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Amphotericin B: Does Fat Make It Better?

ABSTRACT & COMMENTARY

Source: Walsh TJ, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999; 340:764-771.

The niaid mycoses study group compared the safety and efficacy of conventional amphotericin B desoxycholate (AB) to AmBisome, a unilamellar liposomal amphotericin B (L-AB) product in the empirical therapy of persistent fever and chemotherapy induced neutropenia. Patients studied were ages 2-80 and were being treated for malignancy and who had an ANC less than 500/mm^3 and continuing fever despite having received empirically administered antibacterial therapy for at least five days. Three hundred forty-four patients received AB (0.6 mg/kg/d) and 343 received L-AB (3.0 mg/kg/d) for mean durations of, respectively, 10.8 and 10.3 days. The dose could be increased according to a set of guidelines or decreased in response to toxicity. Among the reasons for exclusion from study entry were a serum creatinine concentration greater than twice the upper limit of normal. The patient groups were similar at baseline, with approximately one-third in each being categorized as high risk and approximately 45% in each undergoing bone marrow transplantation. Study drug was continued until recovery from neutropenia.

In a modified intent-to-treat analysis (all patients who received at least 1 dose of study drug were included), there was no significant difference in outcome by any of the following individual end points examined: resolution of fever, survival for seven days after study initiation, lack of study drug discontinuation due to toxicity or lack of efficacy, and cure of baseline fungal infection. The last mentioned of these outcomes was the result of 11 patients in each group having positive blood cultures for *Candida* at baseline, prior to receipt of the first dose of study drug. There was also no difference between groups when a composite score was used. There were, however, significantly fewer proven breakthrough fungal infections among the patients given L-AB (3.2%) than in those given AB (97.8%; P = 0.009). There

INSIDE

were three breakthrough candidemic episodes in the former group and 12 in the latter (P = 0.03). A blinded assessment found that fungal infection contributed to or was the primary cause of death in four L-AB recipients and 11 AB recipients (P = 0.11).

Infusion-related adverse effects, including fever, chills, hypertension, tachycardia, hypotension, and hypoxia, were significantly more common in the AB recipients. Decreased arterial oxygen saturation was seen in 22 AB recipients and only one L-AB recipient (P < 0.001). Premedication was more commonly felt to be required in the AB recipients. An increase in serum creatinine concentration of either two-fold or greater or three-fold or greater was significantly more common in AB than L-AB recipients (P < 0.001); a peak serum creatinine of more than 3.0 mg/dL was observed, respectively, in 26% and 12% (P < 0.001).

COMMENT BY STAN DERESINSKI, MD, FACP

L-AB is one of three lipid-associated amphotericin B preparations currently available in the United States and is the only one of the three that contains true liposomes.[1,2] (*See Table.*) Its phospholipid bilayer, stabilized with cholesterol, provides an intravesicular hydrophilic and external hydrophobic environment. The amphipathic nature of amphotericin B makes it ideal for entrapment in these structures. Transfer of amphotericin B from liposomes to fungal cells may be assisted by the production and secretion of phospholipases by some pathogens; such enzymes are also produced by a variety of mammalian cell types, including phagocytic cells.

Table

Lipid-associated Amphotericin B Products

Product	Lipid Structure
Abelcet (ABLC; amphotericin B lipid complex)	1600-11,000 nm ribbonlike bilayers of 7:3 molar ratio of dimyristoyl phosphatidylcholine & dimyristoyl phosphatidylglycerol
Amphocil (ABCD; amphotericin B colloidal dispersion)	120-140 nm disks of cholesteryl sulfate
AmBisome (liposomal amphotericin B)	80 nm unilamellar bilayered vesicles of hydrogenated soy phosphatidylcholine and distearoylphosphatidylglycerol with cholesterol

Clearance of liposomal vesicles from the bloodstream varies with a number of factors. Smaller vesicles are cleared more slowly than large ones and positively or neutrally charged ones (the charge depending upon the phospholipids used) are also cleared more slowly than positively charged ones. Stabilization of the liposome with cholesterol also decreases its rate of clearance. Liposomes are predominantly removed from the circulation by cells of the reticuloendothelial system; L-AB (and ABLC) concentrate primarily in the spleen and liver, with limited distribution to the kidneys, heart, and lungs. The correlation between this pattern of drug distribution and both organ-specific toxicity and treatment efficacy have been speculated upon, but remain unproven. The observation that liposomal encapsulation of amphotericin reduces production of proinflammatory cytokines by phagocytic cells may account for a reduction in infusion-related toxicity. Despite its clearance by cells of the reticuloendothelial system, administration of L-AB does not interfere with clearance of bacteria from the bloodstream in a rodent model.[3]

Most in vitro and animal studies have demonstrated

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that, compared to AB, lipid-associated amphotericin B products cause less nephrotoxicity but at the cost of reduced (on a weight basis) antifungal activity. The critical question, thus, becomes whether the lipid products have an improved therapeutic toxic ratio in human infection. We are getting closer to an affirmative answer to that question as a result of studies such as the one reviewed above.

In another recent report, 338 adults and children with neutropenia (ANC < 500/mm^3) and fever persisting despite empirical antibacterial therapy for 96 hours were randomized to receive AB at 1 mg/kg/d, L-AB at 1 mg/kg/d, or L-AB at 3 mg/kg/d.[4] The rates of success (no development of fungal infection and no addition of other systemic antifungal therapy) were, respectively, 49%, 58%, and 64%. High-dose L-AB was superior to AB (P = 0.03). There was, however, no difference in time to defervescence. Toxicity was significantly less frequent in the L-AB recipients. Separately, a randomized comparison of amphotericin B colloidal dispersion and AB in a similar group of patients found no difference in efficacy but did find evidence of reduced toxicity with the lipid preparation.[5]

In a smaller study, 66 patients who could be assessed with regard to efficacy of treatment of proven (9 with fungemia, 17 invasive mold infections) or suspected (40 with possible pulmonary aspergillosis) infection were randomized to receive either AB (1 mg/kg/d) or L-AB (5 mg/kg/d).[7] The complete response rate was 44% in the L-AB recipients and 18% (P = 0.03) in the AB recipients. The proportions of partial responders in the two groups were, respectively, 22% and 38%; the comparable failure rates were 34% and 44%. When the entire range of responses was considered, the difference did not reach statistical significance (P = 0.09). Mortality rates, adjusted for malignancy status, were lower in patients given L-AB (P = 0.03). AB administration was more frequently associated with a rise in serum creatinine concentration (P < 0.001).

One important randomized comparison of two doses of L-AB in the treatment of invasive aspergillosis in 87 assessable patients found no difference in outcomes between those who received 1 mg/kg/d and those who received 4 mg/kg/d.[6] There were nine deaths due to aspergillosis infection in each arm.

L-AB (4 mg/kg/d for 3 weeks) has also been compared to AB (0.7 mg/kg/d for 3 weeks) in the initial treatment of cryptococcal meningitis in a small number of AIDS patients.[8] Patients subsequently received fluconazole in each arm. L-AB was significantly less nephrotoxic and was associated with earlier achievement of a negative cerebrospinal fluid culture. There was, however, no apparent difference in clinical efficacy.

As we accumulate evidence to validate the proposed superiority of lipid-associated amphotericin B products such as L-AB over conventional AB, we face another very difficult question—is the benefit sufficient to justify the cost of these expensive products? This question cannot be addressed until the issue of the optimal dose of drug is settled. Until that information is forthcoming and a convincing pharmacoeconomic justification is available, most institutions will likely restrict their use to particular circumstances in which conventional AB therapy is failing or cannot be administered because of toxicity. ❖

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Surviving Ebola Virus

ABSTRACT & COMMENTARY

Synopsis: *New concepts about immunologic responses in humans that determine survival or death from Ebola virus are presented. Recovery from Ebola is related to a progressive set of humoral and cellular responses.*

Source: Baize S, et al. Defective humoral responses and extensive intravascular apoptosis are associated with fatal outcome in Ebola virus-infected patients. *Nat Med* 1999;5: 423-426.

Ebola is a word that has come to signify one of the most feared of infectious diseases: contagious, horrifying in its manifestations, and rapidly fatal for its victims. Work to delineate the pathogenesis of Ebola is worthy in its own right in confronting this emerging infectious disease, but investigative work also offers the prospect of a model for investigating novel pathogens.

Research has progressed on both fronts regarding Ebola over the past decade. The current contribution by Baize and Leroy (equal contributors) and associates advances new concepts about immunologic responses in

humans that determine survival or death.

Specimens for the study were collected during two Ebola outbreaks, the first occurring in February 1996 in Mayibout, an isolated tropical village in northeast Gabon, the second six months later in Booué, about 500 miles from Mayibout. Mortality was 66% in Mayibout and 75% in Booué. Collection of samples from the epidemics was accomplished in heroic fashion, although samples from the Mayibout group of patients was unfortunately incomplete.

The central question of the study was: what factors related to survival in Ebola infection? It turns out that recovery is related to a progressive set of humoral as well as cellular responses. Regarding humoral response, IgM and IgG responses were brisk in certain individuals but, for survival, needed to be followed by activation of cytotoxic cells as antigen was being cleared from the blood. Death, conversely, was associated with poor IgG response and inadequate activation of T cells that underwent premature intravascular apoptosis.

All survivors made markedly more IgG and IgM antibody response to nucleoprotein than nonsurvivors and many survivors continued to make an IgG response to viral protein (VP) 40 and VP35 in the recovery period as measured by Western Blot determination. The discrepancies in IgG and IgM responses between groups were seen as early as 2-3 days and were markedly discrepant at the time of death (survivors vs nonsurvivors).

A large number of cytokine and lymphocyte responses were measured (in 4 survivors and 4 nonsurvivors, respectively), all assayed by RT-PCR of mRNA: IL-2, IL-4, IFN gamma, CD3, CD8, CD28, Fas, FasL, perforin, and Bcl-2. In the nonsurvivors, none made any mRNA indicative of cellular activation whereas in the survivors FasL, perforin, CD28, and IFN-gamma all were measurable. Additionally, T-cell receptor Vß repertoire changes were absent in the last days of fatal infection.

Baize et al also cleverly discovered that intravascular apoptosis of lymphocytes was characteristic in fatal cases. In fact, as measured by DNA fragmentation and release of specific nuclear matrix proteins, apoptosis was "massive" and progressed relentlessly during the last five days of life.

The early immunologic response in Ebola virus infection, thus, determines clinical outcome. When defective, lack of crucial humoral and cellular responses allows progression of programmed cell death that produces a fatal syndrome now familar to clinicians and also mimicked (destruction of lymphocytes in lymph node, spleen, and bone marrow) in monkies infected with Ebola virus. Recovery, on the other hand, is associated with a well-orchestrated sequence of humoral responses followed by activated cytotoxic T-cells.

COMMENT BY JOSEPH F. JOHN, MD

Short articles in *Nature Medicine*, a new journal now in only its fifth year of publication, are unusual because the background, results, and discussion sections flow in one central leading section. A methods section follows at the end. Yet, as in this article, there is a wealth of information packed into these short articles.

In this offering from research groups in Paris and Lyon, we glean an extensive amount of insight into one of the most feared emerging infections. The outbreaks studied in this report date back several years when Ebola was most prominent in the news. Although the media coverage has abated, new alerts suggest a new outbreak, again in the country formerly known as Zaire, now called the Democratic Republic of Congo. Forty-six people have died since January 1999 in response to what was first thought to be Ebola, but now appears to be marburg virus infection. The illness was first seen in gold miners but is now spreading to the community.[1]

What are the major findings of this study? Well, the title says it all. We learn that survival from Ebola virus is associated with rapid destruction of lymphocytes intravascularly by programmed cell death. The normal response is blunting of apoptosis—the programmed cell death—that occurs with efficient humoral response to specific viral proteins, followed by a cytotoxic T-cell response that probably clears residual viral antigen, thus blocking apoptosis. The ending of early IgG and IgM responses in survivors suggest that an amnestic response is occurring, possibly associated with earlier exposure to cross-reacting viruses, perhaps like the gold miner outbreak described above.

What we do not learn from this article is why lymphocytic apoptosis brings with it the hemorrhagic demise of Ebola's victims. Perhaps with deranged cytokine responses as infection progresses, intravascular coagulation occurs in response to lymphocytic dysregulation, although this is my speculation.

This work from France holds promise since it uncovers the need for an early, effective humoral response. Now that we know those proteins to which an IgG and IgM response is needed, vaccine development can progress. A section of *Nature Medicine* called "NEWS & VIEWS" features a perspective on Ebola and this paper by Gary Nabel, MD, a noted investigator from the University of Michigan. Nabel has most recently been appointed to the crucial post of Head, AIDS Vaccine Center. So we will likely see the fruits of his leadership in his new position against

another pathogen originating in central Africa, human immunodeficiency virus (HIV). ❖

Reference

1. ProMED Digest 1999;99:101.

Once Again—It's Experience That Counts

ABSTRACT & COMMENTARY

Synopsis: *HIV care providers with the most experience were more likely to use more complex and newer therapies generally in keeping with recent guidelines than those with less experience.*

Source: Brosgart CL, et al. Clinical experience and choice of drug therapy for human immunodeficiency virus disease. *Clin Infect Dis* 1999;28:14-22.

Brosgart and colleagues from the community consortium in San Francisco assessed the prescription of various drug therapies for 30 HIV-related medical conditions by HIV care providers located throughout the United States in May through June 1996. A total of 524 of 999 providers responded to the survey, although only 343 questionnaires were completed (181 providers were no longer in practice or providing care to patients with HIV). Of those who responded, 93% were physicians, most of whom were infectious disease specialists (35%), internists (34%), or family practitioners (20%). More than one-half provided primary care to more than 50 HIV-infected patients, while 20% cared for 6-20 patients and 8% had five or less. Nearly one-half (44%) worked in private practice or a private hospital.

Providers with the most experience, defined by their number of primary care HIV patients, were significantly more likely to use more complex and newer therapies generally in keeping with recent guidelines than those with less experience. More experienced providers were especially more likely to use more aggressive combination antiretroviral therapy or recently approved agents. For example, providers with more than 50 patients prescribed triple combination therapy to 35% of patients with CD4+ counts between 200-500, 78% of those with CD4+ counts between 50 and 200, and 86% of those with CD4+ counts under 50. In contrast, providers with five or fewer patients used triples in 4%, 35%, and 46% for similarly defined patient groups, respectively ($P < 0.001$ in all instances). Providers with fewer patients were significantly more likely to use a nucleoside analog reverse transcriptor inhibitor as monotherapy. In addition, while 75% of more experienced providers routinely used measurements of viral load, only 42% of those with five or fewer patients did so.

This more aggressive pattern of prescribing extended to several areas of prophylaxis for opportunistic infection. While patterns of use of prophylaxis against PCP were similar for all groups, and almost everyone used trimethoprim-sulfamethoxazole as first-line therapy, providers with greater numbers of patients were significantly more likely to prescribe prophylaxis for toxoplasmosis and cytomegalovirus than their counterparts with fewer patients. They were also more likely to use clarithromycin or azithromycin for *Mycobacterium avium* complex prophylaxis, whereas providers with fewer patients were more likely to use rifabutin.

COMMENT BY CAROL A. KEMPER, MD

Several earlier studies have demonstrated that experience is critical to the successful primary care of patients with HIV. In one study of 403 patients with AIDS, even modest levels of experience led to a 43% reduction in mortality.[1] The median survival of patients cared for by more experienced physicians (who provided care to at least 25 patients) was 26 months compared with only 14 months for those cared for by physicians with five or fewer patients ($P < 0.001$).

While outcomes were not specifically examined in the study by Brosgart et al, these results provide an important link to those earlier studies. Important differences in the level of sophistication and familiarity with newer HIV therapeutics exist for providers with greater levels of experience, defined simply by the numbers of patients for whom they provide primary care. The use of more aggressive combination antiretroviral therapy, as well as prophylaxis for certain conditions such as MAC, have been shown in multiple studies to decrease the risk of opportunistic infection and prolong survival.

However, several compelling questions remain unanswered by these data, chief among them the reasons why providers who care for fewer patients in this study appeared to use older or less aggressive therapies. Numbers of patients under care does not necessarily translate to a greater knowledge base. But, providers with fewer patients obviously have less opportunity to become familiar with newer agents. No other area of primary care moves as quickly or is as complex as HIV care, especially now with 14 different antiretroviral agents presently approved for use, and one other available through expanded access.

The use of newer resistance assays, such as genotype and phenotype assays, will add greatly to this complexity, but even here experience in the interpretation of this information may matter greatly. Data from the CPCRA study showed that the use of an expert virologist's interpretation of the genotype data in the selection of antiretroviral therapy significantly influenced the degree of HIV viral load suppression.[2] At sites where the virologist's suggested regimen was used 100% of the time, the level of plasma HIV RNA fell a mean of 1.5 logs compared with a 0.5 log reduction in patients whose disease was managed using only CD4 and HIV-RNA data without benefit of genotype data. At sites where the expert opinion was not used, however, the availability of genotype data did not provide any additional benefit in viral load suppression.

Are providers with fewer patients unaware of recent published guidelines, is the acquisition and use of newer information simply delayed, or are they more cautious in their interpretation of that information? For example, rifabutin was approved by the FDA for use in the prophylaxis of MAC in December 1992, allowing the drug to be marketed for this use. Rifabutin was subsequently recommended for the prophylaxis of disseminated MAC by an expert advisory panel in 1993,[3] following which additional supportive data became available regarding the cost-benefits of its use as a prophylactic agent. On the other hand, information on the effectiveness of clarithromycin and azithromycin for MAC prophylaxis was published in abstract form in the fall of 1995 and in the winter of 1996, but the peer-reviewed journal articles establishing their efficacy were not published until July 1996,[4,5] after this survey was completed. Therefore, it's conceivable that some physicians were unaware of the newer information available only in abstract proceedings, or perhaps preferred to wait until data had been peer reviewed before altering their practices.

Although "experience," however it may be defined, is important, we should keep in mind that information can be mainstreamed too quickly, in advance of confirmatory data or important follow-up information. I knew a physician in our area whose practice was dedicated to HIV care but who lobbied hard for the expanded use of Compound Q. Prophylaxis for CMV retinitis may have been vogue for a while, at least before more active antiretroviral therapy became available, but could you make the claim that you were a better doctor because you used it? It was never clear who would benefit from this intervention, and preliminary data suggested that prophylactic ganciclovir failed to reduce the risk of CMV retinitis in patients with high plasma levels of circulating CMV DNA who were at the greatest risk for this complication.

Furthermore, saquinavir hard gel was used extensively by AIDS "experts" in our areas as soon as it became available through expanded access protocols. While this practice no doubt spared the lives of some patients, others were doomed to fail this substandard drug. The resultant emergence of cross-resistance to other agents in its same class eliminated future options for many of these patients.

Taking this thought to its extreme, while the use of complex, multidrug antiretroviral therapies has benefited thousands of patients with HIV, the exultation of the AIDS-treating community and patients alike is being confronted by the grim reality of the impossibility of maintaining "100% compliance for life," the emergence of broadly resistant strains in up to 40% of patients, and the increasing appearance of resistant strains in newly infected persons. While the timely availability of information is important, and familiarity with the myriad agents is helpful, a more cautious—or even skeptical—approach is sometimes healthier. ❖

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You Can't Always Believe What You Read—Except in *Infectious Disease Alert*

ABSTRACT & COMMENTARY

Synopsis: *An analysis of abstracts in prominent medical journals found that these journals frequently failed to accurately reflect the data presented in the articles themselves.*

Source: Pitkin RM, et al. Accuracy of data in abstracts of published research articles. *JAMA* 1999;281:1110-1111.

Pitkin and colleagues assessed the information in the abstracts of research articles published in six medical journals to determine whether they accu-

rately reflected the information in the articles themselves. The journals evaluated were: *Annals of Internal Medicine*, *British Medical Journal*, *Journal of the American Medical Association*, *Lancet*, *New England Journal of Medicine*, and the *Canadian Medical Association Journal* (CMAJ). All 44 qualifying articles in the CMAJ over a 15-month period were evaluated, as were random samples of 44 articles from each of the other five published over a 12-month period. Abstracts were considered deficient if they contained data absent or inconsistent with those found in the article.

By these criteria, the proportion of abstracts in each journal that were incorrect ranged from 18-68%. Inconsistencies were more commonly encountered than were omissions, but both types of errors occurred together in 24% of the total. Discrepancies ranged from minor to important.

COMMENT BY STAN DERESINSKI, MD, FACP

Lacking the time necessary for careful analysis of a medical article, physicians commonly rely upon the accompanying abstract. Thus, the presence of inaccuracies in those abstracts is of great concern.

The journals selected for examination are all well-known and respected and the editors of those journals, as pointed out by Pitkin et al, were all founding members of the International Committee of Medical Journal Editors, a group that sets editorial standards. Thus, the results reviewed here may seem startling to many, but not to those of us who labor in the vineyards of *Infectious Disease Alert* (IDA).

While each of the IDA editors works somewhat differently, there is a common theme that I believe is represented by the way in which I approach an article. In each case, I ignore the published abstract and prepare my own summary of pertinent points from the text, tables, and figures of the article itself. This bypasses the problem of the inaccuracies and/or "spin" of the published abstracts and provides the reader of IDA with an independently developed summary and commentary. It also overcomes a potential problem not examined by Pitkin et al—the possible lack of inclusion in the abstract of important information contained in the article. Furthermore, our commentary section provides us with an opportunity to reflect upon the overall results of the article as well as upon the statements made by the authors in their discussion and to place them in context.

As Pitkin et al indicate, the use of structured abstracts is unlikely to overcome this problem. Furthermore, such structure often reduces the readability of the abstract. An accompanying editorial indicates that *JAMA* implemented a set of abstract quality criteria in January 1998, and that a preliminary analysis indicates that this may have improved the accuracy of its abstracts. However, as Pitkin et al state: "As part of the copy editing process, the abstract needs to be scrutinized painstakingly on a line-by-line or even word-by-word basis and each bit of information verified individually and specifically." While you wait for this utopian vision to arrive, I suggest that you and your colleagues continue to rely on IDA to save you time and invigorate your mind. ❖

Reference

1. Winker MA. *JAMA* 1999;281:1129-1130.

CME Questions

33. Which of the following is associated with death in Ebola virus infection?

a. Massive apoptosis of lymphocytes
b. Rapid rise in IgG antibody titer
c. Rapid rise in IgM antibody titer
d. Increased cellular mRNA for interferon gamma

34. In the NIAID Mycoses Study Group comparison of liposomal (L-AB) and conventional amphotericin B (AB) for empiric therapy in persistently febrile neutropenic patients, which of the following was true?

a. L-AB was associated with a greater frequency of decreased arterial oxygen saturation during infusion.
b. Proven breakthrough fungemia occurred more frequently in the L-AB recipients.
c. An increase in serum creatinine occurred more frequently in the AB recipients.
d. Fever resolved more rapidly in the L-AB recipients.

35. Which of the following is correct?

a. Liposomes are predominantly removed from the bloodstream by cells of the reticuloendothelial system.
b. Amphocil is the only true liposomal amphotericin B available in the United States.
c. Liposomal encapsulation of amphotericin B enhances production of proinflammatory cytokines by phagocytic cells in vitro.
d. Administration of liposomal amphotericin B interferes with the clearance of bacteria from the bloodstream in a rodent model.

36. Which of the following is *not* correct?

a. JC virus commonly causes an asymptomatic infection.
b. Infection with JC virus often occurs at a young age.
c. JC virus is the cause of progressive multifocal leukoencephalopathy.
d. JC virus is associated with glioblastoma multiforme.

37. HIV care providers with the most experience:

a. prescribe more complex and newer therapies for HIV patients.
b. routinely use measurements of viral load.
c. are more likely to prescribe prophylaxis for toxoplasmosis and cytomegalovirus.
d. All of the above

UPDATES

By Carol A. Kemper, MD

A Viral Cause of Brain Tumors?

Source: Khalili K, et al. *Lancet* 1999; 353:1152-1153.

While jc virus commonly causes an asymptomatic infection in humans, often early in life, reactivation of viral replication in the neurological tissues of immunosuppressed persons, including those with HIV infection, can result in a progressively disabling and fatal demyelinating illness called progressive multifocal leukoencephalopathy (PML). Recent experiments in transgenic mice suggest that the gene responsible for a regulatory protein of viral replication, called T-antigen, may have oncogenic potential (Krynska B, et al. *Oncogene* 1999;18:39-46). This led Khalili and colleagues to examine the prevalence of JC virus DNA in tumor tissue from 11 pediatric patients with medulloblastomas.

Ten children (91%) had evidence of JC VP1 DNA in tumor tissue and 73% had specific DNA sequences corresponding to the T-antigen of the virus. Using immunohistochemical techniques, JC virus T-antigen was demonstrated within a majority of tumor nuclei, and about 5-20% of tumor cells stained positively for antibody to T antigen. Specimens of brain tissue from five age-matched healthy controls were negative.

Interestingly, the structural organization of the regulatory gene appears to differ between that of the prototype Mad-1 variant of JC virus, which is responsible for the demyelination of neurological tissues, and the JCV (CY) strain commonly isolated in the urine of PML and non-PML individuals. These findings suggest that, in addition to its demyelinating effects in immunosuppressed patients, certain variants of JC virus may have tumorigenic potential. ■

How Lousy Can You Get?

Source: Roux V, Raoult D. *J Clin Microbiol* 1999;37:596-599.

Roux and raoult used pcr assays to assess the prevalence of human body louse infection by three different human disease-causing bacteria, including *Bartonella quintana* (the agent of trench fever), *Borrelia recurrentis* (an agent of relapsing fever), and *Rickettsia prowazekii* (the agent of epidemic typhus). Samples of body lice were collected from 599 subjects residing in six different countries, including refugees in Congo and Burundi, homeless people in Marseille, Moscow, and Zimbabwe, and rural residents of Peru.

Bartonella was found in 9.7% of all lice sampled, varying in frequency from 1.4% obtained from rural Peruvians to as high as 16.7% from Zimbabwean homeless (see also Kemper CA. *Infect Dis Alert* 1999;15:120). In contrast, *R. prowazekii* was only found in refugees from Burundi, where an epidemic of typhus was occurring. Nearly one-third of the specimens collected during the epidemic were positive for *R. prowazekii*, but the organism was not identified in any of the 91 post-epidemic specimens. None of the specimens from any of the groups was positive for *B. recurrentis*. Much the same as our Public Health Department presently uses PCR to monitor the prevalence of *Borrelia burgdorferi* in *Ixodes pacificus* ticks in our area, PCR assay could be a valuable epidemiological and diagnostic tool for tracking endemic disease in body lice in high-risk populations. ■

Dual and Recombinant HIV-1 Infections

Source: Ramos A, et al. *Emerg Infect Dis* 1999;5:65-74.

Dual and even triple co-infection with different subtypes and clades of HIV-1 have been documented in several countries around the globe, including Africa and South America. The potential for infection with multiple serotypes and recombinant strains creating mosaics may significantly affect efforts to develop effective HIV vaccine strategies. For example, in Brazil, which has been selected as a World Health Organization (WHO) field site for HIV vaccine testing, four subtypes (B, F, C, and D) are present in the population, although only the first two are predominant.

Ramos and colleagues evaluated the HIV strains found in 79 patients in 1994, all of whom were participants in pre-vaccine selection studies in Rio de Janeiro. Using combinations of various molecular and sequencing techniques, three dual (3.8%) and six recombinant (7.6%) infections were identified. Each of the recombinant infections was a unique B/F mosaic, whereas the dual infections were different combinations of two of the circulating subtypes B, F, and D.

Based on patterns of infection found five years ago in a major urban area in South America, mixed infections with different subtypes of HIV, including combinations of less common strains found circulating at low levels in the population, were found in up to 11.4% of patients. This finding may have profound affects on worldwide vaccine developmental efforts. ■

In Future Issues:

Use of Tunneled Femoral Catheters to Prevent Catheter-Related Infection