C albicans* bloodstream infection is decreasing,[1] and which comprised 24% of the bloodstream isolates in this study, is also more frequently resistant to fluconazole. While 7% of *C glabrata* in this study had a fluconazole MIC > 64 µg/mL, a recent nationwide survey of 559 *C glabrata* isolates reported a 9% incidence of resistance; 31% were "susceptible-dose dependent" with MICs 16-32 µg/mL, a category not reported here by the CDC.[2] In addition, there was a striking geographic variation in resistance rates ranging from none in New England (a result not reflected in the Connecticut data here) to 15% in the Mid-Atlantic states.[2] *C glabrata* can be problematic in other ways. It evidences delayed growth in blood culture, a feature that could delay institution of antifungal therapy.[3] Similar delayed growth in urine culture can lead to missing its presence altogether in consequence of the early discarding of culture plates. Furthermore, misidentification of *C glabrata* as *C albicans* in blood could lead to inappropriate antifungal therapy with potentially severe consequences.

The changing epidemiology of invasive *Candida*

infections, in particular the increasing proportion due to non-albicans strains, has important consequences for patient management. This change puts increasing demands upon our clinical laboratories, clinicians, and pharmacy budgets. Clinicians must have an increased level of suspicion of the presence of invasive candidiasis, particularly in cases without positive blood cultures or in critically ill patients for whom the delay in institution of antifungal therapy until blood cultures turn positive could prove lethal. Laboratories must ensure the rapid isolation and accurate identification of infecting pathogens, as well as the availability of timely availability of antifungal susceptibility data. Pharmacy budgets are in trouble. ■

References

1. Trick WE, et al. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989-1999. *Clin Infect Dis*. 2002;35:627-630.
2. Pfaller MA, et al. Variation in susceptibility of bloodstream isolates of *Candida glabrata* to fluconazole according to patient age and geographic location. *J Clin Microbiol*. 2003;41:2176-2179.
3. Horvath LL, et al. Detection of simulated candidemia by the BACTEC 9240 system with plus aerobic/F and anaerobic/F blood culture bottles. *J Clin Microbiol*. 2003;41:4714-4717.

Does Eradication of Staphylococci from the Nose Reduce Nosocomial Infection in Nonsurgical Patients?

ABSTRACT & COMMENTARY

Synopsis: *Mupirocin application to the nose of hospitalized* Staphylococcus aureus *carriers did not decrease the incidence of nosocomial* S aureus *infection, but it did delay its appearance.*

Source: Wertheim HFL, et al. Mupirocin prophylaxis against nosocomial *Staphylococcus aureus* infections in nonsurgical patients. *Ann Intern Med*. 2004;140:419-425.

THIS STUDY IS AN ATTEMPT TO DETERMINE WHETHER eradication of *Staphylococcus aureus* from its residence in the nose decreases nosocomial infection from that organism. Wertheim and associates screened more than 17,000 nonsurgical adult patients in 4 hospitals in the Netherlands to detect those colonized with *S aureus*. One-quarter (4479, or 25.6%) of the patients were found to be culture-positive. Some 1600 patients survived exclusion criteria (such as presence of *S aureus* infection at the time of enrollment, discharge from the hospital before enrollment could be accomplished, and declining participation in the study) and were randomized to receive either mupirocin 2% nasal ointment or an odor- and appearance-matching placebo twice daily for 5 days. The presence of nosocomial *S aureus* infection was determined by reviewing all microbiology culture reports during and for 6 weeks after patients' hospitalization. Few medication side effects were reported.

The results? Although the rate of nosocomial *S aureus* infection was slightly lower in the mupirocin group (1.9% vs 2.4%), the difference was not statistically significant. Likewise, duration of hospitalization and in-hospital mortality were similar in both groups. However, in patients who developed nosocomial *S aureus* infection, onset of infection was significantly delayed in the mupirocin group (median time to infection, 32 vs 13 days [P = .02]). Wertheim et al hypothesized that the delay may have resulted from post-prophylaxis *S aureus* recolonization of the nose from extranasal sites since it is known that recolonization may occur in 38-43% of patients 4-6 weeks after mupirocin use. They further opined that a repeat mupirocin application might lead to increased efficacy by preventing such recolonization.

■ COMMENT BY JERRY D. SMILACK, MD

Chronic or persistent nasal colonization by *S aureus* occurs in 10-20% of healthy individuals; transient or short-lived colonization occurs in up to 70-90%. Higher rates of colonization occur in hemodialysis and HIV-infected patients, among others. Given that most staphylococcal infections develop in those already colonized with the organism, it would seem reasonable to speculate that eradicating the colonizing bacteria should reduce the likelihood of infection. Because the most important locus of staphylococcal colonization is the nasal mucosa, application of an antistaphylococcal agent to the nose—and mupirocin (Bactroban®) has emerged as the agent of choice—has been investigated intensively. Several well-designed, placebo-controlled, prospective, double-blinded studies have demonstrated that nasal mupirocin can effectively reduce staphylococcal infections in hemodialysis, peritoneal dialysis, and certain other defined populations.[1,2]

Wertheim et al directed their attention to a different population: the nonsurgical hospitalized patient. The

rationale here is that *S aureus* is a frequent cause of hospital-acquired infections. If these infections could be prevented, morbidity and mortality associated with hospitalization could be reduced, and both patients and the health care system in general would be the winners. From a population of more than 17,000 hospitalized patients over a 2-year period, Wertheim et al identified one-quarter with *S aureus* nasal colonization. After a large number of patients were excluded for what appear to have been valid exclusionary criteria, half of the remaining 1600-plus patients were then randomized to receive a 5-day treatment course of either nasal mupirocin or a placebo. *S aureus* infections were then identified by positive cultures for the organism over the period of hospitalization and for 6 weeks thereafter. One could quibble with this method of defining nosocomial infection. A number of patients may well have developed staphylococcal infection and not had cultures performed; their infections would have escaped detection. Wertheim et al argue that such events may well have occurred, but should have done so with equal frequency in treatment and placebo groups and should therefore not have altered their findings.

Why did this study not find a significant benefit to the use of nasal mupirocin? There are several possible explanations. Perhaps most important is that the population Wertheim et al studied was at low risk for development of the end point in question, namely nosocomial *S aureus* infection. Their pre-study estimate of nosocomial *S aureus* infection among staphylococcal nasal carriers was 6%. Their study was designed to enroll a sample size sufficient to detect a 50% reduction of infection with 80% certainty. In fact, they found the nosocomial infection rate due to *S aureus* to be only 2.8% in the placebo group. Therefore, a much larger group of patients would have been necessary to detect a statistically significant benefit from any intervention. It is possible that greater rates of infection would have occurred had there been more high-risk patients in the study population (for example, greater numbers of dialysis or intensive care unit patients). Other reasons for the failure to detect benefit include questions about (1) whether repeat mupirocin dosing might be helpful, and (2) whether extranasal colonization may have been an important source for staphylococcal infection. Another unanswered question is if mupirocin did, in fact, eradicate nasal colonization in the study patients. Wertheim et al did not report results of any follow-up nasal cultures in patients who received the antibacterial agent.

Even if nasal mupirocin were to have been shown to have a salutary effect, the question then becomes whether the findings are transferable to other hospitals and other types of patients. How should screening for nasal colonization be accomplished? Should it be done before hospital admission? Should it be done only in those nonsurgical patients who are at highest risk (eg, dialysis patients)? But the biggest question—the one that has prevented widespread use of mupirocin in certain surgical or other settings, where it has clearly been shown to be of benefit—is whether resistance to mupirocin will emerge with increasing usage. Substantial resistance has already been demonstrated in several studies.[3,4] ■

References

1. Tacconelli E, et al. Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: A meta-analysis. *Clin Infect Dis*. 2003;37:1629-1638.
2. Raz R, et al. A 1-year trial of nasal mupirocin in the prevention of recurrent staphylococcal nasal colonization and skin infection. *Arch Intern Med*. 1996;156:1109-1112.
3. Miller MA, et al. Development of mupirocin resistance among methicillin-resistant *Staphylococcus aureus* after widespread use of nasal mupirocin ointment. *Infect Control Hosp Epidemiol*. 1996;17:811-813.
4. Cookson BD. The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice. *J Antimicrob Chemother*. 1998;41:11-18.

ICAAC/IDSA/ASTMH 2003

CONFERENCE COVERAGE

The following summary of selected abstracts from 3 meetings will be published in multiple parts. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) met in Chicago September 14-17, 2003. The Infectious Disease Society of America (IDSA) met in San Diego October 9-12, 2003. The American Society of Tropical Medicine and Hygiene met in Philadelphia December 3-7, 2003. ***— Stan Deresinski, MD, FACP***

Gastrointestinal Infection

C difficile

Piperacillin-tazobactam exposure failed to induce *C difficile* toxin production in a human chemostat gut model. Increased use of piperacillin/tazobactam was reported to be associated with reduced rates of *C difficile*

diarrhea. Separately, a 68% reduction in piperacillin-tazobactam use resulting from a nationwide shortage, with a concomitant increased use of other antibiotics, was associated with a 47% decrease in the incidence of *C difficile* colitis (*ICAAC K-728, K-730, K-732*).

In addressing the issue of how many tests for *C difficile* toxin are necessary to effectively rule out its presence, a retrospective review found that 97.4% of cases of *C difficile* disease were detected with the first 2 cytotoxicity assays performed (*IDSA 336*).

Given the apparently increased frequency of treatment failure and relapses of *C difficile*-associated disease, novel effective therapies are urgently required. Ramoplanin was active against strains of *C difficile* resistant to vancomycin or metronidazole. Five patients with protracted and/or recurrent diarrhea due to *C difficile* were given 1-6 doses of intravenous immunoglobulin. Three "had a good therapeutic response," and 1 had recurrence at 6 weeks. The patient who received 6 doses died of intractable *C difficile*-associated disease (*ICAAC K-729, E-2188*).

E coli 0157:H7

A retrospective review of 362 patients with *E coli* 0157:H7 enteritis found that 16% who received antibiotics developed hemolytic uremic syndrome, while 29% of those who did not developed this complication. This finding stands in contrast to previously published studies that have reported that antibiotic therapy of this infection is associated with an increased risk of hemolytic uremic syndrome (*IDSA 864*).

Salmonella

Multistate outbreaks of *S newport* infection were associated with fresh tomatoes from a single packing-house and with imported honeydew melon. An outbreak of *S javiana* infections occurred in organ transplant recipients who had attended the US Transplant Games, a 4-day athletic competition among 1500 recipients held at a Florida theme park (*IDSA 870, LB-9, 871*).

Children with typhoid fever were treated with either oral azithromycin for 5 days (n = 32) or IV ceftriaxone for 5 days (n = 36). Blood cultures remained positive on day 3 in 37% of azithromycin recipients but in no cetriaxione recipients. All day 8 blood cultures were sterile, and microbiological cure was achieved in 100% and 97%, respectively, and clinical cure in 94% and 97% (*IDSA 869*).

V cholerae

A single dose of ciprofloxacin was as effective as 12 doses of erythromycin in the treatment of childhood cholera in a randomized trial in South Africa (*ICAAC G-1551*).

Norovirus

Outbreaks of norovirus acute gastroenteritis occurred during several consecutive voyages of a cruise ship. Investigation suggested both foodborne and person-to-person transmission. Detection of identical strains of norovirus among case passengers before and after ship sanitization suggested environmental contamination (*IDSA 880*).

Despite early institution of control measures, an outbreak of norovirus on a ship continued throughout its cruise, affecting 399 of 1038 (38%) passengers. The strain of norovirus detected was genetically indistinguishable from that identified during an outbreak on the same ship that occurred 15 months earlier. Smaller outbreaks involving 3%, 13%, and 5% of passengers occurred on the next 3 voyages of the ship, but none has occurred since the ship was removed from service and aggressively cleaned. Epidemiologic investigation suggested person-to-person transmission (*IDSA 879*).

Cruise ships are not the only site of norovirus outbreaks. The overall mortality rate in a nursing home during a norovirus outbreak was 3 times higher than in the months preceding and following it (*IDSA 524*).

Traveler's Diarrhea

Traveler's diarrhea is not always a trivial self-limited event. Six of 62 students who developed diarrhea while in Mexico subsequently developed irritable bowel syndrome (*IDSA 876*).

Bloodstream Infection, Endocarditis

Patients with peripheral intravenous catheters were randomized on day 3 of catheterization to either have routine catheter replacement every 3 days or no replacement. Routine, peripheral IV-catheter change did not reduce the incidence of phlebitis or of a positive catheter culture (*ICAAC K-2041*).

Infants and children who had undergone cardiac surgery were randomized to have a transparent dressing alone or covering a chlorhexidine-impregnated dressing placed over their central venous catheter access sites. While the chlorhexidine dressing was associated with reduced site colonization, there was no difference in related bloodstream infections (4% in each group) (*ICAAC K-580*).

A meta-analysis of 40 studies concluded that the most accurate diagnostic method for intravascular device-related bloodstream infection was the use of paired

quantitative blood cultures. The most accurate rapid test not requiring catheter removal was the acridine orange leukocyte cytospin. (For a recent prospective analysis of the latter technique, see *JPEN J Parenter Enteral Nutr*. 2003;27:146.) Separately, the use of quantitative blood cultures obtained simultaneously through a central venous catheter and from a peripheral vein had sensitivity, specificity, and negative predictive values of 94-98% when the CVC specimen had > 15 CFU (*ICAAC K-2038, D-1698*). It has also been recently reported that a differential time to blood culture positivity between central and peripheral samples ≥ 120 minutes is highly accurate in the diagnosis of catheter-related bloodstream infection (*Ann Intern Med. 2004;140:18*).

The necessity for immediate IV catheter removal in patients with suspected infection of a vascular access device was addressed in a clinical study. Sixty-four patients with suspected catheter-related infection, but who were hemodynamically stable and did not have proven bacteremia, insertion-site infection, or an intravascular foreign body, were randomized to immediate catheter removal or "watchful waiting." There was no difference in outcome associated with the 2 approaches (*ICAAC K-2039*).

Valve surgery in patients with complicated left-sided native-valve endocarditis was independently associated with reduced mortality at 6 months, especially in patients with moderate-to-severe congestive heart failure (*IDSA 492*).

Sepsis

Deterioration or lack of improvement in hemodynamic status, fever, and leukocyte count during the first 48-72 hours of sepsis management is associated with a 62% likelihood that the empirical antibiotic therapy administered is inappropriate. Examination of 1342 patients entered in a multicenter, controlled trial of etanercept in the treatment of severe sepsis found that inappropriate initial antimicrobial therapy was independently associated with increased mortality (OR, 1.5; $P = .02$) (*ICAAC L-118, L-112*).

A meta-analysis of 64 randomized trials involving non-neutropenic patients with sepsis found that the combination therapy with an aminoglycoside plus a β-lactam was not associated with reduced mortality compared to monotherapy with a β-lactam (*ICAAC L-621*).

Neutropenia

Maybe it's OK to eat the salad after all! Twenty patients undergoing remission induction therapy for acute leukemia with selective decontamination of the digestive tract were randomized to receive either a low-bacterial or a standard hospital diet. There was no difference in fecal contamination with potential pathogens or in number of infections (*ICAAC K-1372*).

Ninety-two percent of 36 episodes of low-risk febrile neutropenia treated with orally administered gatifloxacin responded, with defervescence occurring at a median of 2 days. A meta-analysis of 15 trials comparing oral to intravenous antibiotic therapy for febrile neutropenia in the absence of hemodynamic instability, altered mental status, end-organ failure, inability to swallow, pregnancy, and lactation found that the 2 strategies yielded equivalent results (*ICAAC L-115, IDSA 375*).

Two randomized trials found that piperacillin/tazobactam and cefepime yielded comparable results as initial empiric antibacterial therapy in febrile neutropenic patients with hematologic malignancies (*ICAAC L-114, IDSA 373*).

In a randomized trial, caspofungin and itraconazole, each administered intravenously as antifungal prophylaxis in patients with myelodysplastic syndrome undergoing induction chemotherapy, yielded similar results (*ICAAC M-984*).

Caspofungin was compared to liposomal amphotericin B (3 mg/kg/d) as empiric antifungal therapy in persistently febrile neutropenic patients in a large, randomized trial. Caspofungin proved comparable to the liposomal amphotericin B in overall success and was better tolerated (*ICAAC M-1761*).

Surgical Infections

The isolation of clindamycin-resistant *B fragilis* from the peritoneal cavity of patients with intra-abdominal infection was associated with worse outcome than was isolation of susceptible isolates in a case-control study. Cure rates at end of treatment in patients with intra-abdominal infections originating in the colon were 83% both in patients randomized to receive ertapenem 1 g q24h and in those randomized to receive piperacillin/tazobactam 3.375 g q6h (*ICAAC K-563, IDSA 328*).

A study of 30 cirrhotics with peritonitis and bacteremia due to *E coli* found that the expected increase in C-reactive protein, a protein synthesized by the liver, was intact but attenuated relative to patients without liver dysfunction (*IDSA 733*).

Only 2.45% of 937 patients undergoing bariatric surgery developed nosocomial infection, but 21.7% of the 23 infected patients died (*IDSA 546*).

Forty percent of surgical-site infections after mastectomy and breast reconstructive surgery were initially diagnosed > 30 days after surgery (*ICAAC K-1302*).

The use of nasal mupirocin was associated with a reduction in deep sternal wound infections due to *S aureus* in patients undergoing coronary artery bypass grafting, when compared to noncontemporaneous controls (*IDSA 560*).

A meta-analysis of 7 randomized trials found that vancomycin prophylaxis was not more effective than beta-lactam prophylaxis in patients undergoing cardiac surgery (*ICAAC K-1295*).

Orthopedic Infections

Sixteen of 509 (3%) patients undergoing revision arthroplasty were discovered to have previously unsuspected prosthetic joint infection. One-half were due to coagulase-negative staphylococci and one-quarter to *Propionibacterium* spp. Nine had antibiotic impregnated cement placed at revision, and 12 received IV antibiotics for a median of 28 days (range, 2-42). Nine received chronic oral suppression. One failure occurred 2.9 years after revision and consisted of infection with the "same" organism with a different antibiogram (*IDSA 579*).

The synovial fluid of patients with aseptic knee implant failure (n = 21) or infection (n = 21) who did not have underlying inflammatory joint disease was prospectively studied. Gross purulence was absent in the aseptic group but was present in two-thirds of the latter. The synovial fluid of the aseptic group had a lower mean WBC count (742/mm^3 vs 56,422/mm^3) and percentage of neutrophils (15% vs 94%). While there was overlap in the total WBC, there was none when the percentage of neutrophils was examined (*ICAAC K-568*).

Ninety-nine of 509 (19%) episodes of prosthetic joint infection were treated with debridement and retention of the prosthesis with a 2-year cumulative probability of success of 59%. IV antibiotics were administered for a median of 28 days, with suppressive oral antibiotics given for a median duration of 280 days to 89% of patients. Variables associated with an increased risk of treatment failure included *S aureus* infection, the presence of a sinus tract at presentation, and a duration of symptoms prior to debridement of more than 7 days (*IDSA 493*).

The median interval between resection and reimplantation arthroplasty in 232 patients with prosthetic joint infection treated with a 2-stage exchange was 67 days (range, 8-1900). Cultures were negative at the time of reimplantation in 91%. An antibiotic impregnated spacer was placed in 72%, and the median duration of IV antibiotic therapy was 42 days. The 2-year probability of success was 85% but was only 70% in 23 patients with acute inflammation present at the time of reimplantation (*IDSA 283*).

Twenty patients with staphylococcal or enterococcal infections involving orthopedic hardware were treated with linezolid, as well as debridement and, in 10 patients, device removal. Patients were followed for a mean of 9 months after completion of 5-422 days (median, 32 days) of therapy. Clinical cure or improvement occurred in 90%, but bacterial persistence was documented in 3 patients (15%). Eight (40%) developed reversible "myelosuppression," and 1 (5%) developed irreversible painful neuropathy. Separately, 53 patients with osteomyelitis were treated with linezolid for a mean duration of 54 days (range, 1-390 days). Clinical cure or improvement was achieved in 72% with follow-up of 6-24 months. Treatment was "well tolerated" (*IDSA 318, 319*).

A retrospective review of 639 patients with vertebral osteomyelitis found that the mean duration of IV antibiotic administration was 6.4 weeks, and total duration of antibiotic therapy (IV plus oral) was 13.4 weeks; 2 patients remained on suppressive therapy. Only 1 relapse of infection occurred—the affected patient had received IV antibiotic for 12 weeks (*IDSA 322*). ■

CME Questions

17. The prostaglandins of *Candida albicans* are involved in:

a. cell growth.
b. hyphal formation.
c. cell division.
d. adhesion to surfaces.
e. antifungal resistance.

18. True or false? Nasal mupirocin has been shown to reduce the incidence of nosocomial *Staphylococcus aureus* infection in surgical, as well as nonsurgical, hospitalized patients.

19. Concerns about mupirocin use have focused on:

a. development of resistance among *S aureus* isolates.
b. development of resistance among Gram-negative isolates.
c. the cost of treating large numbers of individuals.
d. None of the above

Correct answer: a

Answers: 17(b); 18(False); 19(a)

In Future Issues:

Conference Updates

UPDATES

By Carol A. Kemper, MD, FACP

Animal Reservoirs for SARS

Source: ProMED-mail post. April 17, 2004.

LAST YEAR, CHINA DESTROYED thousands of civet cats, either hoping to eradicate a primary reservoir for human infection or to impress an anxious public that their government was doing something. However, the SARS Control and Prevention Team in the Guangdong Province recently reported that in addition to civets, several wild animals, including foxes, hedge-shrews, and cats, also carry antibodies for SARS virus. In addition, screening recipients in 16 different cities in this southern province, the team also found that 105 of 994 people (11%) working in animal markets tested positive for SARS antibodies, but only 4 of 123 (3%) civet handlers tested positive. These data suggest that SARS has been present in a number of different animals, as well as humans, in Southern China, probably for some time. Whether there was a recent shift in transmission patterns or violence remains to be determined. ■

SARS Screening Identifies TB Cases Instead

Source: *MMWR Morb Mort Wkly Rep*. 2004;53(15):321-322.

SCREENING FOR SARS IN HOSPITAL workers in Taipei, Taiwan, last spring ultimately led to the diagnosis of 60 cases of documented or suspected nosocomial tuberculosis. Increased vigilance for SARS in health care workers in April 2003 initially identified a health care worker with fever and respiratory illness with evidence of a pleural effusion. A pleural biopsy grew *Mycobacterium tuberculosis* (MTb). Further investigation found 6 coworkers who also had evidence of MTb. Hospital administration then expanded their search for nosocomially acquired cases and over the next 6 months screened 2872 health care workers, identifying 53 additional cases of suspected or documented MTb. Most of the cases were women (85%), with a median age of 30. The majority of the cases (72%) had chest radiographic evidence consistent with a diagnosis of pulmonary MTb, 8% had pleural involvement, 2% had lymphadenitis, and 18% were unclassified. Most of these were suspected of having early pulmonary involvement, as only 5 of 59 with pleural and pulmonary disease reported symptoms. Sputum smears and/or cultures were positive in 19%; thus, the diagnosis was confirmed in only a small number of cases. Seven of 8 culture-confirmed cases had matching genotypes by RFLP technique.

Further investigation tied the cases back to a single patient with a lengthy 3-month hospital course who required admission to the intensive care unit for ventilatory support. This patient was eventually diagnosed with smear-positive pulmonary MTb. Subsequent analysis confirmed that this patient's genotype matched that of the 7 HCWs above. While most of those affected were nurses, respiratory technicians and radiology technicians were the hardest hit—reinforcing the need for good infection control techniques during respiratory treatment and suctioning, as well as the vigilant use of personal respiratory protection. ■

Measles Outbreak Among Chinese Adoptees

Source: *MMWR Morb Mortal Wkly Rep*. 2004;53(15):323-324.

AN OUTBREAK OF MEASLES HAS been identified among 12 young adoptees from China who traveled to the United States with their new families on March 26. Nine of the children, 4 of whom were probably acutely infectious during their flight to the United States, developed measles-like rash; 6 cases have been confirmed serologically. The 12 children were traveling with a group of 11 families and spent ~10 days together during the adoption process in China before boarding their flights. They started out on March 26th on 2 separate flights, with several connecting flights to various destinations within the United States on March 27th (Washington, Alaska, Florida, New York, and Maryland). They were adopted out of 2 orphanages in the Hunan Province, 1 of which had reported a recent outbreak of measles.

The 9 children were aged 12-18 months and should have been previously vaccinated for measles, according to both Chinese and US health recommendations. Although the United States does not require adoptees to have been vaccinated before entry to the United States (they must be vaccinated within 30

days of entry), prospective parents should be aware of the risk of measles in unvaccinated children and review their children's vaccination records closely. Having said that, some countries (not necessarily China) have been known to forge vaccine records. Given the excellent track record of vaccination in the United States, people from the United States who traveled on those flights are at low risk for measles. Since the incubation period for measles (7-21 days) has just passed, no secondary cases are likely to occur, although the various public health departments remain vigilant.

The United States remains committed to the goal of eliminating endemic measles in the Western Hemisphere, although the biggest threat to this goal remains the risk of imported measles cases from endemic countries. While measles cases in the Western Hemisphere have dropped by > 90% in the past 10 years, a total of 105 cases were reported in 2003 from 6 different countries—Chile (1), Costa Rica (1), Brazil (2), Canada (15), Mexico (44), and the United States (42). Only Mexico and the United States continue to experience outbreaks. Three outbreaks occurring in Mexico in 2003 were traced back to imported cases, and 2 of 3 outbreaks occurring in the United States in 2003 were the result of imported infections. The origin of the third outbreak was not determined. Two measles-related deaths occurred in the United States in 2003, for a case-fatality rate of 4.8%. One of these deaths was an immunosuppressed child who developed neurologic complications; the other was an older man in his 70s. These 2 deaths underscore the risk of imported measles in the United States, despite our excellent track record of vaccination. ■

Recovery of Vaccinia after Smallpox Inoculation

Source: *Clin Infect Dis*. 2004;38:536-541.

A GOOD QUESTION RAISED DURing President Bush's foiled directive to vaccinate health care workers against smallpox was: How occlusive were those occlusive dressings that individuals wore following inoculation? And what were the risks of autoinoculation or transmission to close contacts? These authors from Vanderbilt University evaluated the recovery of vaccinia virus from the lesions and dressings of 148 subjects who received voluntary smallpox vaccination in 2003. The subjects were divided into 3 groups, who were randomized to receive undiluted vaccine, or 1:5 or 1:10 dilutions of vaccine. Subjects were directed to wear 2 occlusive dressings (an initial waterproof gauze-impregnated transparent bandage [OpSite Post-op] and an outer waterproof semipermeable bandage [Tegaderm]). Inoculation site evaluations were performed by trained personnel every 3-5 days. At each visit, specimens were obtained from the inoculation site, outer dressing surface, and from the contralateral hand for vaccinia culture.

The mean interval to lesion healing was 24 days, with a mean of 9.6 dressing changes. During this time, all 148 vaccinees had positive cultures obtained directly from the lesions. However, only 6 of 918 dressings (0.65%) and 2 of 929 (0.22%) hand specimens were positive. The 6 positive dressings included 2 subjects from each of the 3 vaccine groups. The mean time to a positive dressing was 10 days, although 5 of the 6 occurred within 7-10 days of inoculation. The peak viral titer from dressing and hand specimens was ~ 3-4 logs lower than cultures obtained directly from the lesions, suggesting a lower potential for infectivity.

Although largely reassuring, these data do confirm a low level of risk of transmission of vaccinia virus following inoculation, even with dual occlusive dressings and fairly careful monitoring. While no cases of autoinoculation occurred during this study, it required a total of 1421 dressing changes by trained personnel. Such intensive monitoring and handling of dressing changes would not be feasible on a larger scale, from either a manpower or a cost standpoint. ■

Risk of Hepatitis A in Travelers to Developing Countries

Source: Teitelbaum P. *J Travel Med*. 2004;11:102-106.

ABOUT 4-28% OF CASES OF hepatitis A occur in travelers. This estimated risk has let to recommendations for hepatitis A vaccination (HAV). Teitelbaum assessed the annual incidence of acute HAV infection in Canadian travelers from 1996 to 2001. During that time, Canadians logged ~36 million days/year of travel to developing countries with an average incidence of HAV infection of 6.15 per 100,000 people. Based on these data, ~1 in 3000 travelers are at risk for HAV infection if they spent 1 month traveling in a developing country—considered the usual duration of such travel. Obviously this risk may vary, depending on the types of activity and the country visited. Extrapolating from these figures (based on USD figures for HAV vaccine), about $360,000 of vaccine would be administered to prevent a single HAV infection in travelers to developing countries. I bet the Canadian Health Care System is trying to decide if the expense is worth it. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Missing Link Between Vaccines and Diabetes

A large cohort study from Denmark suggests no link between childhood vaccines and type 1 diabetes. The potential for such a link has been of concern for years because of the association between certain infections and the development of type 1 diabetes in children. Epidemiologists also noted that the incidence of type 1 diabetes has increased in developed countries along with a widespread use of vaccines in those countries. Danish researchers studied the records of children born in Denmark between 1990 and 2000, which represented 4,720,517 person-years of follow-up. In the cohort, 681 cases of type 1 diabetes occurred. The rate ratios for developing diabetes among children who received at least 1 vaccine compared to unvaccinated children were: 0.91 for *Haemophilus influenzae* type B vaccine, 1.02 for diphtheria/tetanus/polio vaccine, 0.96 for diphtheria/tetanus/pertussis/polio vaccine, 1.06 for whole cell pertus! sis, 1.14 for measles/mumps/rubella vaccine, and 1.08 for oral polio vaccine. No clusters of diabetes cases were found at any age level. The authors conclude that the data do not support the causal relationship between childhood vaccine and type 1 diabetes (*N Engl J Med*. 2004; 350:1398-1404).

Breast Cancer and the Use of Statins

Adding to the considerable evidence regarding the safety and efficacy of statins, it now appears that statins may slightly reduce the risk of breast cancer. Published in the "Early View" online journal *Cancer*, this case-control study was designed to assess whether statins were associated with an increased risk of breast cancer. At least 1 previous study has suggested an increased risk of breast cancer with statin use. The study looked at 975 women in Washington state who were diagnosed with primary invasive breast carcinoma, and were between 65 and 79 years old at the time of diagnoses. The comparison group was 1007 randomly selected women from the same residence area. Compared with non-users, current users, or ever-users of statins were not found to be at an increased risk for breast carcinoma. And in fact, the odds ratio of statin users was 0.9 compared to non-statin users (95% CI, 0.7-1.2). Long-term statin use of > 5 years was related to an even lower odds ratio of 0.7. The authors conclude that statins are not associated with an increase risk of breast carcinoma, and may in fact impart a reduced risk among long-term users (*Cancer* April 26, 2004).

Warnings Issued for IBS Drugs

Tegaserod (Zelnorm-Novartis), the heavily promoted serotonin 5-HT4 partial agonist for the treatment of irritable bowel syndrome (IBS), is the subject of new warnings by the FDA. The drug is indicated for women with IBS whose pri-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5413. E-mail: christie.petrone@thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

mary symptom is constipation. The warning is the result of reports of diarrhea leading to hypovolemia, hypotension, and syncope in a small number of patients. There have also been rare cases of bowel ischemia in patients taking tegaserod, although no causal relationship has been found. Novartis has issued a "Dear Doctor" letter regarding the change in labeling dated April 26 (for more information see www.FDA.gov/medwatch). This is the second IBS drug to come under FDA scrutiny. The serotonin 5-HT3 antagonist alosetron (Lotronex-GlaxoSmithKline), for the treatment of IBS in women with severe diarrhea, was briefly withdrawn from the market in June 2002 because of over 80 cases of ischemic colitis associated with use of the drug. Alosetron became available again in December 2002 under a restricted use program.

What is the risk of a re-prescribing penicillin to penicillin allergic patient? The risk may be quite low according to a new study. Researchers looked at a database from the UK General Practice Research Database which included over 3.3 million patients who received penicillin. More than 6000 patients reported an allergy to the initial prescription, however, 48.5% of those patients were given the second prescription for penicillin at least 60 days later. Of those 3014 patients, only 57 (1.89%) had another event after the second prescription. This was much higher than the rate of reactions in patients who had not had an initial reaction (odds ratio, 11.2; [95% CI 8.6-14.6]), however, the absolute rate of reactions in patients who had an initial allergic reaction was quite small (*J Allergy Clin Immunol.*2004:113; 764-770). An accompanying editorial pointed out that even anaphylactic reaction had a low rate of recurrence with repeat exposure (1 out of 16) (*J Allergy Clin Immunol.*2004:113;605-606). And, while no one is recommending rechallenging patients with penicillin allergies, the low rate of repeat reactions is a far cry from the reported 60% rate of previous studies

FDA Actions

The FDA has removed the warning for lactic acidosis from metformin (Glucophage) and metformin extended release (Glucophage XR). Once considered the most serious side effect associated with metformin, a recent meta-analysis showed that there were no reports of lactic acidosis during more than 20,000 patient years use of the drug (*Arch Intern Med.*2003;163:2594-2602).

The FDA has approved apomorphine injection (Apokyn-Bertek) for hypomobility associated with Parkinson's disease. Hypomobility or "off periods" become more frequent with advanced Parkinson's disease and may occur at the end of a dosing interval or may occur spontaneously. A subcutaneous injection of apomorphine is effective for both types of “off periods.” However, because the drug causes severe nausea, it must be taken with an anti-emetic—although, not a 5HT3 antagonist because the combination may cause hypotension and syncope.

Aventis has received approval to market insulin glulisine (Apidra), a new rapid-acting insulin. The drug is a novel recombinant DNA human insulin analogue that is designed to be given 15 minutes before a meal or within 20 minutes after starting a meal. With a rapid onset and short duration of action, it is designed to cover mealtime blood sugar spikes. Aventis is marketing insulin glulisine to be used in combination with insulin glargine (Lantus), the company's long-acting basal insulin preparation.

The FDA has approved changes in prescribing information for finasteride (Proscar-Merck) that include concomitant use of the alpha-blocker doxazosin for the treatment of benign prostatic hyperplasia. Finasteride is a 5-alpha-reductase inhibitor. The combination was recently found to be better than either drug alone in reducing the overall clinical progression of benign prostatic hyperplasia (NEng J Med.2003;349:2387-2398).

Telithromycin (Ketek-Aventis) has been approved by the FDA for marketing for the treatment of community-acquired pneumonia including pneumonia caused by drug-resistant pneumococcus, sinusitis, and acute exacerbations of chronic bronchitis. Telithromycin represents the first of a new class of antibiotics known as ketolides. It is an oral tablet that is given once a day. ■

THOMSON

The Evolution of Antiretroviral Therapy: Applying Clinical Trial Data to Optimize HAART in the Management of HIV

Introduction

The primary therapeutic goals when initiating therapy in patients infected with HIV are maximal and long-lasting suppression of viral replication, maintenance or restoration of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[1] Highly active antiretroviral therapy (HAART) using combinations of antiretroviral agents has been shown to achieve these goals to a significant degree and reduce morbidity and mortality in the population of HIV-infected patients.[2]

Despite the proven efficacy of HAART, virologic failure may occur due to a number of identifiable factors.[3–5] These factors include the potency of the specific antiretroviral regimen,[4] patient adherence to the prescribed treatment regimen, and the ability of a chosen regimen to select for antiviral-resistant mutations.[3]

Although once-daily dosing of certain HAART agents may increase adherence, the most convenient regimens do not necessarily provide the most optimal efficacy. Recent data concerning the efficacy of certain triple nucleoside reverse transcriptase inhibitor (NRTI)-containing regimens in patients with HIV are important, since such data ultimately affect evidence-based guidelines for the selection of initial therapy in HIV-infected patients. This continuing education supplement will focus on studies that assessed triple nucleoside-containing regimens and the most recent guidelines from the Department of Health and Human Services (DHHS) for the timing of HAART initiation and recommended antiretroviral drug classes for managing treatment-naïve patients with HIV.

History and Goals of Antiretroviral Therapy

Since the recognition of HIV disease, the primary medical goal has been to decrease morbidity and mortality related to HIV infection and AIDS. Initially, there were no treatments for HIV itself, and health care providers largely treated opportunistic infections to forestall death. In 1987 zidovudine (ZDV, or AZT), an NRTI, was the first antiretroviral approved. Used as monotherapy, ZDV delayed HIV disease progression, but its efficacy was relatively short lived. As other NRTIs were approved, sequential monotherapy—discontinuing one NRTI and replacing it with another—and dual NRTI therapy were employed. While both approaches provided some benefit, they were not sufficient enough to make a substantial impact on disease progression. When non-nucleoside reverse transcriptase inhibitors (NNRTIs), a second class of antiretrovirals, became available, they were commonly added to patients' current, failing regimens. As with the earlier approaches, this use of NNRTIs had little, if any, efficacy.

Today we understand why the earlier approaches did not work; monotherapy and dual therapy are not potent enough to suppress viral replication, allowing HIV to develop drug resistant mutations. Similarly, adding an NNRTI to a failing regimen did not provide sufficient antiviral activity, and resistance to the NNRTI would quickly develop. With the approval of protease inhibitors (PIs), researchers also discovered how to use antiretrovirals effectively. Using 3 drugs—initially a PI and 2 NRTIs—simultaneously suppressed viral replication in many patients. Because replication was minimized, development of mutations was uncommon. Two surrogate markers used in HIV clinical research—HIV RNA (viral load [VL]) and CD4 cell counts—responded well to what became know as combination therapy or HAART, and morbidity and mortality associated with HIV disease dropped dramatically.

According to the 2004 DHHS HIV treatment guidelines, the goals of antiretroviral therapy are:[1]

- Maximal and long-lasting suppression of viral replication;
- Maintenance or restoration of immunologic function;
- Improved quality of life; and
- Reduction of HIV-related morbidity and mortality.

Although these goals have been consistent over time, how to achieve them undergoes change as greater understanding of HIV and its treatment is attained through clinical research. For instance, while PI-based regimens are potent and can suppress viral replication, these regimens were and sometimes still are inconvenient and difficult to tolerate. Because long-term toxicity was also a concern, new approaches were sought. Regimens consisting of 3 NRTIs had early evidence of efficacy, and these regimens were often better tolerated, had a better long-term safety profile,

This CME activity was produced with an unrestricted educational grant from Bristol-Myers Squibb Company.

and were convenient. Use of 2 NRTIs plus an NNRTI, rather than a PI, also demonstrated efficacy with good tolerability, safety, and convenience.

Clinical Trials: Recent Assessments of Various Triple Nucleoside Regimens as HAART for Treatment-Naïve HIV-Infected Patients

From a historical perspective, it is useful to review efficacy results from 2 earlier trials that assessed triple NRTI regimens when considering some of the emerging data from the past year. Early studies of triple NRTIs found comparable efficacy to PI-based regimens, at least for patients starting with a baseline VL <100,000 copies/mL. The convenience of triple NRTI regimens, particularly fixed dose ABC/3TC/ZDV, and their improved safety profile, made all NRTI regimens an attractive option for treatment-naïve patients. However, recent clinical studies have found comparatively poor results with several different triple NRTI combinations as first-line therapy.

CNAAB3005/CNA3014: Efficacy of Triple NRTI Therapy With ABC/3TC/ZDV

A phase 3, multicenter, randomized, double-blind trial, CNAAB3005, was conducted by Staszewski and colleagues to evaluate the efficacy and safety of ABC/3TC/ZDV (4 pills/day) compared with indinavir (IDV)/3TC/ZDV (8 pills/day) in antiretroviral-naïve HIV-infected patients.[6] At week 48, in this treatment population in which approximately one-third of patients possessed baseline HIV RNA values >100,000 copies/mL, approximately half of patients in each arm had a VL <400 copies/mL. However, virologic suppression to ≤50 copies/mL was better in the IDV arm, and this difference was statistically significant when stratified by baseline VL >100,000 copies/mL. Analyses at week 48 showed advantages for the ABC arm for HIV RNA <400 copies/mL and <50 copies/mL. In contrast with CNAAB3005, ABC resulted in better virologic outcomes than IDV regardless of whether baseline VL was < or >100,000 copies/mL.[7]

Accreditation Information

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Thomson American Health Consultants (AHC) and Thomson Interphase.

Thomson American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Thomson American Health Consultants designates this continuing medical education activity for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit he/she actually spend in the activity.

Intended Audience

This activity is intended for infectious disease physicians and all those who treat HIV/AIDS.

Faculty

Philip Keiser, MD
Assistant Professor of Internal Medicine; Medical Director of Parkland Health & Hospital System's HIV/AIDS Clinic, Division of Infectious Diseases, UT Southwestern Medical Center, Dallas, Texas

Financial Disclosure

Dr. Keiser discloses that he receives grants and research support and honorarium fees from Abbott Laboratories, GlaxoSmithKline, and Bristol-Myers Squibb Company.

Objectives

At the conclusion of this program, the physician should be able to:

• Relate recent clinical trial data concerning antiretroviral combinations that demonstrate suboptimal virologic outcomes.

• List standard preferred and alternative regimens for the treatment of antiretroviral-naïve adults and adolescents with HIV according to nationally recognized guidelines.

• State recommendations according to the Department of Health and Human Services for the timing of initial therapy for the treatment of adults and adolescents with HIV.

Effective Dates

This activity is approved for release May 15, 2004, until May 14, 2005.

How to Obtain Credit

To obtain CME credit for this activity, read the material and consult referenced sources as necessary. Study the questions at the back of the material, and mark your answers on the enclosed answer form. Also complete the evaluation questions, making sure to print clearly the name and address to which the CME certificate is to be sent. Mail the completed answer sheet and evaluation form to:

Thomson American Health Consultants
Attn: Continuing Education Department
P.O. Box 740058
Atlanta, GA 30374-0058

All those who score 70% or higher will receive certificates.

ACTG 5095 and Observational Cohort Study of ABC/3TC/ZDV

The efficacy of the triple NRTI regimen ABC/3TC/ZDV has been assessed in ACTG 5095 (A5095) and in a large observational cohort study. In A5095, Gulick and colleagues conducted a phase 3, randomized, double-blind, placebo-controlled comparison of 3 PI-sparing regimens for the initial treatment of HIV infection in patients with a VL of >400 copies/mL and any CD4 cell count.[8] Patients were monitored for virologic response and safety following randomization to a triple NRTI regimen (ABC/3TC/ZDV), a 4-drug regimen (ABC/3TC/ZDV + efavirenz [EFV]), or ZDV/3TC+EFV (control arm). The primary objectives of A5095 were to determine the safety and tolerability of the regimens. A5095 was also designed to compare virologic failure rates (defined as 2 consecutive HIV RNA ≥ 200 copies/mL at week 16 or later) for ABC/3TC/ZDV + EFV and ZDV/3TC + EFV. Patients were stratified on the basis of whether they had a pretreatment VL ≥ or <100,000 copies/mL. Baseline characteristics were comparable between study groups and patient demographics are listed (*Table 1*).

Virologic failure occurred in 167 patients, 82/382 (21%) in the ABC/3TC/ZDV compared with 85/765 (11%) in the pooled EFV arms of the study; P<0.001, log rank test. Moreover, virologic failure occurred significantly earlier in the ABC/3TC/ZDV group compared with the EFV-containing treatment groups (P<0.001, log rank treatment comparisons). This finding was consistent, regardless of baseline VL < or >100,000 copies/mL (P<0.001 for each). At 48 weeks, 74% and 89% of patients had their HIV RNA sup-

pressed to ≤200 copies/mL and 61% and 83% of patients achieved HIV RNA <50 copies/mL, in the ABC/3TC/ZDV and the EFV-containing treatment groups, respectively (intent-to-treat analysis). Grade 3 and 4 adverse events were similar between groups. In post-hoc analysis it was shown that even among patients who had their HIV RNA suppressed to at least 200 copies/mL, virologic failure occurred earlier in the ABC/3TC/ZDV group compared with EFV-containing treatment groups (P<0.001). The risk of virologic failure was approximately 7% over 3 months for patients receiving ABC/3TC/ZDV compared with 3.5% for subjects on the combined EFV-containing treatment groups.[9] Based upon these interim results, the ABC/3TC/ZDV arm of A5095 was terminated.

Table 1. Study ACTG 5095 Patient Demographics[8]

PATIENT DISPOSITION	
Number enrolled	1147
Started randomized study	1136
Remained on initial randomized study	940
SEX	
Male	81%
Female	19%
RACE	
White	40%
Black	36%
Latino	21%
Other	2%
BASELINE HIV RNA	**4.9 LOG_{10} COPIES/ML**
>100,000 copies/mL	43%
BASELINE CD4	**238 CELLS/MM^3**
MEDIAN FOLLOW-UP	**32 WEEKS**
Range	0-80 weeks

Similar results were found in an observational cohort comparison of ZDV/3TC+EFV to ABC/3TC/ZDV conducted in antiretroviral-naïve patients.[10] In this cohort, the time to virologic failure was shorter in the ABC-containing arm (1.3 years) than in the EFV-containing arm (2.5 years) (P<0.001) (*Figure 1*). This difference in time to treatment failure between the 2 groups also was demonstrated when results were stratified by baseline VL (< or >100,000 copies/mL) or by patients who responded to antiretroviral therapy by suppressing HIV RNA to <400 copies/mL.

Lower Efficacy With Stavudine, Didanosine, and ABC Triple NRTI Regimen

The triple NRTI regimen stavudine (d4T), didanosine (ddI), and ABC was evaluated in a randomized, controlled, open-label trial by Gerstoft and colleagues who compared it to ZDV + 3TC in combination with either ritonavir (RTV)/saquinavir (SQV) or nelfinavir (NFV)/nevirapine (NVP). It had been assumed that the triple NRTI regimen possessed a low potential for the cross-resistance mutations K65R and L74V—previously relatively rare in vivo when ABC and ddI were combined.[11] The primary endpoint was plasma HIV RNA ≤20 copies/mL after 48 weeks. At week 48 (intent-to-treat [ITT] population), a significantly lower proportion of patients demonstrated a VL ≤20 copies/mL in the d4T/ddI/ABC arm (43%) compared with the NFV/NVP-containing arm (69%) (P<0.01). This regimen was particularly poor for patients with a higher baseline VL or AIDS, who were significantly less likely to achieve a VL ≤20 copies/mL by week 48. Additionally, side effects were also more frequent in the triple NRTI arm (e.g., mitochondrial toxicity, neuropathy, and lactatemia). The investigators suggest that a reason for the frequent treatment failure with this NRTI combination might have been an acceleration of cross-class resistance. Also, the K65R mutation that was presumably avoidable with this triple NRTI regimen was found in 5 patients.

Tenofovir DF (TDF)/ABC/3TC Versus EFV/ABC/3TC in Antiretroviral-naïve HIV Patients

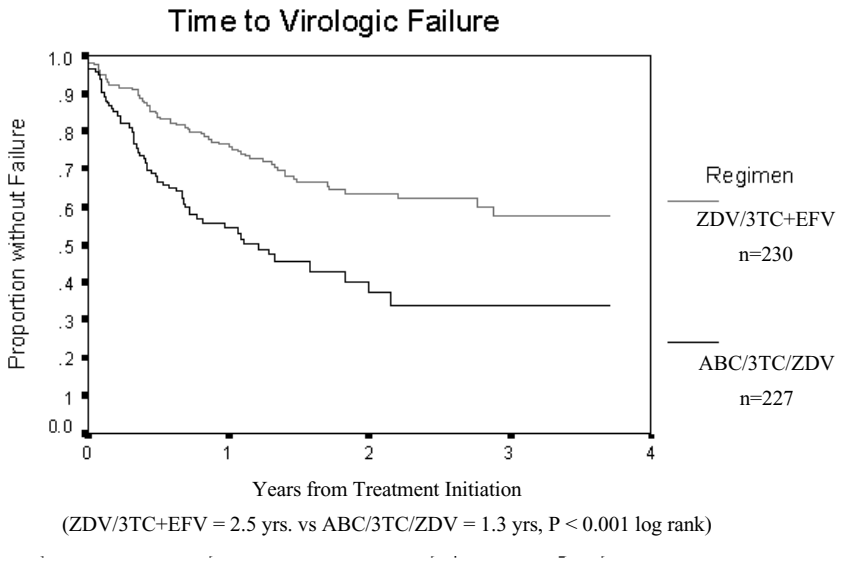
TDF/ABC/3TC in treatment-naïve HIV-infected patients was evaluated in ESS30009 and a pilot study by Farthing. In ESS30009, an open-label, randomized, multicenter trial, Gallant and colleagues compared the virologic suppression associated with TDF/ABC/3TC versus EFV/ABC/3TC in adult, antiretroviral-naïve HIV patients with a VL ≥5000 copies/mL.[12] Subsequent to several cases of early virologic non-response in the TDF/ABC/3TC treatment arm, an unplanned interim analysis was conducted in patients with 8 or more weeks of HIV RNA data (*Table 2, Figure 2*). Virologic non-response was defined as <2.0 $\log_{10}$ decline in HIV RNA by treatment week 8 or a 1.0 $\log_{10}$ increase above nadir on any subsequent visit. By week 8, virologic non-response was reported for 50/102 (49%) in the TDF/ABC/3TC treatment group compared with 5/92 (5.4%) patients in the EFV/ABC/3TC group (P<0.001). For subjects with virologic non-response to TDF/ABC/3TC, with available genotypes (n=36), 100% had developed the M184V mutation. Over half of those patients with M184V also had developed K65R (n=23). Because of these results,

the TDF/ABC/3TC arm was terminated with no change in the EFV/ABC/3TC arm. Long-term data from the EFV/ABC/3TC treatment group are forthcoming.

Similarly, Farthing and colleagues have reported early virologic failure in a pilot study in treatment-naïve HIV-infected patients who received TDF/ABC/3TC.[13] In that study (n=20 enrolled; 9 patients with a VL >100,000 copies/mL; 3 withdrawals), the mean VL declined from 82,381 copies/mL at baseline to only 14,898 copies/mL by week 4; 8219 copies/mL by week 8. Moreover, from 17 patients, 9 (52%) demonstrated VL rebound: 1 at week 4, 6 at week 8, and 2 at week 16. The study was prematurely terminated due to these suboptimal efficacy findings, which also suggest a particularly high risk for early virologic failure with this regimen in patients with an initial VL >100,000 copies/mL. A small retrospective observational study prompted by results of the Farthing study found that 5 of 8 patients had virologic failure subsequent to a switch from an antiretroviral regimen in which they were fully suppressed to the TDF/ABC/3TC combination.[14] As such, this combination also appears to be suboptimal as an alternate treatment for patients on successful regimens, as well as in treatment-naïve HIV-infected patients.

A number of explanations for these high rates of virologic failure with the TDF/ABC/3TC regimen have been proposed, including low genetic barrier to resistance and pharmacokinetic interactions. However, preliminary results from another pilot study in which early virologic failure occurred in patients who

Figure 1. Time to Virologic Failure



Kaplan Meier analysis of time to virologic failure from Parkland HIV Database for regimens ZDV/3TC+EFV vs ABC/3TC/ZDV.[10]

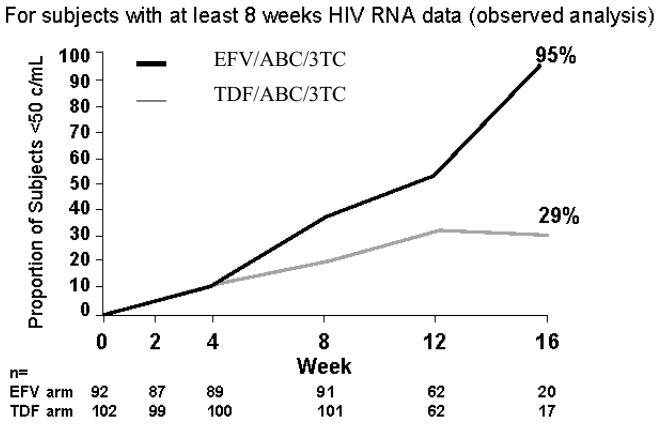
Reprinted with permission from Keiser P et al. 2nd IAS Conference on HIV and Pathogenesis. July 13-16, 2003. Poster 554.

Table 2. Early Virologic Failure with TDF/ABC/3TC QD [12,28]

	Number (%) of Patients with Virologic Non-response	
	TDF/ABC/3TC	**EFV/ABC/3TC**
<2.0 $\log_{10}$ decline from baseline by week 8(a)	32/102 (31.4%)	3/92 (3.3%)
≥1.0 $\log_{10}$ rebound from nadir (b)	8/102 (7.8%)	0/92 (0%)
Failure defined as both (a) and (b)	10/102 (9.8%)	2/92 (2.2%)
Total failures ≥ 8 weeks	50/102 (49%)*	5/92 (5.4)*
Total failures ≥ 12 weeks	30/63 (48%)	3/62 (5%)

* Difference between arms P<0.001

Figure 2. Proportion of Subjects with HIV RNA <50 copies/mL[12]



Adapted from Gallant JE et al. 43rd ICAAC, September 2003. Oral Poster H-1772a

received this combination point to a low genetic barrier to resistance as the major cause of failure. In that study, this hypothesis is supported by the association of adequate expected plasma C_{min} of the 3 antiretroviral agents, high proportion of early virologic failure, and high rate of rapid selection for the K65R and M184V mutations in patients with a plasma VL above 4 $\log_{10}$ copies/mL.[15]

Atlantic Study: An Assessment of d4T/ddI/3TC

The Atlantic Study, a randomized, open-label trial compared the relative efficacy of 2 convergent treatment regimens (in which all antiretrovirals target reverse transcriptase [i.e., NRTIs and NNRTIs]) and one divergent regimen (targeting reverse transcriptase and protease) in treatment-naïve HIV-infected patients with plasma HIV RNA >500 copies/mL and CD4 counts ≥200 x 10^6 cells/L.[16] Patients were recruited from the regular patient population at 17 international centers and randomized to receive d4T and ddI plus either IDV, NVP, or 3TC. The primary endpoint was the proportion of patients in the ITT population with a plasma VL <500 copies/mL after 48 weeks of treatment. Treatment failure was defined as plasma VL <500 copies/mL at any point after 24 weeks follow-up.

Of the 298 patients enrolled in the study, 198 (66%) were observed through week 48; 139 (47%) through week 96. At 48 weeks follow-up, suppression of VL to <50 copies/mL in the on-treatment (OT) population was significantly lower in the 3TC-containing arm (58.7%) compared with the IDV- (80.3%) and NVP-containing arms (80.7%) (P=0.004). Moreover, at 96 weeks follow-up, both the ITT and OT populations in the 3TC arm had a significantly lower proportion of patients with a VL <50 copies/mL. The incidences of grade 3 and 4 adverse events, as well as the rate of discontinuation due to an adverse event, were comparable between the treatment arms, indicating equivalent tolerability. The convergent regimen used in this trial, then, was inferior with regard to the potency of viral suppression compared with the divergent regimens.

CLASS: Triple NRTI d4T/3TC/ZDV Versus NNRTI- and PI-based HAART

In the 96-week, open-label, randomized, multicenter Clinically Significant Long-term Antiretroviral Sequential Sequencing (CLASS) study, Bartlett and colleagues compared EFV, amprenavir (APV)/RTV, or d4T added to the nucleoside backbone 3TC/ABC in treatment-naïve, HIV-infected adults with plasma HIV RNA ≥5000 copies/mL.[17] Forty-two percent of patients presented with a VL >100,000 copies/mL. At week 48, the proportion of patients who achieved a VL <50 copies/mL were 76%, 59%, and 62% for the EFV-, APV/RTV-, and d4T-containing arms, respectively (ITT: P=0.047; observed: P=0.008) (*Figure 3*). Moreover, of patients with a baseline VL >100,000 copies/mL, 77% of patients who received EFV achieved a VL <50 copies/mL compared with 55% in the triple NRTI arm.

Efficacy From Trials With Quadruple PI-Sparing Therapy

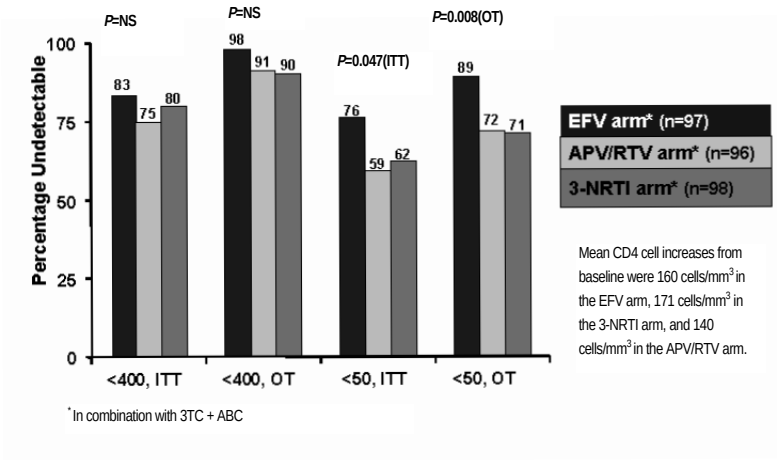
In light of the recent evidence of suboptimal efficacy with certain triple NRTI regimens reviewed above, the efficacy of PI-sparing quadruple therapy (i.e., triple NRTI + NNRTI or triple NRTI + a nucleotide) is of substantial clinical interest.

ABC/3TC/ZDV in combination with TDF was studied in a pilot, open-label, multicenter study in 88 treatment-naïve subjects with HIV (baseline median VL and CD4 count 5.1 $\log_{10}$ copies/mL and 226 cells/mm^3, respectively).[18] By week 24, 78% (42/54) and 67% (36/54) had VL <400 copies/mL and <50 copies/mL, respectively (observed analysis). Those with virologic non-response were more likely to have had baseline VL >100,000 copies/mL.

ABC/3TC/ZDV + EFV was assessed in a multicenter, open-label, pilot study (CNAF3008) conducted in 31 treatment-naïve HIV-infected adults (baseline VL 4.69 $\log_{10}$ copies/mL, CD4 cell count 322 cell/mm^3, 13/31 VL >100,000 copies/mL).[19] Potent and durable antiretroviral activity resulted from this combination by week 48 with a median reduction of 2.7 $\log_{10}$ copies/mL by week 4 and 58% of patients having reduced their VL to <50 copies/mL at week 8.

ACTG 384, a randomized, double-blind comparison of EFV and NFV paired with either 3TC/ZDV or ddI/d4T, used a multifactorial approach to evaluate a number of treatment strategies. Results of this study showed improved outcomes when first-line treatment consisted of EFV/3TC/ZDV and no significant difference in durability between a single 4-drug regimen and 2 sequential 3-drug regimens.[20,21]

Figure 3. CLASS Study Virologic Results from the Preliminary 48-week Analysis [17]



Adapted from Bartlett JA et al. XIV International AIDS Conference, July 2002. TuOrB1190 and Poster 1189.

Summary

Results from earlier studies comparing the triple NRTI regimen ABC/3TC/ZDV with PI-based regimens found comparable efficacy results, at least for patients with lower baseline viral loads. The convenience, tolerability, and safety profile of ABC/3TC/ZDV made it, and other triple NRTI combinations, an attractive option for first-line treatment. More recent studies, however, have found high rates of virologic failure with ABC/3TC/ZDV and several other triple NRTI regimens. In addition, HIV treatment has changed considerably over the last few years. NNRTIs offer a low pill burden, with EFV dosed QD and NPV dosed BID. With PIs, ritonavir boosting allows greater convenience with high potency. Newer PIs also offer advantages. For instance, atazanavir is dosed once daily and has a favorable lipid profile, and fosamprenavir has a lower pill burden than the parent drug, amprenavir. As a result, while potent, tolerable, convenient, and safe regimens are still needed, today's options are much better than a few years ago.

The Use of HAART in Treatment-Naïve HIV-Infected Patients

HAART is the standard of care in the treatment of HIV/AIDS; and the *DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* specify a number of multiple-drug combinations.[1] Due to the vast armamentarium of antiretroviral agents available, many combinations are possible. The timing and proper selection of the initial therapy for HIV infection is a clinical decision with profound consequences. For instance, the use of PI-based HAART (NNRTI-sparing) regimens preserves NNRTIs for use in the event of treatment failure; NNRTI-based (PI-sparing) regimens preserve PIs for subsequent antiretroviral use. The use of a triple NRTI regimen preserves both PI- and NNRTI-based regimens. The timing for initiation of HAART is also important and requires consideration of the benefits and risks of early versus delayed therapy. A substantial body of evidence now exists to guide clinicians as to the timing and selection of initial therapy in the untreated patient with HIV.

PI-based and PI-sparing First-line HAART Regimens. The proper selection of the initial antiretroviral regimen is important because: 1) initial therapy generally is more successful than subsequent regimens in reducing VL; and 2) proper sequencing of initial therapy will not limit possibilities for second-line treatment in the event of treatment failure.[6] Regimens of a PI plus 2 different NRTIs have the advantage of the longest experience and most available clinical data. Conversely, the disadvantages of traditional PI-based regimens may include complexity, the large number of pills patients must take (as many as 14–16 pills daily), long-term toxicity, and the potential to compromise the effectiveness of future PI regimens. However, newer treatment strategies, such as using ritonavir as a boosting agent, and newer PIs, such as atazanavir, can mitigate these drawbacks.

PI-sparing HAART regimens have been shown to provide long-term control of HIV replication,[20] and there are a number of advantages to NNRTI-based regimens, including their antiretroviral potency and possibility of reserving PIs for potential use in the event that they are required.[16] An additional advantage of NNRTI-based therapy is the regimen's simplicity and requirement for fewer pills. Triple-NRTI therapy, another PI-sparing approach, appears to have relatively inferior potency for initial use in HIV-infected patients based upon the recent evidence presented in this supplement.

DHHS Recommended Regimens for the Initial Treatment of HIV. Selection of any regimen should be individualized and based upon respective advantages and disadvantages, and when possible, selected in an evidence-based

Table 3. Factors to Consider Upon Initiating Antiretroviral Therapy[1]

- Patients' willingness and readiness to begin therapy
- Potential adverse drug effects
- Potential of patient to be adherent to therapy
- Comorbidity or conditions such as tuberculosis, liver disease, depression or mental illness, cardiovascular disease, chemical dependency, pregnancy, and family planning status
- Preference of patient concerning pill burden, dosing frequency, and fluid and food considerations
- Potential for drug-drug interactions with concomitant medications
- Severity of HIV infection according to CD4 T-lymphocyte count, VL, and presence or history of AIDS-defining conditions

manner. A number of factors need to be considered when initiating antiretroviral therapy in previously untreated patients (*Table 3*). The most recent DHHS guidelines define either preferred or alternative HAART regimens. Regimens designated as preferred have clinical data that suggest optimal efficacy and durability with acceptable tolerability and ease of use. Alternative regimens have clinical data to support their efficacy, but have inherent disadvantages compared with preferred regimens, such as inferior antiretroviral activity, durability, tolerability, or ease of use. The most extensively studied and well-characterized HAART regimens are NNRTI-based (e.g., 1 NNRTI + 2 NRTIs), PI-based (1 or 2 PIs + 2 NRTIs), or triple NRTIs.[1] The DHHS (March 2004) preferred and alternative HAART regimens are listed in *Figures 4a, 4b, and 4c.*

The recommendation that EFV be utilized as the preferred NNRTI-based regimen is based upon evidence from 2 large studies that compared it to PI-based regimens. At 48 weeks in the open-label DMP006 (assessed EFV and IDV on a backbone of ZDV/3TC [n=450]), significantly more patients in the EFV arm (70%) achieved a VL <400 copies/mL, compared with the IDV arm (48%; P<0.001). Moreover, a subgroup analysis determined the EFV-containing regimen is significantly more effective than the IDV-containing regimen in its ability to achieve VL <50 copies/mL in patients with a baseline VL >100,000 copies/mL.[22] Importantly, the durability of response (DOR) of the EFV regimen was substantiated by a 144-week follow-up in which 55% and 52% in the EFV/ZDV/3TC arm compared with 34% and 30% in the IDV/ZDV/3TC arm had a VL <400 copies/mL and <50 copies/mL, respectively (P<0.05).[22] Further, in a 6-arm comparison of sequential 3-drug regimens (ACTG 384), patients received EFV or nelfinavir (NFV) as part of an initial regimen, with background NRTI agents randomized by factorial design (ddI + d4T versus ZDV + 3TC). Compared with NFV, patients who received EFV initially demonstrated fewer events of virologic failure; also, a more favorable benefit was observed for EFV among those assigned to ZDV + 3TC. As such, this study strongly suggested EFV/ZDV/3TC as a particularly useful initial antiretroviral regimen.[24]

The use of PIs in combination with NRTIs has been evaluated in a number of controlled trials. Due to its low tolerability, regimens with full-dose ritonavir (RTV) are not recommended. However, low-dose (RTV-boosted) regimens often are used due to their reduced pill burden, improved scheduling, and elimination of food restrictions (i.e., IDV). A large study evaluated the DHHS-preferred PI-based regimen of the boosted PI lopinavir (LPV)/RTV (400 mg/100 mg BID) compared with NFV (750 mg TID), each with 2 NRTIs. At week 48, the boosted PI was demonstrated superior to NFV in maintaining a VL <400 copies/mL (75% vs 63%; P<0.001), VL <50 copies/mL (67% vs 52%; P<0.001), and was well tolerated.[1,24] Noting that there are few trials comparing LPV/RTV with other boosted-PI regimens or with EFV-based regimens, the authors base the preference for LPV/RTV on "virologic potency, patient tolerance, and pill burden."[1]

The DHHS guidelines now recommend triple NRTI regimen ABC + 3TC (or d4T) + ZDV only be used for the initial treatment of HIV when NNRTI- and PI-based regimens cannot or should not be used. Moreover, the triple RTI regimens ABC + TDF + 3TC or ddI + TDF + 3TC are not recommended for use as the sole combination antiretroviral regimen initially or at any time.[1] These new recommendations are based upon the literature reviewed previously in this supplement.[6–8,12,16,17,26]

Guidelines: Initiating Antiretroviral Therapy for the HIV-Infected Patient. Although there is strong evidence in favor of treating HIV-infected patients with CD4 counts <200 cells/mm^3, the optimal time to initiate therapy for asymptomatic patients with CD4 counts >200 cells/mm^3 is not known.[1] A carefully balanced assessment of the pros and cons of initiating therapy must be undertaken.

Early initiation of antiretroviral therapy for HIV-infected patients has significant advantages, which include:[1]

- Earlier suppression of viral replication;
- Preservation of immune function;
- Prolongation of disease-free survival;

- Reduced risk of developing treatment resistance with complete viral suppression; and
- Possible decreased risk of HIV transmission.

Conversely, a number of potential risks are associated with early initiation of antiretroviral therapy, such as:

- Drug-related reduction in quality of life;
- Inconvenience of some treatment regimens with high daily pill counts resulting in reduced adherence;
- Serious drug-related toxicities associated with certain antiretroviral drugs;
- Development of treatment-associated resistance if viral suppression is suboptimal;
- Limitation of future treatment options due to premature cycling of available drugs; and
- Unknown durability of current treatment regimens.

Although delayed therapy postpones treatment-related negative effects on quality of life and the development of drug-associated toxicities, preserves treatment options for later in the course of the disease, and delays the development of drug resistance, potential risks must be considered. These risks include possible preventable—but irreversible—damage to the immune system, more difficult suppression of viral replication associated with later-stage disease, and increased risk for HIV transmission to other individuals during the longer untreated period.[1]

All of these factors must be considered in the clinical decision concerning whether to initiate antiretroviral therapy. Accordingly, the DHHS and International AIDS Society (IAS) recommendations for the timing of initial therapy are shown in *Figures 5a and 5b.* Although it is clear that patients with CD4 cell counts <200 cells/mm^3 should receive treatment, the decision to initiate treatment for asymptomatic patients with higher cell counts should be based upon several criteria, including patient comprehension of the regimen and interest in participation in a complex treatment protocol.[27]

Figure 4. NNRTI-based, PI-based, and Triple RTI Recommendations from DHHS[1]

Figure 4a. Recommended Initial NNRTI-based Antiretroviral Regimens for Treatment of HIV infection[1]

Preferred	EFV + 3TC + (AZT or TDF or d4T*) except for pregnant women or women with pregnancy potential	3–5 pills/day
Alternative	EFV + FTC + (AZT or TDF or d4T*) except for pregnant women or women with pregnancy potential	3–4 pills/day
	EFV + (3TC or FTC) + ddI or abacavir except for pregnant women or women with pregnancy potential	3–5 pills/day
	NVP + (3TC or FTC) + (AZT, d4T* or ddI or abacavir)	4–5 pills/day

* Higher incidence of lipoatrophy, hyperlipidemia, and mitochondrial toxicities reported with d4T than with other NRTIs.

Figure 4b. Recommended Initial PI-based Antiretroviral Regimens for Treatment of HIV Infection[1]

Preferred	LPV/r + 3TC + (AZT or d4T*)	8–10 pills/day
Alternative	ATV + (3TC or FTC) + (AZT or d4T* or ABC)	4–5 pills/day
	fosAPV + (3TC or FTC) + (AZT or d4T* or ABC)	6–8 pills/day
	fosAPV/RTV + (3TC or FTC) + (AZT or d4T* or ABC)	6–8 pills/day
	IDV/RTV† + (3TC or FTC) + (AZT or d4T* or ABC)	8–11 pills/day
	LPV/RTV + FTC + (AZT or d4T* or ABC)	8–9 pills/day
	NFV‡ + (3TC or FTC) + (AZT or d4T* or ABC)	12–14 pills/day
	SQV (sgc or hgc)§/RTV† + (3TC or FTC) + (AZT or d4T* or ABC)	14–16 pills/day

* Higher incidence of lipoatrophy, hyperlipidemia, and mitochondrial toxicities reported with d4T than with other NRTIs.
† Low-dose (100-400mg) RTV
‡ NFV available in 250 mg or 625 mg tablet
§ sgc = soft gel capsule; hgc = hard gel capsule

Figure 4c. The Triple NRTI Regimen Is an Alternative Option Only When an NNRTI- or PI-based Regimen Cannot or Should Not be Used as First-line Therapy[1]

Preferred	None	
Alternative†	ABC + 3TC + (AZT or d4T*)	2–6 pills/day
Not Recommended	ABC + TDF + 3TC	
	TDF + ddI + 3TC	

* Higher incidence of lipoatrophy, hyperlipidemia, and mitrochondrial toxicities reported with d4T than with other NRTIs.
† Only as alternative when an NNRTI- or PI-based regimen cannot or should not be used as first-line therapy

Adapted from DHHS Guidelines, March 2004.

Summary

The DHHS guidelines for the initial treatment of HIV-infected patients continue to evolve according to emerging evidence. The current guidelines present treatment recommendations in a user-friendly format for the health care pro-

Figure 5. The DHHS and IAS Guidelines for Initiating Therapy in Treatment-naïve HIV-infected Patients

Figure 5a. DHHS Guidelines[1]

Clinical Category	CD4 Count	Plasma HIV RNA	Recommendation
Symptomatic	Any value	Any value	Treat
Asymptomatic, AIDS	<200 cells/mm^3	Any value	Treat
Asymptomatic	>200/mm^3 but ≤350 cells/mm^3	Any value	Offer treatment, although controversial
Asymptomatic	>350 cells/mm^3	>55,000 c/mL	3-year risk of developing AIDS in untreated patient >30%; Some would defer therapy and monitor CD4 and HIV RNA
Asymptomatic	>350 cells/mm^3	<55,000 c/mL	Many would defer therapy and observe; 3-year risk of developing AIDS is <15% in untreated patients

Adapted from DHHS Guidelines, March 2004.

Figure 5b. IAS Guidelines[26]

Disease Type	Recommendation
Symptomatic HIV disease	Treatment recommended
Asymptomatic HIV disease, CD4 cell count ≤200 cells/mm^3	Treatment recommended
Asymptomatic HIV disease, CD4 cell count >200 cells/mm^3	Treatment decision should be individualized; recommendations based on: • CD4 cell count and rate of decline • Plasma HIV RNA • Patient interest in and potential for adherence • Individual risks of toxicity and drug-drug interactions

Adapted from Yeni PG, et al. JAMA. *2002;288:222-235.*

fessional. It is clear that the selection of a particular antiretroviral drug regimen for the initial treatment of HIV is an important clinical decision with potential long-term therapeutic implications. Recent evidence concerning suboptimal efficacy supports the DHHS recommendation that antiretroviral triple NRTI combinations should only be used when NNRTI- or PI-based regimens cannot or should not be used; certain triple NRTI regimens are not recommended for use initially or at any time as sole therapy. In the current DHHS guidelines, the preferred NNRTI is efavirenz and the preferred PI is the combination LPV/RTV.[1] Another important clinical decision in the management of the untreated patient with HIV is the timing of initiation of antiretroviral therapy in asymptomatic patients whose CD4 count is >200 cells/mm^3. This decision should be individualized with consideration given to the advantages and disadvantages of early versus delayed therapy for each patient.

References

1. Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda, Maryland, March 23, 2004.
2. Palella FJ Jr, Delaney KM, Moornay AC, et al. Declining morbidity and mortality among patients with advanced Human Immunodeficiency Virus infection. *N Engl J Med*. 1998; 338:853–860.
3. Masquelier B, Peytavin G, Leport C, et al. Mechanisms of early virologic failure in antiretroviral-naive patients starting protease-inhibitor-containing regimens: The APROVIR study. *Infect Dis.* 2002; 186:1503–1507.
4. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilège (Agence Nationale de Recherches sur le SIDA 072) study team.

JAMA. 2000;283:205–211.
5. Peyrière H, Guillemin V, Lotthe A, et al. Reasons for early abacavir discontinuation in HIV-infection patients. *Ann Pharmacother.* 2003;37:1392–1397.
6. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA.* 2001;285:1155–1163.
7. Vibhagool A, Cahn P, Schechter M, et al. Abacavir/combivir (ABC/COM) is comparable to indinavir/combivir in HIV-1 infected antiretroviral therapy naive adults: Preliminary results of a 48-week open label study (CNA 3014). 1st International AIDS Society Conference on HIV Pathogenesis and Treatment; July 8–11, 2001; Buenos Aires, Argentina. Abstract 63.
8. Gulick RM, Ribaudo HJ, Shikuma CM, et al. ACTG 5095: A comparative study of 3 protease inhibitor-sparing antiretroviral regimens for the initial treatment of HIV infection. 2nd IAS Conference on HIV Pathogenesis and Treatment; July 13–16, 2003; Paris, France. Abstract 41.
9. NIH National Institute of Allergy and Infectious Diseases (NIAID). Notice to Physicians. Bethesda, Maryland; March 10, 2003.
10. Keiser P, Nassar N, Smillie J, et al. An observational cohort comparison of zidovudine-lamivudine-efavirenz to zidovudine-lamivudine-abacavir in anti-retroviral naïve individuals. 2nd IAS Conference on HIV and Pathogenesis; July13–16, 2003; Paris, France. Poster 554.
11. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine, and didanosine. *AIDS*. 2003;17:2045–2052.
12. Gallant JE, Rodriguez A, Weinberg W, et al. Early non-response to tenofovir DF (TDF) + abacavir (ABC) and lamivudine (3TC) in a randomized trial compared to efavirenz (EFV) + ABC and 3TC: ESS30009 unplanned interim analysis (oral presentation). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 14–17, 2003; Chicago, Illinois. Oral Poster H-1722a.
13. Farthing C, Khanlou H, Yeh V, et al. Early virologic failure in a pilot study evaluating the efficacy of once-daily abacavir (ABC), lamivudine (3TC), and tenofovir DF (TDF) in treatment-naive HIV-infected patients. 2nd Annual AIDS Society Meeting; July 13–16, 2003; Paris, France. Abstract 43.
14. Hoogewerf M, Regez RM, Schouten WEM, et al. Change to abacavir-lamivudine-tenofovir combination treatment in patients with HIV-1 who had complete virologic suppression. *Lancet.* 2003;362:1979–1980.
15. Landman R, Peytavin G, Descamps D et al. Low genetic barrier to resistance is a possible cause of early virologic failurs in once-daily regimen of abacavir, lamivudine, and tenofovir: The Tonus Study. 11th Conference on Retroviruses and Opportunistic Infections; February 8–11, 2004; San Francisco, CA. Session 13, Oral Abstract 52.
16. van Leeuwen R, Katlama C, Murphy RL et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS*. 2003;17:987–999.
17. Bartlett JA, Johnson J, Herrera G, et al. Abacavir/lamivudine (ABC/3TC) in combination with efavirenz (NNRTI), amprenavir/ritonavir (PI), or stavudine (NRTI): ESS40001 (CLASS) preliminary 48-week results. XIV International AIDS Conference, July 7–12 2002, Barcelona, Spain. Abstract 1189.
18. Elion R, Cohen C, DeJesus E, et al. COL40263: Resistance and efficacy of once-daily Trizivir and Tenofovir DF in antiretroviral naïve subjects. 11th Conference on Retroviruses and Opportunistic Infections. Feb. 8–11, 2004; San Francisco, CA. Session 13, Oral Abstract 53.
19. de Truchis P, Force G, Welker Y, et al. Efficacy and safety of a quadruple combination Combivir + abacavir + efavirenz regimen in antiretroviral treatment-naive HIV-1-infected adults: La Francilienne. *J AIDS*. 2002;31:178–182.
20. de la Rosa R, Ruiz-Mateos E, Rubio A, et al. Long-term virological outcome and resistance mutations at virological rebound in HIV-infected adults on protease inhibitor-sparing highly active antiretroviral therapy. *J Antimicrob Chemother*. 2004;53:95–101.
21. Shafer R, Smeaton L, Robbins G, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003;349(24):2304-2315.
22. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med.* 1999;341:1865–1873.
23. Arribas J, Staszewski S, Nelson M, et al. 3-year durability of response with an efavirenz (EFV)-containing regimen: 144-week follow-up of Study 006. Presented at: 11th European Congress of Clinical Microbiology and Infectious Diseases; April 1, 2002; Istanbul, Turkey. Abstract 043.

24. Robbins G, De Gruttola V, Shafer R, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003; 349:2293–2303.
25. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonovir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. 2003;346:2039–2046.
26. Jemsek J, Hutcherson P, Harper E. Poor virologic responses and early emergence of resistance in treatment naïve, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF. 11th Conference on Retroviruses and Opportunistic Infections. Feb. 8–11, 2004; San Francisco, CA. Session 13, Oral Abstract 51.
27. Yeni PG, Hammer SM, Carpenter CC, et al. Antiretroviral treatment for adult HIV infection in 2002: Updated recommendations of the International AIDS Society-USA Panel. *JAMA.* 2002;288(2):222-235.
28. Manion DJ. Early virologic non-response in patients with HIV infection treated with lamivudine, abacavir, and tenofovir. GlaxoSmithKline Drug Warning, July 2003.

CME Questions

1. Which of the following statements is *false* about earlier approaches to HIV therapy?
   A. Didanosine was the first antiretroviral approved.
   B. Monotherapy and dual therapy were not potent enough to suppress viral replication.
   C. The addition of an NNRTI to a failing regimen did not provide sufficient antiviral activity.
   D. All of the above statements are true.

2. According to the 2004 DHHS guidelines for the treatment of HIV, the goals of antiretroviral therapy are:
   A. maximal and long-lasting suppression of viral replication.
   B. maintenance of restoration of immunologic function.
   C. improved quality of life.
   D. reduction of HIV-related morbidity and mortality.
   E. All of the above.

3. Concerning the ACTG 5095 trial, all of the following are true *except*:
   A. All arms of the trial are currently ongoing with results forthcoming.
   B. Patients were randomized to receive ABC/3TC/ZDV, ABC/3TC/ZDV + EFV, or ZDV/3TC/EFV.
   C. Virologic failure occurred significantly more often in patients in the ABC/3TC/ZDV arm compared with the pooled EFV arms.
   D. Virologic failure occurred earlier in the ABC/3TC/ZDV group compared with the EFV-containing treatment groups.

4. In the open-label trial in which the triple NRTI regimen d4T/ddI/ABC was compared with RTV/SQV or NFV/NVP:
   A. It was determined that the triple NRTI regimen is particularly effective for patients with higher baseline VL.
   B. The primary endpoint was plasma RNA ≤50 copies mL after 48 weeks.
   C. Side effects were more frequent in the triple NRTI arm.
   D. The K65R mutation was not found in any patients.

5. Which of the following statements is *false*?
   A. ESS30009 compared the virologic suppression associated with ABC/3TC/ZDV versus EFV/ABC/3TC.
   B. A pilot study by Farthing and colleagues reported early virologic failure in treatment-naïve HIV-infected patients who received TDF/ABC/3TC.
   C. A possible explanation for the high rate of virologic failure with TDF/3TC/ABC is a low genetic barrier to resistance .
   D. Both B and C are false.

6. The Atlantic Study was a randomized, open-label trial that compared the relative efficacy of 1 convergent and 2 divergent regimens.
   A. True
   B. False

7. Which of the following statements is true?
   A. In the CLASS study, a high baseline VL was predictive of a better virologic response in the triple NRTI arm.
   B. A pilot study with ABC/3TC/ZDV +TDF resulted in a VL <50 copies/mL in 67% of patients by week 24.
   C. A pilot study with ABC/3TC/ZDV + EFV resulted in a VL <50 copies/mL in 58% of patients at week 8.
   D. Both B and C are correct.

8. According to the DHHS guidelines, which of the following is *not* a preferred antiretroviral regimen for the initial treatment of HIV?
   A. EFV + 3TC + ZDV
   B. LPV/r + 3TC + ZDV
   C. ABC + TDF + 3TC
   D. LPV/r + 3TC + d4T

9. Regimens with a PI plus 2 different NRTIs for the initial treatment of HIV possess the longest clinical experience and most available clinical data.
   A. True
   B. False

10. The advantages of initiating antiretroviral therapy early in HIV-infected patients include:
    A. earlier suppression of viral replication.
    B. preservation of immune function.
    C. reduced risk of developing treatment resistance with partial viral suppression.
    D. increased risk of viral transmission.
    E. Both A and B are correct.