AGA Technical Review: Malnutrition and Cachexia, Chronic Diarrhea, and Hepatobiliary Disease in Patients With Human Immunodeficiency Virus Infection

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Disorders of the gastrointestinal tract and hepatobiliary system are among the most common complications associated with human immunodeficiency virus (HIV) infection. These disorders not only result in major morbidity but mortality as well. With increasing use of prophylaxis against Pneumocystis carinii pneumonia, the incidence of opportunistic gastrointestinal disorders has increased.1-3 Significant progress has been made in the last decade in characterizing the spectrum of pathogens involving the gastrointestinal and hepatobiliary systems, determining the pathophysiological mechanisms of these diverse processes, and defining management options. Despite these encouraging advancements, many questions remain unanswered. The purpose of this review is to evaluate and synthesize the published clinical research pertaining to three important HIV-related complications: malnutrition and cachexia, chronic diarrhea, and hepatobiliary disease. A separate review addresses disorders of the esophagus.4 Attention here is focused on etiology and pathogenesis, clinical features, diagnostic strategies, and efficacy of current treatment options. Recommendations for managing patients with these complications are provided based on the weight of the clinical evidence.

Methods

Literature searches for the section on malnutrition and cachexia were performed for the period from 1980 to 1994 using MEDLINE and the medical subject heading terms “cachexia” and “malnutrition” and cross-referenced with “HIV” and “AIDS.” Secondary searches were performed using the terms “nutrition” and “malabsorption.” Relevant articles for the section on chronic diarrhea were identified by searching the MEDLINE database for the period from 1989 to 1994. The initial search strategy used the medical subject heading terms “chronic diarrhea” and “diarrhea” cross-referenced with “HIV” and “AIDS.” Secondary searches were undertaken using “enteric bacteria,” “enteric parasite,” “enteric pathogen,” “mycobacteria,” “cryptosporidia,” “microsporidia,” and “cytomegalovirus,” which were cross-referenced with “HIV,” “AIDS,” “intestine,” “colitis,” and “gut.” Articles for review for the section on hepatobiliary disease were obtained by searching the MEDLINE database for the period from 1985 to 1994 using the search terms “AIDS and liver,” “HIV and liver,” and “hepatitis and HIV.” We identified further articles from the references cited in the literature identified by the MEDLINE searches. In selecting articles to include in this review, we gave preference to primary rather than secondary sources such as review articles and book chapters. We also gave preferences to larger series (n > 15) when available. Abstracts, articles from developing countries, and articles not published in English were excluded. Letters were included when they contained the only available data on a specific issue that was considered necessary for completeness. Articles pertaining to pediatric HIV infection were not reviewed.

Malnutrition and Cachexia

Since the initial descriptions of acquired immunodeficiency syndrome (AIDS), weight loss has been recognized as a cardinal feature. The HIV wasting syndrome, which is an AIDS-defining illness, is defined as involuntary weight loss of >10% of baseline body weight plus either chronic diarrhea (at least two loose stools per day for ≥30 days) or chronic weakness and documented fever (for at least 30 days and either intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that explains these findings.5 Given that opportunistic infections and neoplasms frequently cause fever, weight loss, and diarrhea, only a small subset of patients may truly have wasting in the absence of these complications.

Abbreviations used in this paper: AIDS, acquired immunodeficiency syndrome; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; ERCP, endoscopic retrograde cholangiopancreatography; HIV, human immunodeficiency virus; MAC, Mycobacterium avium complex; PCR, polymerase chain reaction; TPN, total parenteral nutrition.

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Prevalence

Studies evaluating the nutritional status of hospitalized patients with AIDS have documented that 60% or more are underweight (>10% weight loss) at the time of admission. Even asymptomatic patients in the early stages of disease may have a reduction in body cell mass. A retrospective cohort study of 258 HIV-infected patients found a 37% incidence of weight loss during a 36-month period; weight loss was associated with a CD4 count of <500/mm$^3$ (approximate normal range, 500–1500 mm$^3$). In a study of 186 patients undergoing either upper or lower endoscopy for clinical indications, weight loss was reported in 26% of patients in Centers for Disease Control and Prevention (CDC) category IV disease compared with 7% of patients in categories II or III. Of a total of 147,225 adults or adolescents with AIDS reported to the CDC from September 1, 1987, to August 31, 1991, 17.8% had the HIV wasting syndrome, in 7.1% of whom it was the AIDS-defining illness. Geographic variations in the prevalence of wasting have been reported; in Puerto Rico, 47% of patients with AIDS had wasting in contrast to 11% in the northeastern United States. In developing countries, the symptom complex of weight loss, fever, and/or chronic diarrhea is particularly common and has been termed “slim disease.” The diagnosis of wasting syndrome may be frequent in developing countries and in earlier published studies from the United States because complete evaluation for enteric opportunistic infections was not performed.

Risk Factors

A number of risk factors for weight loss have been identified. Wasting has been associated with injection drug use as the route of HIV exposure (subsequently referred to as transmission category). Specific disorders most frequently associated with wasting included isosporiasis, pulmonary and/or esophageal candidiasis, HIV encephalopathy, chronic mucocutaneous herpes simplex virus infection, and coccidioidomycosis. Gastrintestinal cytomegalovirus (CMV) disease is also commonly accompanied by weight loss. Disseminated Mycobacterium tuberculosis plays an important role in weight loss in developing countries.

Two prospective studies have determined risk factors for weight loss. In a cohort of 104 HIV-infected patients, a single risk factor was predominant in most patients with anorexia being most frequent. Other important risk factors included diarrhea, fever, and acute infections. In 1809 participants followed up semiannually for up to 6 years in the Multicenter AIDS Cohort Study, fever, thrush, and a CD4 count of <100/mm$^3$ were each independently associated with a decrease in body mass. Although diarrhea was important, it was not as strongly associated with weight loss as these other factors. No significant decrease in body mass was found for those with a CD4 count of >200/mm$^3$. Elevations in β₂-microglobulin and urinary neopterin levels have also been linked to subsequent weight loss, suggesting the importance of immune system activation.

Implications

Malnutrition has long been recognized to have deleterious effects on immune function. In non–HIV-infected patients, findings caused by malnutrition include alterations in B cell and phagocyte function as well as decreased secretory immunoglobulin A and complement activity. Lymphopenia commonly accompanies malnutrition, and reductions in B and T lymphocytes are well recognized. Non–HIV-infected malnourished patients also have decreased CD4 cells as well as moderate reductions in CD8 cells, which may normalize with improvement of nutritional status. These immune system derangements may play a role in the increased risk of infection found in malnourished patients. Nevertheless, it is often difficult to separate out the effect of malnutrition from the underlying disease on immune dysfunction.

Micronutrient deficiencies have been documented to result in immune system dysfunction. Deficiencies of zinc, iron, fat-soluble vitamins, and vitamins C and B have been linked to defects in cellular immunity in non–HIV-infected individuals. In HIV-infected patients, reduced serum concentrations of zinc, vitamin B₁₂, and some fat-soluble vitamins have been reported, which may contribute to immunodeficiency. However, clinically significant improvements in immune function after repletion of micronutrient deficiencies have not been well documented in patients with AIDS.

Both retrospective and prospective studies suggest a strong link between nutritional status and survival in patients with AIDS. Kotler et al. observed a critical level of body cell mass and weight at which death occurred (>66% of ideal body weight) independent of the cause of wasting. In a study of 71 patients, death was strongly associated with reduced serum albumin concentration and percent weight loss. Similar observations by Guenter et al. indicate that this relationship is maintained even after controlling for CD4 lymphocyte count. In a prospective case-control study, a CD4 count of <200/mm$^3$, wasting, and vitamin A deficiency were found to be independent risk factors for death. In a study of 100 outpatients, body cell mass of >30% of body weight or a serum albumin level of >3 mg/dL were associated with a longer survival independent of CD4
count.$$ Body cell mass may be a better predictor of survival than weight loss; however, weight is a more readily available clinical measure. Although evaluation of a larger number of patients would be required to evaluate the importance of other factors, such as specific AIDS-defining conditions, the evidence strongly suggests that nutritional status is an important predictor of survival. Whether poor nutritional status is an additional cause of immune deficiency is not known.

**Pathophysiological Mechanisms**

A number of pathophysiological mechanisms have been documented as potential causes of weight loss in HIV-infected patients (Table 1). More than one mechanism may be operative at one or more times during the course of HIV infection, particularly in the late stages of disease. These mechanisms will be briefly reviewed as a background for understanding treatment options.

**Inadequate oral intake.** Sharkey et al.\(^\text{35}\) evaluated nutritional status and food intake for a 1-week period in HIV-infected and HIV-seronegative homosexual men. The HIV-infected patients were clinically stable (no detectable opportunistic infection, afebrile), were in the later stages of immunodeficiency, had >90% of ideal body weight, and were free of enteric pathogens. Overall, HIV-infected patients were thinner. As a whole, no differences were detected in food intake between the groups. Intake seemed to be compromised only in those patients with very low CD4 counts and reduced intake correlated with weight loss, suggesting a cause and effect relationship. Another study\(^\text{36}\) compared nutritional intake in clinically stable patients with AIDS, patients with AIDS-related complex, and asymptomatic HIV-infected controls. Similar to the study by Sharkey et al.,\(^\text{35}\) no overall differences in oral intake were observed among the three groups during the 72-hour recording period. Kotler et al.\(^\text{37}\) found no difference in weight as percent of ideal between clinically stable patients with AIDS and homosexual or heterosexual HIV-seronegative patients, although body cell mass, as determined by total body potassium, was significantly reduced in the patients with AIDS. In the study by Kotler et al.,\(^\text{37}\) caloric intake during the 6-week monitoring period was no different among the three groups, although intestinal absorption of both xylene and lipids was significantly reduced in the patients with AIDS. These and other studies\(^\text{35–38}\) suggest that, during periods of up to 6 weeks, stable patients with AIDS have adequate oral intake; thus, it seems that other mechanisms are important in these patients.

Studies evaluating oral intake in HIV-infected patients with acute opportunistic infections have found significant reductions in caloric intake.\(^\text{39,40}\) In a longitudinal study of 27 HIV-infected men, assessments of energy metabolism during stable periods were compared with episodes of weight loss.\(^\text{40}\) Most of these episodes were associated with a documented secondary infection. Although resting energy expenditures were higher in the HIV-infected men than in controls (9.6%), no differences were found in total energy expenditures. During weight loss episodes, total energy expenditures were reduced, primarily related to reductions in activity. However, evaluation of energy intake showed that the reduced oral intake exceeded the reduction in total energy expenditures. These studies suggest that, in patients with AIDS, acute systemic infections cause significant reductions in oral intake and play the major role in short-term weight loss (see below).

**Intestinal malabsorption.** HIV-related chronic diarrhea is frequently accompanied by weight loss, particularly in those with more severe reductions in CD4 count. Evaluation of gastrointestinal function in these patients has documented reductions in D-xylose and fat absorption.\(^\text{41–46}\) The degree of fat malabsorption in some patients with diarrhea may be striking (i.e., >20 g/day).\(^\text{47}\) In one study,\(^\text{48}\) serum carotene, a marker of fat malabsorption, was decreased in 77% of HIV-infected patients and was associated with a decreased CD4 count. Vitamin B\(_2\) deficiency, which may be detected in 10%–20% of patients with AIDS,\(^\text{45,46}\) has been considered the result of intestinal malabsorption. Protein exudation\(^\text{49}\) may contribute to hypoalbuminemia, which is common in patients with AIDS\(^\text{10,50}\). Pancreatic insufficiency does not seem to be the cause of fat malabsorption in patients with AIDS and diarrhea.\(^\text{51}\)

Table 1. Potential Pathophysiological Mechanisms in HIV Wasting Syndrome

<table>
<thead>
<tr>
<th>Inadequate oral intake</th>
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<tr>
<td>Intestinal malabsorption</td>
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<td>Alterations in metabolism</td>
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<td>Cytokines</td>
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**Alterations in metabolism.** The normal response to malnutrition caused by fasting is a reduction in metabolic rate (resting energy expenditures).\(^\text{52}\) In contrast, patients with severe acute infections or critically ill pa-
tients typically have an increase in metabolic rate. Most studies have documented an increase in resting energy expenditures depending on the stage of immunodeficiency (denoted by the CD4 count) and the presence of active infections. In these studies, metabolic rate is typically measured by indirect calorimetry. The resting metabolic rate in HIV-infected patients with a normal CD4 count was 8% greater than observed in a group of HIV seronegative patients. Compared with healthy controls, patients with AIDS and active infections had a 34% increase in metabolic rate; stable patients with AIDS were found to have a 21% increase. Grunfeld et al. measured resting energy expenditures and caloric intake in HIV-infected patients and normal subjects. As documented in other studies, resting energy expenditure was increased in HIV-infected patients compared with controls. These increases were as follows: HIV infected without immunodeficiency, 11%; AIDS without systemic infections, 25%; and AIDS with systemic infection, 29%. Caloric intake in HIV-infected patients was similar to the controls, and no change in weight was observed except for the patients with AIDS with systemic infections in whom a 36% reduction in caloric intake occurred, accompanied by a 5% decrease in weight. Although smaller studies have reported a decrease in metabolic rate in stable patients with AIDS, patients with AIDS with systemic infections maintain an increased metabolic rate despite decreased caloric intake, similar to patients with sepsis, burns, or major trauma.

The pattern of weight loss may vary, depending on the patient’s clinical manifestations of HIV infection. Acute weight loss may occur before or during acute infections or may occur as a preterminal event. In patients who recover from an acute infection (e.g., P. carinii pneumonia), weight may return to baseline without specific nutritional intervention. In contrast, patients with chronic progressive weight loss were more likely to have a gastrointestinal complication, particularly a diarrheal illness.

These data in aggregate suggest that, even in early HIV infection, resting energy expenditures may be mildly increased although weight remains stable. In the absence of opportunistic infections, patients with AIDS may maintain a stable weight despite an increase in resting energy expenditures by appropriately increasing caloric intake and/or decreasing activity. An acute systemic illness seems to cause weight loss primarily through significant reductions in oral intake, although increased energy expenditures play an important role. With effective therapy for the systemic illness, weight gain may occur without specific nutritional interventions, although full recovery of weight may not necessarily occur with repeated infections. Progressive weight loss seems to be more characteristic of patients with gastrointestinal complications in whom decreased oral intake and malabsorption may occur. In patients with multiple simultaneous infections (e.g., P. carinii pneumonia and intestinal cryptosporidiosis), weight loss may result from multiple pathophysiological mechanisms.

**Endocrine dysfunction.** Disturbances in a variety of endocrine systems have been documented in patients with AIDS. A reduction in serum testosterone hormone concentration, adrenal dysfunction, and an alteration in thyroid hormone levels have been documented, especially in patients with severe wasting, although not consistently. However, it is unclear whether these hormonal aberrations are causally related to wasting. In contrast to immunocompetent patients with severe systemic illness in whom serum T₃ concentrations are reduced and reverse T₃ concentrations are increased (euthyroid sick syndrome), some patients with AIDS maintain normal T₃ concentrations, suggesting that thyroid function may be “overstimulated” for the degree of wasting, thus potentially contributing to weight loss. However, thyroid stimulation testing is usually normal in these patients. Grunfeld et al. found that thyroid hormone concentrations were normal in asymptomatic HIV-infected patients but decreased appropriately in those with systemic illnesses. In addition, for those with acute infections, anorexia, and weight loss, reduction in T₃ concentrations occurred, consistent with euthyroid sick syndrome. In these patients, the resting energy expenditures were greater than in asymptomatic patients or normal individuals. These studies taken together suggest that endocrine dysfunction plays a minor role, if any, in HIV-related wasting.

**Cytokines.** Tumor necrosis factor has been suggested as a potential etiologic factor in HIV wasting syndrome. Conflicting data exist regarding serum concentrations of tumor necrosis factor. Recent studies using improved bioassays show elevated tumor necrosis factor levels in HIV-infected patients, which progressively increase with increasing immunodeficiency regardless of concurrent illness. Immunocompetent HIV-negative patients with acute illness and intravenous drug users may have slightly increased concentrations of tumor necrosis factor. Although an increased serum concentration of tumor necrosis factor may induce anorexia, its contribution to weight loss is unknown. In one study, serum concentrations of soluble tumor necrosis factor were significantly increased in HIV-infected patients compared with controls; there was an associated decrease in serum albumin and transferrin concentrations and reduced body cell mass. Whether the interaction of tumor
necrosis factor with other cytokines such as interleukin 1 plays a role in wasting remains undefined.\textsuperscript{81} As a determinant of wasting, the paracrine effects of tumor necrosis factor may be more important in vital tissues rather than the serum concentrations.\textsuperscript{82} Despite the association of increased serum tumor necrosis factor concentrations with disease progression, the precise role of this cytokine in weight loss remains undefined.

**Treatment**

**Nutritional supplementation.** As with any malnourished patient, repletion of nutritional deficiency represents sound clinical care. The goals of nutritional therapy should be to minimize loss of body mass, prevent micronutrient deficiencies, and restore body weight. Patient education regarding diet alone has been shown to significantly increase caloric intake.\textsuperscript{83} Although an aggressive approach to nutritional therapy has been advocated,\textsuperscript{84} its effects on outcome measures such as the incidence of opportunistic infections or mortality have not been documented.

A prospective randomized nonblinded trial of 80 patients compared a routine diet supplemented with standard enteral formula (Ensure; Ross Products, Columbus, OH), with a new peptide-based formula\textsuperscript{85} that contained greater amounts of fiber and carbohydrate content, less fat, and a "patented" polypeptide. The 56 patients (70\%) who completed the trial (25 receiving Ensure and 31 receiving the new formula) consumed equal quantities of the treatment formula (approximately 1 1/2 cans per day), although less than the targeted amount. Both formulas were well tolerated. Patients in the new formula group had a net weight gain of 4 lb compared with a loss of 1.5 lb in the standard formula group ($P = 0.04$). Interestingly, more patients receiving the standard formula were hospitalized after 3 months of treatment. The reasons for hospitalization were not reported, and survival differences were not evaluated. Although statistically significant differences were detected in some nutritional parameters such as triceps skin-fold thickness, these were not meaningful clinically.

**Enteral alimentation.** Studies of the safety and efficacy of nutritional supplementation by percutaneous endoscopic gastrostomy tubes are limited. In a 2-month study of 6 patients,\textsuperscript{86} a 14\% increase in body mass was observed, which was accompanied by an increase in body fat content. However, no change in weight was detected from baseline. Although no procedure-related complications were reported, a subsequent case-control study suggests that HIV-infected patients are at a higher risk for major complications such as infection.\textsuperscript{87}

**Parenteral alimentation.** Although personal clinical experience suggests that total parenteral nutrition (TPN) is frequently administered to patients with AIDS, there are no studies documenting the frequency of its use. Few studies have evaluated the nutritional effects and safety of TPN in HIV-infected patients. Kotler et al. studied the effects of TPN in 12 malnourished patients with AIDS.\textsuperscript{88} Malnutrition was caused by reduced oral intake or malabsorption in 5 patients and by underlying systemic infections with or without a malabsorption syndrome in 7 patients. Nutritional assessments were performed monthly for 4–42 weeks of follow-up. For the full study group, no change in mean body cell mass was observed, although body fat content increased significantly. The 5 patients in whom malnutrition was caused by reduced oral intake or malabsorption experienced weight gain and repletion of body cell mass, whereas only 2 of 7 patients with systemic infections had an increase in body cell mass; these differences were not significant. In a retrospective study of 22 patients with AIDS, TPN administration for a period of 1–11 months was evaluated.\textsuperscript{89} In these patients, 10 had an underlying neoplasm (Kaposi’s sarcoma or lymphoma) and 9 developed \textit{Pneumocystis carinii} pneumonia during the study period. In contrast to the findings of Kotler et al.,\textsuperscript{88} 15 of the 22 patients gained weight, 5 maintained their weight, and only 2 lost weight.\textsuperscript{89} Metabolic disturbances related to TPN were uncommon, and the overall complication rate was low (0.12/100 catheter days). However, 2 patients developed catheter infections and 9 had to have their catheters replaced for other complications such as venous thrombosis. No difference in catheter-related complications was found when compared with a historical control group of patients with cancer receiving TPN. These small studies\textsuperscript{88,89} suggest that TPN is relatively safe; larger studies of HIV-infected patients receiving TPN or intravenous therapy for opportunistic infections by a central venous catheter have documented variable complication rates of 0.13–0.47/100 catheter days.\textsuperscript{90–92}

In summary, weight gain may be achieved in some patients using enteral nutrition or TPN. However, the safety of TPN has not been evaluated in a sufficiently large number of patients to draw firm conclusions. In addition, weight gain has been modest at best, and no significant reduction in the incidence of opportunistic infections or hospitalizations or improvement in survival has been documented. Trials of TPN in patients with cancer have similarly failed to show improved survival.\textsuperscript{93} Nutritional supplementation may benefit selected patients; however, the available data do not help identify these patients or indicate which therapy is more appropriate.
Appetite stimulants. Given the prevalence of anorexia, particularly in patients with end-stage disease, appetite stimulants have received attention. Megesterol acetate, a synthetic progestational agent, has been associated with appetite stimulation, an improved sense of well-being, and weight gain in patients with breast cancer. Following a pilot study showing weight gain in patients with AIDS, randomized placebo controlled trials were undertaken. In these two trials, entry criteria included AIDS with a 20% or greater decrease in body weight and a minimum weight loss of 10% below ideal body weight. Patients with impaired food intake, overt gastrointestinal disorders resulting in malabsorption (specific tests for malabsorption were not performed), dementia, malignancies, or opportunistic infections were excluded. One trial compared placebo with 800 mg daily of megesterol acetate, whereas the other was a dose-ranging trial comparing placebo with 100, 400, and 800 mg. The results from the two trials were remarkably similar. In both, caloric intake and body weight increased and sense of well-being improved in the patients treated with megesterol acetate. No difference in Karnofsky scores, opportunistic infections, or survival were observed between the treatment groups in either trial. Megesterol acetate was well tolerated with no significant side effects. However, one may question the clinical importance of a weight gain of 9–17 lb, particularly because this resulted from increased body fat and not lean body mass, which may be a more important determinant of survival. Finally, although an improved sense of well-being is important to patients, this must be weighed against the cost of the agent as well as lack of any survival benefit or reduction in the occurrence of opportunistic infections.

Dronabinol, the major active ingredient in marijuana, has also been used as an appetite stimulant. A multicenter randomized double-blind placebo-controlled trial of 139 HIV-infected patients was performed to evaluate the efficacy of this agent. In the 88 evaluable patients (63%), dronabinol was associated with statistically significant improvements in appetite and mood. However, no significant differences in weight were observed during the 6-week study period, and those who received dronabinol were twice as likely to discontinue therapy because of side effects. Survival differences were not reported.

A variety of other pharmacological therapies are currently undergoing evaluation. Pentoxifylline, a drug that reduces tumor necrosis factor concentrations and HIV replication, has been evaluated with inconclusive results in a pilot study of 5 patients. Growth hormone is also currently under investigation. In a study of 10 patients, intravenous administration of insulin-like growth factor resulted in only transient nitrogen retention, suggesting partial resistance to the anabolic effects of this drug. These novel pharmacological treatments must be evaluated in carefully conducted randomized clinical trials to determine their effect on overall patient nutritional status and/or survival.

Conclusions

Malnutrition is an important complication of HIV infection, although weight loss is not universal even in the later stages of disease. Alterations in metabolism that can be documented in early HIV infection become more pronounced in the later stages of disease. Opportunistic infections not only cause altered body metabolism but are also associated with reduced oral intake, which seems to be the most important determinant of weight loss. In patients with weight loss, the identification of treatable opportunistic infections, including gastrointestinal tract complications, should be the first concern. In the absence of any identifiable cause of weight loss, nutritional assessment should be performed followed by dietary counseling to increase nutritional intake. Although enteral supplements may promote weight gain, their effects have not been well documented. The use of TPN may be inappropriately aggressive, particularly in patients with advanced disease. In addition, no randomized clinical trials of TPN in patients with AIDS have been performed to evaluate the effects on quality of life and survival. Nevertheless, given the relationship between nutritional status and survival as well as the use of TPN in other situations in which data are lacking, the use of TPN for patients in whom gut function is inadequate may be appropriate. Although treatment with appetite stimulants has physiological rationale, randomized clinical trials have not documented meaningful improvement in important end points such as the occurrence of opportunistic infections or mortality. What these studies have shown are improvements in the patient’s sense of well-being and modest weight gain, primarily body fat. Further studies are clearly needed to identify which patients are likely to benefit from nutritional supplementation and to determine the best approach.

Chronic Diarrhea

Definition of Chronic Diarrhea

Accurate definition is fundamental to systematic investigation and precise communication. The CDC defines chronic diarrhea as two or more loose stools per day for ≥30 days. However, this definition fails to capture the spectrum and severity of diarrheal patterns observed in clinical practice. For example, using this definition, no distinction is made between an individual passing three mushy stools per day who is otherwise functionally
unimpaired and a bedridden patient who is incontinent with profuse, watery diarrhea. Given the lack of a valid, reliable, and widely accepted method for classifying diarrhea pattern and severity, various definitions have been used, making comparison among the published studies difficult.

In addition, from the standpoint of patient management, other features of the diarrheal illness beyond stool frequency are important because they provide clues to the etiology. As in non–HIV-infected patients, the passage of large-volume stools associated with periumbilical pain usually indicates small bowel disease. On the other hand, the passage of frequent, small-volume stools (which may be bloody) associated with urgency, tenesmus, and lower abdominal cramps or perianal pain usually indicates colonic and/or anorectal disease. The presence of fever is also important, because it may indicate mucosal invasive disease or the presence of an associated bacteremia.

Scope of the Problem

Although diarrhea is frequently stated to be very common in HIV-infected individuals, few estimates of the magnitude of the risk of developing diarrhea are available. Two factors that predict a higher risk of diarrhea are decreased CD4 cell count and male homosexuality. In the Multicenter AIDS Cohort Study, which evaluated 493 HIV-infected homosexual men at two 6-month intervals, 0.9% of men with CD4 cell counts of >700/mm$^3$ had diarrhea compared with 6% of men with CD4 counts of <250/mm$^3$. A retrospective cohort study of 169 predominantly homosexual HIV-infected men, one third of whom had CD4 cell counts of <200/mm$^3$, was performed for a 4-year period. The prevalence of diarrhea at any 6-month outpatient visit was 3%–7%. Diarrhea was three times more common among homosexual men than among those in other transmission categories. In a retrospective survey of gastrointestinal symptoms in 258 predominantly homosexual HIV-infected outpatients with a mean CD4 cell count of 502/mm$^3$, 14% had diarrhea at the initial outpatient clinic visit. Thus, in these outpatient studies, the prevalence of diarrhea at any single visit ranged from 0.9% to 14%. On the other hand, in studies focusing on patients with more advanced disease, diarrhea is more common. For example, in a small study ($n = 22$) of severely ill hospitalized patients with AIDS, 50% had diarrhea.

Findings on Diagnostic Evaluation

Although HIV-related chronic diarrhea can be attributed to infection with one or more common or opportunistic enteric pathogens in many patients, no cause can be identified despite intensive investigations in a significant proportion. Several hypotheses have been proposed to account for these cases of unexplained chronic diarrhea, including direct mucosal HIV infection. Although a full appraisal of the laboratory evidence supporting these hypotheses is beyond the scope of this report, the issues are summarized in a subsequent section. Because the goal of this report is to evaluate the clinical research and develop clinical guidelines for patient management based on this evidence, the main focus here is on enteric pathogens because they play the major role in HIV-related chronic diarrhea.

Spectrum of enteric pathogens. The prevalence and spectrum of enteric pathogens vary in published reports for at least two reasons. First, patient characteristics are important. The prevalence of enteric pathogens is greater among homosexual men, those with weight loss, and probably those with prolonged diarrhea. Another important patient characteristic is the severity of the immunologic deficit. For example, pathogens such as Mycobacterium avium complex (MAC) will not be observed unless patients with more advanced disease, denoted by a CD4$^+$ cell count of <100/mm$^3$, are included. Second, the prevalence and spectrum of enteric pathogens depends on the intensity of diagnostic workup. If diagnostic workup does not include endoscopic mucosal biopsies, organisms such as CMV will not be detected.

Table 2 summarizes seven relevant published studies and lists the two most common enteric pathogens reported in each study. Excluded from Table 2 are studies that focused on specific pathogens, mucosal structure, or patients with negative stool examinations. All of the studies listed in Table 2 are cross-sectional. In the retrospective study, only patients with diarrhea were evaluated. Chronic diarrhea was not defined in three studies, and the definitions varied in the remainder. The patients were referred for gastroenterological workup in all but one study. The patients were severely ill, and all had AIDS except for one study in which 75% had AIDS. Inpatients, who tend to be sicker, were included in the six studies in which this could be determined and were the sole focus in two studies. For the four studies in which patient characteristics could be determined, the mean CD4 cell count was 62/mm$^3$ and mean weight loss was 8.2 kg in the first study, the mean CD4 cell count was 126/mm$^3$ and mean weight loss was 8.6% in the second study, the mean weight loss was 15 kg in the third study, and >15% body weight loss was present in 64% of patients in the fourth study. Taken together, in the six studies that reported the transmission category,
### Table 2. Summary of Published Literature on the Prevalence of Enteric Pathogens in HIV-Infected Patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intensity of diagnostic workup</th>
<th>Patients with diarrhea (%)</th>
<th>Patients without diarrhea (%)</th>
<th>Enteric pathogen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dworkin et al.(^{105})</td>
<td>Stools</td>
<td>22 (55)</td>
<td>38(^{\ast})</td>
<td>MAC, Cryptosporidia</td>
</tr>
<tr>
<td>Laughon et al.(^{113})</td>
<td>Stools</td>
<td>77 (64)</td>
<td>50</td>
<td>Cryptosporidia, Campylobacter species</td>
</tr>
<tr>
<td>Smith et al.(^{115})</td>
<td>Stools, EGD, colonoscopy</td>
<td>30 (67)</td>
<td>85</td>
<td>CMV, Entamoeba histolytica</td>
</tr>
<tr>
<td>Antony et al.(^{106})</td>
<td>Stools</td>
<td>66 (100)</td>
<td>55</td>
<td>NA, CMV, Entamoeba histolytica</td>
</tr>
<tr>
<td>Rene et al.(^{116})</td>
<td>Stools, EGD, colonoscopy</td>
<td>132 (52)</td>
<td>59</td>
<td>Cryptosporidia, CMV</td>
</tr>
<tr>
<td>Cotte et al.(^{114})</td>
<td>Stools</td>
<td>81 (73)</td>
<td>64</td>
<td>Cryptosporidia, CMV</td>
</tr>
<tr>
<td>Kotler and Orenstein(^{112})</td>
<td>Stools(^{\dagger})</td>
<td>194 (73)</td>
<td>83</td>
<td>Microsporidia, Cryptosporidia</td>
</tr>
</tbody>
</table>

\(^{\ast}\)Number of patients studied and proportion with diarrhea (%).

\(^{\dagger}\)The two most common organisms detected in the patients with diarrhea are listed, except for Dworkin et al.\(^{105}\) and Rene et al.\(^{116}\) in which the overall results are given.

\(^{\dagger}\)Endoscopic procedures are listed only if they were performed in all patients.

\(^{\dagger}\)Stool examinations performed in patients with diarrhea.

\(^{\dagger}\)Prevalence of pathogens (38%) not reported separately for patients with and without diarrhea.

EGD, esophagogastroduodenoscopy.

thirds of the patients were homosexual men. Diagnostic workup was intense. In six studies, esophagogastroduodenoscopy and colonoscopy or flexible sigmoidoscopy with biopsies was performed in all\(^{115,116}\) or in selected patients.\(^{105,106,112–114}\) Examination of biopsy tissue included viral culture in two studies.\(^{115,116}\)

Three conclusions can be drawn from the data summarized in Table 2. First, the prevalence of enteric pathogens was greater among patients with chronic diarrhea (range, 50%–85%) than among those without diarrhea (2%–28%). Second, while common enteric parasites and bacteria such as *Giardia lamblia* and *Campylobacter* species were detected in all studies, some opportunistic agents such as CMV were identified only when mucosal biopsies were performed. Third, the most common opportunistic pathogens were MAC, cryptosporidia, CMV, and microsporidia.

### Specific Opportunistic Pathogens

In this section, the focus is on the epidemiology, clinical features, diagnosis, and treatment of the four most commonly reported opportunistic enteric pathogens listed in Table 2.

**MAC.** Epidemiological features. Organisms of the MAC comprise two closely related species: *M. avium* and *M. intracellulare*. The organism is ubiquitous in the environment, and disseminated infection results from recent infection rather than reactivation of previous infection.\(^{117}\)

The gastrointestinal tract is an important portal of entry from which the organism may disseminate, especially to the blood, bone marrow, liver, and lymph nodes. The major risk factor for MAC infection is the severity of the immunologic deficit. Infection is rare in patients with CD4 cell counts of >100/mm\(^3\).\(^{110,118}\) No differences have been observed in the frequency of MAC infection across transmission categories.\(^{118,119}\) The widespread use of prophylaxis against *P. carinii* pneumonia has prevented or delayed death from this infection, shifting clinical manifestations to illnesses that occur when immune function is more severely suppressed, such as MAC. For example, among 844 homosexual men in the Multicenter AIDS Cohort Study diagnosed with AIDS by January 1992 and followed up until April 1993, MAC infection developed in 33% of men who received prophylaxis compared with 17% of men who did not receive prophylaxis.\(^{1}\)

Clinical features. The largest case series is a retrospective study of 114 patients with AIDS in whom MAC was first diagnosed by blood culture.\(^{120}\) The most common findings at diagnosis were fever and severe anemia (denoted by a hematocrit of <26%). Night sweats and ≥10% weight loss were less common. Findings referable to the gastrointestinal or hepatobiliary tract, which were present in 76% of patients, included diarrhea, abdominal pain, hepatomegaly, and increased alkaline phosphatase levels.

The largest published case series of patients with gas-
Gastrointestinal MAC infection is a retrospective study of 35 patients with AIDS. The patients had been referred for gastrointestinal evaluation because of weight loss (30 patients); fever, sweats, or chills (21 patients); diarrhea (17 patients); and abdominal pain (7 patients). Endoscopic biopsy specimens showed duodenal involvement in 30 of 34 patients (88%). Unusual, characteristic white nodules (1–3 mm diameter) were observed in the duodenum in 12 patients. Of 11 patients who underwent flexible sigmoidoscopy with biopsies, 7 had involvement of the rectum. Gastrointestinal tract involvement was associated with dissemination; 25 of 28 men (89%) had bone marrow infection and 28 of 33 (85%) had bacteremia.

Diagnosis. Although the gastrointestinal tract is a major portal of entry, gut colonization is uncommon, and routine screening of stool specimens with acid-fast stains and mycobacterial cultures is not an effective method for detecting MAC before dissemination.

Disseminated MAC infection is most readily diagnosed by mycobacterial culture of blood or bone marrow. Using commercially available rapid blood culture systems, the average time required to establish a diagnosis can be decreased to 5–12 days. A single mycobacterial blood culture is adequate. Disseminated MAC infection may be diagnosed from mycobacterial culture of lymph node or liver biopsy specimens. New methods based on DNA probes are becoming available to replace the conventional approach of mycobacterial identification from colony growth; polymerase chain reaction (PCR) is being evaluated for detecting the organism in peripheral blood.

In the diagnosis of gastrointestinal infection using stool samples, mycobacterial culture is more sensitive than acid-fast stain. For patients undergoing gastrointestinal endoscopy, MAC infection can be detected in mucosal biopsy specimens examined under light microscopy using H&E and Ziehl–Neelsen staining. However, because granuloma formation is poor and Ziehl–Neelsen stains may be negative, mycobacterial culture of mucosal biopsy specimens is needed to increase the diagnostic yield for patients in whom the diagnosis is suspected.

Prophylaxis and treatment. Two randomized placebo-controlled clinical trials showed that rifabutin prophylaxis (300 mg once daily by mouth) reduced the frequency of MAC bacteremia in patients with AIDS with CD4 cell counts of <200/mm³, although survival was not affected. On the basis of these results, a U.S. Public Health Service Task Force recommends rifabutin prophylaxis for HIV-infected patients with CD4 cell counts of <100/mm³. MAC infection occurs in patients with advanced disease; in the large case series cited above, the median survival after the initial diagnosis was 110 days.

No randomized placebo-controlled trial has evaluated the effect of antimicrobial therapy on survival. In uncontrolled studies, single-agent therapy with azithromycin or clarithromycin was associated with suppression of bacteremia. Kemper et al. reported a prospective case series of 31 patients treated for 12 weeks with rifampin, ethambutol, clofazime, and ciprofloxacin. Suppression of bacteremia and reduction in fever at 4 weeks occurred, although many patients experienced subsequent recurrence of fever and most continued to experience weight loss. Although patients with gastrointestinal involvement may experience improvement in symptoms, it is unknown whether antimicrobial therapy is associated with sustained microbiological or clinical benefit. Nonetheless, the U.S. Public Health Service Task Force recommends treating patients with MAC infection with at least two agents, including azithromycin or clarithromycin.

Ethambutol can be used as a second drug and one or more of the following can be added as a third or fourth drug: clofazimine, rifabutin, rifampin, ciprofloxacin, and, in some situations, amikacin.ISONiazid and pyrazinamide are not recommended. Adverse drug reactions are a common problem with such multiple drug regimens. In the study by Kemper et al., one or more agents had to be withdrawn in 46% of the patients.

Cryptosporidia. Epidemiological features. Organisms of the genus Cryptosporidium, which belong to the phylum Apicomplexa, are protozoans. Cryptosporidium parvum is the species that infects both humans and cattle. The modes of transmission are water contamination, which has been responsible for community outbreaks, and direct fecal-oral, which may occur during male sexual contact.

Clinical features. The clinical course of infection is variable and depends on at least two factors. The first is the immunologic competence of the host. In immunocompetent persons, cryptosporidiosis is a self-limited diarrheal illness with an incubation period of 7 days and a mean duration of 12 days. In immunodeficient HIV-infected individuals, however, infection may be prolonged. The diarrhea is nonbloody and may be associated with nausea, vomiting, and abdominal cramps. Patients with CD4 cell counts of >180/mm³ tend to clear the infection. The largest reported case series describes the clinical course of cryptosporidiosis infection in 128 HIV-infected patients, of whom 38 (37%) had an additional enteric infection, most commonly CMV.

Four clinical patterns of infection were observed: (1) asymptomatic (4% of patients); (2) transient symptomatic (28%), which spontaneously resolved within 2 months;
(3) chronic (60%), which persisted for at least 2 months; and (4) fulminant (8%), which was refractory to therapy and was characterized by the passage of 2 L or more of liquid stool daily. Transient disease was more common in less immunosuppressed patients, whereas fulminant disease occurred in patients with CD4 cell counts of <50/mm³.

The second factor that may be an important determinant of the clinical course of cryptosporidiosis is the intensity of infection or number of organisms present in the intestine. Given the variability in the clinical course of cryptosporidiosis infection, the importance of randomized placebo-controlled trials in evaluating potential therapies is clear.

Diagnosis. Although the organism can be detected using light-microscopic examination of duodenal or, less commonly, colonic mucosal biopsy specimens, the availability of stool tests has lessened the need for endoscopy in the diagnostic workup. In many clinical laboratories, routine stool examination for ova and parasites does not include testing for cryptosporidia, which must be specifically requested. Cryptosporidia oocysts can be shown in stool samples using either a modified acid-fast stain or a commercially available kit based on an immunofluorescence technique. Current evidence indicates that the commercial kit is more sensitive than acid-fast staining. Recently, infection with Cyclospora species has been recognized in HIV-infected patients. When the acid-fast stain is used to examine stool samples, it is important that the larger Cyclospora species oocysts (8–9 µm) be distinguished from the smaller Cryptosporidium species oocysts (5 µm) because treatment is different.

Treatment. Paromomycin, an orally administered and poorly absorbed aminoglycoside, has been evaluated in uncontrolled studies, the largest of which included 24 patients. In this study, paromomycin therapy was associated with a reduction in stool frequency and clearance of stool oocysts in some patients. The only published randomized clinical trial included 10 patients who were assigned to treatment with placebo or 500 mg paromomycin by mouth three or four times daily for 2 weeks and then crossed over to the other treatment group. Paromomycin therapy was accompanied by a decrease in total oocyst and daily stool excretion. Other agents that have been used to treat patients with HIV-related cryptosporidiosis, reported in uncontrolled studies and case reports, include spiramycin, erythromycin, zidovudine, and bovine serum colostrum. Important but unresolved issues include the length of therapy, the use of maintenance therapy, and the efficacy of preventive measures such as drinking boiled or bottled water rather than tap water.

CMV. Epidemiological features. In immunodeficient individuals, CMV disease can result from reactivation of latent virus, reinfection with a new virus, or primary infection in a previously uninfected host. In patients with AIDS, the source of CMV disease is either reactivation or reinfection because most individuals have been previously exposed to the virus. For example, CMV is sexually transmitted among homosexual men, 90% of whom have serological evidence of infection. Distinguishing between latent infection and disease is important. CMV gastrointestinal disease is defined as submucosal hemorrhage, mucosal erosions, or ulcerations in which the virus is present in a person in whom other causes of the lesion(s) have been excluded.

In a cohort study of patients with AIDS or symptomatic HIV infection followed up for 2 years, the cumulative probability of developing CMV disease was 21% for those with initial CD4 counts of <100/mm³. In this study, the major risk factors for CMV disease were a CD4 cell count of <100/mm³ and male homosexuality.

Clinical features. CMV disease may involve any site in the gastrointestinal tract; however, small bowel and colonic disease are most relevant to this report. No large series of patients with small bowel disease exists, although case reports show that pain, diarrhea, bleeding, and perforation may occur. Patients with colonic CMV disease may present with diarrhea, passage of blood per rectum, and/or abdominal pain. In the largest case series of patients (n = 44) with CMV colitis, 31 patients (70%) had persistent diarrhea, 13 (30%) had intermittent diarrhea, 28 (64%) had crampy abdominal pain, 10 (23%) had hematochezia, and 1 had colonic perforation. Case reports or small series of patients with CMV colitis indicate that patchy or confluent submucosal hemorrhage, erosion, and ulceration may be observed.

Diagnosis. Because of the high prevalence of anti-CMV antibodies due to previous exposure to the virus, serology is not helpful in diagnosing CMV gastrointestinal disease. Viral cultures of blood and urine are also unhelpful. In tissues, CMV infection produces a characteristic cytopathic effect, which is a large cell (referred to as a cytomegalic cell) containing an intranuclear inclusion and, frequently, intracytoplasmic inclusions. The presence of cytomegalic cells on light-microscopic examination of mucosal biopsy specimens stained with H&E is considered the gold standard for establishing a diagnosis of CMV infection. In some patients, however, the inclusions are atypical in appearance and few in number, making a definitive diagnosis difficult. The detection of cytomegalic cells in mucosal biopsy specimens obtained from areas of submucosal hemorrhage, erosion, or ulceration in the absence of other causes of the lesion...
indicates CMV gastrointestinal disease. The frequency with which cytomegalic cells are detected depends in part on the intensity of the search (number of biopsy specimens examined, effort of the pathologist).

Because the sensitivity of cytomegalic cells in detecting disease is <100%, other diagnostic methods have been proposed. The disadvantage of viral cultures is the length of time between specimen collection and viral growth, which may be up to 2 weeks. Also, tissue specimens may be contaminated by blood, which in the presence of viremia may give rise to positive cultures. Immunohistochemistry detects CMV antigens using monoclonal or polyclonal antibodies, and PCR amplifies and detects minimal quantities of the viral genome in tissue specimens. In a comparison of light-microscopic examination, PCR, and immunohistochemistry, PCR was the most sensitive method for detecting CMV infection. However, further evaluation of immunohistochemistry and PCR is needed before recommending that these techniques replace light-microscopic examination for routine clinical use.

Treatment. Patients with gastrointestinal CMV disease may be treated with ganciclovir or foscarnet, both of which are administered intravenously. In a case series of 17 patients with gastrointestinal CMV disease who were administered 2.5 mg/kg ganciclovir every 8 hours for 10 days, 9 of 14 patients (64%) had resolution of pain and 8 of 11 (73%) had resolution of diarrhea. A subsequent randomized placebo-controlled trial evaluated ganciclovir (5 mg/kg) every 12 hours for 14 days in 62 patients with AIDS and CMV colitis. Colitis severity was graded from 0 to 3 according to gross and histological criteria. Although ganciclovir therapy was associated with improvement in colitis scores, no improvement in symptoms (diarrhea, abdominal pain) was observed. However, the duration of therapy may have been too short (14 days). Because ganciclovir suppresses but does not eradicate the virus, relapse of CMV disease may occur after therapy. However, no accurate estimates of the magnitude of the risk for relapse are available for colitis. A prospective study of patients with CMV esophagitis reported a relapse rate of 39% at a median of 4 months of follow-up (range, 2–18 months). The usual duration of full-dose treatment (referred to as induction therapy) is 3–4 weeks, at which point symptoms and endoscopic features are reassessed. If no symptomatic or endoscopic response has occurred, a repeat course of induction therapy may be administered. In patients with a symptomatic and endoscopic response, the decision whether to advise maintenance therapy with 5 mg/kg ganciclovir daily should be individualized. No studies are available regarding the use of oral ganciclovir for maintenance therapy. For patients in whom a symptomatic but not an endoscopic response occurs, management should also be individualized. The toxicities of ganciclovir include renal impairment, neutropenia, and thrombocytopenia. The risk of cytopenia is greater when the drug is administered to patients receiving zidovudine.

The largest case series of HIV-infected persons treated with foscarnet is a retrospective study of 66 patients with gastrointestinal CMV disease. In this study, the most commonly used dose of foscarnet was 60 mg/kg every 8 hours for 2–3 weeks. Improvement in symptoms and endoscopic healing of lesions occurred in 16 of 28 patients (57%) with colonic disease. In another case series of 19 patients with AIDS and gastrointestinal CMV disease who had failed a course of ganciclovir therapy, 60 mg/kg foscarnet was administered every 8 hours for 14 days followed by maintenance therapy in a dose of 90 or 120 mg/kg daily. After 3 weeks of therapy, improvement in symptoms and gross and histological parameters was observed. As with ganciclovir, many would advise maintenance foscarnet after induction therapy. A randomized open label trial that compared ganciclovir with foscarnet for gastrointestinal CMV disease showed similar efficacy. The toxicities of foscarnet include renal insufficiency, hypocalcemia, hypomagnesemia, hypophosphatemia, anemia, and nausea. Ganciclovir and foscarnet may be safely administered together in patients with a poor response to either agent alone.

Microsporidia. Epidemiological and clinical features. The term microsporidia is a nontaxonomic designation used to describe organisms belonging to the order Microsporida of the phylum Microspora. Microsporidia are obligate intracellular protozoan parasites. In HIV-infected individuals, gastrointestinal infection with organisms of two genera, Enterocytozoon and Septata, have been reported. The most common microsporidian intestinal infection is attributable to Enterocytozoon bieneusi. In six studies from different institutions encompassing 494 patients with HIV-related chronic diarrhea, E. bieneusi was detected in 137 (28%; range, 14%–33%). Few studies have evaluated the frequency of microsporidiosis in HIV-infected patients without diarrhea, taking into account CD4 cell count and the presence of other enteric organisms. In two studies in which this comparison has been made, the prevalence of microsporidia in the patients without diarrhea was low (3%) in one study, while the prevalence was higher (25%) and not significantly different from that observed in the patients with diarrhea in the other study. These discrepant findings may be accounted for by differences in the methods used to detect E. bieneusi infection. Light microscopy
was used in one study, whereas electron microscopy, which is probably a more sensitive technique, was used in the other study. Clearly, \textit{E. bieneusi} infection can be detected in patients without diarrhea, indicating a need for further study to identify factors that determine the presence of illness.

Recently, gastrointestinal infection with a second microsporidian species, \textit{Encephalitozoon intestinalis}, has been reported in HIV-infected individuals. This organism can be distinguished from \textit{E. bieneusi} using electron microscopy. In some patients, the diagnosis may be suggested by the larger size of \textit{S. intestinalis} as well its presence in lamina propria macrophages.

\textbf{Diagnosis.} In clinical practice, the detection of microsporidia infection has been hampered by lack of a simple, noninvasive diagnostic test. Light-microscopic detection of microsporidia in paraffin sections of mucosal biopsy tissue is difficult because the organisms are small and stain poorly with routinely used histological stains, such as H&E. Other stains have been used in light-microscopic examination of mucosal biopsy tissue, including Warthin–Starry, Gram, Giemsa, and modified chromotrope stains. Giemsa-stained touch preparations and semithin (1 μm) plastic sections stained with toluidine blue have also been used. In the past, the gold standard for detecting the parasite has been electron microscopy. However, more recently, a modified trichrome stain and other techniques for identifying the spores in stool specimens have been reported. No large comparative study of the different techniques for detecting intestinal microsporidia infection has been performed.

\textbf{Treatment.} No randomized placebo-controlled clinical trial of therapy for intestinal \textit{E. bieneusi} infection has been published. The largest study is a case series of 29 patients with AIDS, chronic diarrhea, and \textit{E. bieneusi} infection who were treated with 400 mg albendazole by mouth twice daily. Of 26 patients who completed 1 month of treatment, 13 had a 50% or greater decrease in the mean daily stool frequency. Further study of albendazole and other agents is clearly needed.

\textbf{AIDS enteropathy.} In addition to symptoms (diarrhea, weight loss), abnormalities of gastrointestinal mucosal structure and absorptive function may occur. The term “AIDS enteropathy” was first used in 1984 in the context of these abnormalities. However, since then, confusion has arisen regarding the term itself. A critical appraisal of the published clinical research has shown that no consensus exists regarding the term “AIDS enteropathy,” to whom it applies, the elements on which it is based, and the criteria for its definition. To avoid misunderstanding, it may be preferable to avoid the term “AIDS enteropathy” and to simply describe the abnormalities of mucosal structure and function that are observed, such as villus flattening and decreased D-xylose absorption.

Although the pathogenesis of these abnormalities of mucosal structure and function remains unclear, several hypotheses have been proposed to account for them. First, they may be due to as yet unknown or known but undetected enteric pathogens. Second, they may be a result of direct mucosal HIV infection. Third, bacterial overgrowth, possibly related to gastric hypoacidity, may play a role. In addition, decreased local (mucosal) immune function and altered enteric nerve and enteroendocrine cell function may be important.

The relationships between the abnormalities of mucosal structure and function, symptoms (diarrhea, weight loss), and CD4 cell count remain unclear. Further research in this area is clearly needed to clarify the nomenclature, to define the pathogenesis of the alterations of mucosal structure and function, and to identify their relationships to other clinical features.

\textbf{Diagnostic Workup: Review of the Published Evidence}

The main focus of diagnostic workup of patients with HIV-related chronic diarrhea is detecting enteric pathogens. However, the intensity of diagnostic workup remains controversial. On the one hand, some advise an intensive workup including upper endoscopy and colonoscopy with mucosal biopsies to identify all detectable enteric pathogens. Alternatively, others favor a minimal workup, consisting of stool cultures and microscopy followed by nonspecific antidiarrheal therapy if no treatable pathogen is identified. What evidence exists to support each approach?

The strongest evidence for minimal workup was obtained from a decision analysis model that compared three management strategies: full evaluation (stool culture, ova and parasite examination, blood cultures, upper endoscopy, and colonoscopy with biopsies), limited evaluation (stool culture, ova and parasite examination, and blood cultures), and minimal evaluation (stool cultures). For those patients in whom an enteric pathogen was detected, specific therapy was given; the remainder received a nonspecific antidiarrheal agent (diphenoxylate). The same diarrhea remission rate (75%) was obtained for each strategy; after taking cost into account, minimal evaluation was recommended.

Evidence cited to support an intensive workup was obtained in several studies in which enteric pathogens were detected in a large proportion of patients. For example, in one study, 85% (17 of 20) of homosexual men
with AIDS and diarrhea (defined as 7 or more stools/day for at least 7 days) had detectable enteric pathogens. Diagnostic workup included microbiological evaluation of stool specimens, light-microscopic examination, and viral culture of duodenal and colonic mucosal biopsies. Based on these findings, the investigators advised intensive workup.\textsuperscript{111}

However, an intensive, costly diagnostic workup of all HIV-infected patients with diarrhea cannot be advocated solely on the basis of such findings for several reasons.\textsuperscript{111} First, these results may not be generalizable to other clinical practice settings. One should not expect to identify enteric pathogens in \textit{85\%} of individuals with HIV-related diarrhea unless similar patients with advanced disease are seen and investigated with similar intensity. Second, even if an enteric organism is detected, its role as a cause of chronic diarrhea may be uncertain. Third, no specific effective treatment is available for many enteric pathogens, and nonspecific antidiarrheal agents may be as effective as specific treatment. Fourth, the presence of enteric pathogens is not the only outcome to consider. Other outcomes such as quality of life must be addressed.\textsuperscript{189} Fifth, the presence of coexisting disease must be taken into account. In a patient with HIV-related chronic diarrhea, a severe coexisting illness may be the dominant clinical problem and the major determinant of the patient’s quality of life. In such patients, the inconvenience, discomfort, and cost associated with intensive diagnostic workup may not be offset by any meaningful improvement in the patient’s quality of life, even if a treatable enteric pathogen is detected and eradicated.\textsuperscript{111}

Strategies intended to identify patients in whom further investigations are likely to improve patient outcomes have been devised. For example, a system based on the extent of weight loss and the Schilling test result has been reported,\textsuperscript{107} although this method has not met with widespread acceptance in clinical practice.

Further research is clearly indicated in this area. A full evaluation of the outcomes associated with alternative diagnostic and therapeutic interventions is needed so that evidence-based clinical guidelines can be developed. Such guidelines would assist clinical decision-making by identifying patients in whom intensive workup is unlikely to improve outcome so they can be spared this intervention.

\textbf{Diagnostic Evaluation: A Suggested Approach}

A stepwise approach is suggested here to identify enteric pathogens using few diagnostic tests, tailoring the workup to the patient. This approach relies on the patient’s clinical features and CD4 cell count to guide investigations. The hypothesis underlying this approach is that identifying and treating the cause(s) of HIV-related chronic diarrhea improves patient outcomes, such as quality of life. This approach is based on the following principles: (1) the CD4 cell count is helpful because the presence of severe immunodeficiency (defined as a CD4 cell count of \textless 100/mm$^3$) denotes a subgroup of patients at significant risk for CMV disease and MAC infection\textsuperscript{108,190}; (2) compared with colonoscopy, the yield of flexible sigmoidoscopy is adequate for detecting enteric pathogens\textsuperscript{108,190}; and (3) endoscopic mucosal biopsies are preferable to barium radiographs, because the goal is to detect enteric pathogens.

As Table 3 indicates, the first step begins with stool tests to identify common enteric bacteria (e.g., \textit{Salmonella} species) and parasites (e.g., \textit{G. lamblia}) as well as specific opportunistic agents (e.g., \textit{C. parvum}). A stool sample should be sent for \textit{Clostridium difficile} toxin assay if the patient is at risk for antibiotic-associated diarrhea.\textsuperscript{191} The number of stool samples that should be submitted is unknown, although many would advise at least three specimens. In febrile patients, blood should be drawn for bacterial culture, and in those with severe immunodeficiency (a CD4 cell count of \textless 100/mm$^3$), blood should also be drawn for mycobacterial culture.

If stool tests fail to reveal an enteric pathogen in patients with nonbloody diarrhea, some would consider a course of empiric antidiarrheal therapy. Others would consider a course of empiric antimicrobial therapy (e.g., metronidazole), although no data are available to substantiate this approach. Alternatively, many prefer to obtain gastrointestinal mucosal biopsy specimens as the second step.

In patients with rectal symptoms (small volume stools, tenesmus, passage of blood per rectum) or those whose symptoms suggest a colonic process (bloody diarrhea, lower abdominal cramps or pain), flexible sigmoidoscopy

\begin{table}[h]
\centering
\caption{Diagnostic Workup of HIV-Related Chronic Diarrhea}
\begin{tabular}{|l|}
\hline
\textbf{Stool tests} \tabularnewline
Bacterial culture (to detect \textit{Salmonella} species and so on) \tabularnewline
Ova and parasite examination (\textit{Giardia lamblia} and so on) \tabularnewline
\textit{C. difficile} toxin assay \tabularnewline
Modified acid-fast stain or immunofluorescence kit (cryptosporidia) \tabularnewline
Modified trichrome stain (microsporidia) \tabularnewline
Add blood cultures if febrile (bacteria, mycobacteria) \tabularnewline
Flexible sigmoidoscopy with mucosal biopsies \tabularnewline
Light microscopy (mycobacteria, CMV, cryptosporidia) \tabularnewline
Mycobacterial culture (mycobacteria) \tabularnewline
Upper endoscopy with duodenal biopsies \tabularnewline
Light microscopy (CMV, mycobacteria, cryptosporidia, microsporidia) \tabularnewline
Mycobacterial culture (mycobacteria) \tabularnewline\hline
\plusminus electron microscopy (microsporidia) \tabularnewline
\hline
\end{tabular}
\end{table}
is the next step. In patients with a CD4 cell count of <100 cells/mm³, CMV disease should be kept in mind; a careful search for submucosal hemorrhage, mucosal erosions, or ulcerations should be undertaken. Rectal and colonic mucosal biopsy specimens should be obtained for light-microscopic examination. Mycobacterial culture of the biopsy specimens may be considered, depending on the clinical presentation. An additional mucosal biopsy specimen may be placed in glutaraldehyde and kept aside for subsequent electron-microscopic examination (if available) if other studies are unrevealing and microsporidiosis is suspected.

The third step is to perform esophagogastroduodenoscopy. Duodenal mucosal biopsy specimens should be obtained for light-microscopic examination. In patients with a CD4 cell count of <100/mm³ and clinical features suggestive of MAC infection, biopsy specimens may also be obtained for mycobacterial culture. An additional mucosal biopsy specimen may be put aside for subsequent electron-microscopic examination, as noted above.

This stepwise approach is intended as a guideline. Clearly, clinical judgment plays an important role in determining the sequence and content of the investigations. In selected patients whose symptoms suggest a small bowel process (large volume diarrhea, periumbilical cramps), one may omit flexible sigmoidoscopy and proceed directly from stool tests (if negative) to esophagogastroduodenoscopy with biopsies. In selected patients, colonoscopy may be performed rather than flexible sigmoidoscopy.

Nonspecific antidiarrheal therapy. As noted above, opinion varies regarding the role of empiric antidiarrheal therapy in patient management. A case for such therapy can be made in patients with nonbloody diarrhea and negative stool test results before deciding whether to proceed with endoscopic evaluation. A variety of agents may be used, including loperamide and diphenoxylate and atropine (Lomotil). Tincture of opium may be useful in some patients. Although octreotide, a synthetic analogue of somatostatin, initially showed promise, recent results indicate that this agent is not more effective than placebo in patients with HIV-related chronic diarrhea.¹⁹²

Conclusions

An important problem in HIV-infected individuals is chronic diarrhea, which occurs with greater frequency in male homosexuals and those with severe immunodeficiency. The major cause of HIV-related chronic diarrhea is infection with enteric pathogens. In published reports, the prevalence and spectrum of enteric pathogens varies depending on the characteristics of the study population and the intensity of the diagnostic workup. In patients with advanced immunodeficiency who undergo intensive workup, the opportunistic agents most commonly identified are MAC, C. parvum, CMV, and E. bieneusi.

In clinical practice, the main goal of diagnostic workup in patients with HIV-related chronic diarrhea is to detect enteric pathogens. However, the intensity of diagnostic evaluation remains controversial. On the one hand, some advise an intensive evaluation that includes esophagogastroduodenoscopy and colonoscopy with mucosal biopsies to identify all detectable enteric pathogens. Alternatively, others favor a minimal workup, consisting of stool cultures followed by nonspecific antidiarrheal therapy if no treatable pathogen is identified. No prospective studies have compared the full effects of alternative management strategies on broad patient outcomes, including quality of life. In the absence of such evidence, a stepwise workup is reasonable based on the assumption that identifying and treating the cause of HIV-related chronic diarrhea improves patient outcomes. According to this approach, the first step is to obtain stool tests to identify common enteric bacteria and parasites as well as specific opportunistic agents. If stool tests fail to detect an enteric pathogen, the second step is to perform flexible sigmoidoscopy with mucosal biopsies. If these studies are unrevealing, the third step is to perform esophagogastroduodenoscopy with duodenal mucosal biopsies. Appropriate antimicrobial therapy is prescribed if specific enteric pathogens are identified. In patients in whom either enteric pathogens are not identified or antimicrobial therapy is ineffective, nonspecific antidiarrheal agents are prescribed.

Hepatobiliary Disease

The causes of hepatobiliary disease differ depending on the extent of immunocompromise. In earlier-stage HIV infection (a CD4 cell count of >500/mm³), hepatic complications usually represent liver-specific processes, such as drug-related hepatotoxicity, primary neoplasms, or infection with hepatotrophic viruses. With progression of immunodeficiency to AIDS (a CD4 cell count of <200/mm³), the liver is generally involved as part of a systemic opportunistic infection due to MAC, fungi, or CMV.

Because the liver is often one of many sites involved with disseminated opportunistic infections in patients with AIDS, liver disease per se is rarely the primary cause of death.¹⁹¹–¹⁹⁵ Nonetheless, the progressive jaundice, fever, and/or abdominal pain that may accompany hepatobiliary disease can significantly reduce quality of life and therefore merits evaluation in most patients.
**Table 4. Causes of Hepatic and Biliary Disease in Patients With HIV Infection**

<table>
<thead>
<tr>
<th>Hepatic disease</th>
<th>Biliary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>AIDS cholangiopathy</td>
</tr>
<tr>
<td>Drug induced, especially sulfa, zidovudine</td>
<td>Lymphoma</td>
</tr>
<tr>
<td><em>M. tuberculosis</em></td>
<td><em>P. carinii</em></td>
</tr>
<tr>
<td>Bacillary peliosis hepatitis</td>
<td>Microsporidium</td>
</tr>
<tr>
<td>CMV</td>
<td><em>Bartonella quintana</em></td>
</tr>
<tr>
<td>Cryptococcus, histoplasmosis</td>
<td><em>Bartonella henselae</em></td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td></td>
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<tr>
<td>Hepatitis C</td>
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<tr>
<td>Hepatitis B, D</td>
<td></td>
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<tr>
<td><em>P. carinii</em></td>
<td></td>
</tr>
<tr>
<td>Microsporidium</td>
<td></td>
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<tr>
<td>Biliary disease</td>
<td></td>
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<tr>
<td>AIDS cholangiopathy</td>
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<tr>
<td>Lymphoma</td>
<td></td>
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<tr>
<td>Kaposi’s sarcoma</td>
<td></td>
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<tr>
<td>Acalculous cholecystitis</td>
<td></td>
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<tr>
<td>Non-AIDS disorders, including gallstone disease</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. In decreasing order of frequency.

Most published studies of the manifestations of hepatobiliary disease in HIV infection have been descriptive. Initial observations were made in autopsy studies, but more recently case series have clarified the prevalence, clinical features, and clinical course of several HIV-related hepatobiliary complications. For some diseases, such as bacillary peliosis hepatitis, findings previously considered to be nonspecific are now recognized as manifestations of a specific infection. Continued clinical experience with HIV disease will likely lead to further refinements in our understanding of how the liver responds to opportunistic infection. Studies examining the optimal mode of diagnosis and therapy have only begun to appear, and greater progress in these areas is anticipated in the next 5–10 years.

**Clinical Manifestations of Liver Disease**

Clinical manifestations of hepatobiliary disease in HIV infection range from asymptomatic liver biochemical abnormalities to hepatic failure. Few studies have attempted to correlate clinical and biochemical abnormalities with specific diagnoses, although patterns have been recognized that suggest the most likely possibilities (see below).

Specific causes of hepatobiliary disease are listed in Table 4 and are reviewed individually below.

**Opportunistic infections.** MAC is the most common pathogen identified in the liver in autopsy series.\(^{193,196–198}\) It is typically a late-stage complication, associated with disseminated infection and characterized by fevers, night sweats, weight loss, and diarrhea. Although liver involvement can be documented in up to 46% of patients,\(^{199}\) the infection is usually clinically silent. Liver biopsy appears to be more sensitive than bone marrow biopsy in diagnosing infection (75% positive vs. 25% in patients with documented MAC)\(^{200}\) and usually shows large numbers of acid-fast organisms; granulomas, if present, are usually poorly formed.\(^{197,201,202}\)

*Mycobacterium tuberculosis,* unlike MAC, can occur in earlier stages of HIV infection and is more prevalent in injection drug users than other transmission categories.\(^{196}\) Tuberculosis is usually a pulmonary infection in patients with a CD4 count of >200/mm\(^3\), whereas atypical presentations are more likely, including hepatic involvement, in patients with more severe immunodeficiency.\(^{203}\) Clinical disease in most cases arises from reactivation rather than primary infection.\(^{204}\) As with hepatic MAC infection, clinical expression of liver disease is unusual.

CMV, like MAC, involves the liver late in the course of HIV disease as part of a systemic infection. Although a frequent finding in autopsy series,\(^{198}\) for unclear reasons, hepatic CMV is rarely diagnosed antemortem. The infection is associated with fever and weight loss, giant cell formation, and mononuclear cell infiltration in infected tissue.

Bacillary peliosis hepatitis is a lesion characterized by dilated vascular lakes in the hepatic parenchyma and is associated with one of two bacillary organisms, either *Bartonella quintana* or *Bartonella henselae*. Autopsy series initially described peliosis hepatitis in patients with AIDS as a nonspecific finding\(^{205,206}\) until the reports by Perkocha et al.\(^{207}\) and Kemper et al.\(^{208}\) in 1990 identified its cause. The infections are systemic and associated with fever, lymphadenopathy, hepatosplenomegaly, and cutaneous and bony lesions.\(^{209,210}\) The syndrome is virtually identical to cat-scratch fever.\(^{190}\) The bacteria can be identified in hepatic sinusoidal endothelial cells\(^{211}\) and are most easily visualized using silver-based stains such as Warthin–Starry.\(^{209}\) Peliotic spaces, which may be macroscopic or microscopic, resolve with appropriate antibiotic therapy.\(^{212}\)

Fungal infections of the liver are almost exclusively seen in late-stage HIV disease as part of a systemic infection. Histoplasmosis occurs predominantly, but not exclusively, in endemic areas, with the infected liver showing fungal organisms within granulomas. In a series of 48 patients, 5 had documented hepatic involvement.\(^{213}\) Clinically, disseminated histoplasmosis presents as a severe systemic illness; hepatomegaly is a common finding.\(^{215}\) Typically the organism is first identified in other sites such as bone marrow, lung, or on blood smear, so liver biopsy is rarely required for diagnosis. Indeed, pulmonary disease is observed in one half of patients with disseminated histoplasmosis,\(^{214,215}\) often with cutaneous
involvement. Relapse may be detectable by capsular antigen assay.\(^{216}\) Cryptococcus neoformans, like Histoplasma capsulatum, may be detected in the liver during systemic involvement and typically incites only a weak inflammatory response.\(^{217}\) Similarly, hepatic involvement from coccidiomycosis\(^{218}\) or blastomycosis\(^{219}\) has been reported.

Disseminated \textit{P. carinii} has been reported to involve the liver.\(^{220,221}\) This appears to occur primarily, but not exclusively, in patients receiving inhaled pentamidine therapy for prophylaxis. Microsporidia have also been reported to cause hepatitis.\(^{222}\)

**Viral hepatitis.** Evidence of infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and/or hepatitis delta virus (HDV) is frequently recognized in patients with HIV disease, in part because risk factors for acquiring these infections are similar to those for HIV (e.g., unprotected sex with multiple partners, needle use, or transfusions received before the introduction of screening methods for HCV and HIV). Behavior of hepatotropic viruses is altered in the setting of HIV infection, especially as immunocompromise becomes severe. Only the more recent studies have stratified patients based on the extent of immunodeficiency (i.e., CD4 cell count).

For HBV, the prevalence of seropositivity indicating past or present infection is unchanged in HIV-infected individuals; however, there can be marked alterations of antibody and/or antigen levels with late-stage infection and AIDS.\(^{223}\) Reactivation of HBV is not unusual with the onset or progression of HIV infection. For example, several reports have described the reappearance of hepatitis B surface antigen in patients previously believed to be immune to HBV based on the presence of circulating hepatitis B surface antibody.\(^{223,224}\) Additionally, increased expression of \(e\) and core antigens and increased DNA polymerase levels may result from coinfection with HIV.\(^{225-229}\) These serological findings have not been confirmed in all studies, even when stratifying based on HIV stage.\(^{230,231}\) Most but not all studies have noted that while an increased risk of reactivation or chronic carriage of HBV exists in homosexual men with HIV infection, the liver disease is not histologically more severe\(^{226,231,232}\) and survival is not affected by HBV.\(^{205}\) In contrast, histological progression and worsened survival have been reported by Housset et al.\(^{232}\) in those chronic HBV carriers who were injection drug users. The difference between these two transmission categories may be the higher prevalence of HCV among drug users, which was not assessed in the study by Housset et al.\(^{232}\) Indeed, in a study of 122 HIV-infected injection drug users, severity of liver disease was significantly greater in patients with both HBV and HCV infections compared with those with either HBV or HCV alone.\(^{233}\) The presence of HIV infection does not increase the prevalence of HDV within specific transmission categories. However, as in HIV-negative patients, HDV in those with HIV infection is associated with much more severe liver disease than in those with HBV alone.\(^{234}\) Unfortunately, in patients with HIV who have no HBV markers, for unclear reasons, vaccination is not effective in generating immunity.\(^{235,236}\) Lack of vaccine efficacy seems to be unrelated to the stage of HIV disease.

The reported prevalence of HCV in patients with HIV infection primarily depends on the transmission category of the patients studied and the specificity of the assay used. Studies using first-generation anti-HCV assays may have overestimated HCV prevalence.\(^{237}\) However, antibody assays alone may underestimate the true HCV prevalence, because loss of antibody has been associated with progressive HIV infection.\(^{238-239}\) HCV RNA does not correlate closely with positive HCV immunoassay in HIV-infected patients, because it is only detectable in 53\% of patients with a positive second-generation immunoassay.\(^{240}\) Prevalence is vastly higher in injection drug users than all other transmission categories, ranging from 52\% to 89\%.\(^{238,241}\) The prevalence is 1\%–3.5\% in HIV-infected military personnel,\(^{242,243}\) 7\% in a university clinic setting,\(^{237}\) and 4\%–11\% in non–drug users (including homosexual men).\(^{240,244}\) Many HIV-infected hemophiliacs are coinfected with HCV.\(^{245}\) These prevalence data are consistent with the notion that HCV is almost always transmitted parenterally, even in patients with HIV infection. However, HIV infection seems to increase the risk of sexual or perinatal transmission of HCV to HIV-seronegative female sex partners\(^{246,247}\) and possibly to newborns of HIV-infected mothers, respectively.\(^{248}\)

Clear evidence for acceleration of HCV replication and related liver injury by HIV has emerged from studies of hemophiliacs. Eyster et al. have shown a 58-fold increase in HCV RNA levels during a several-year period after HIV seroconversion (by branched chain complementary DNA assay or PCR) compared with a 3-fold increase during the same interval in those who were HCV seropositive but HIV seronegative.\(^{249}\) Moreover, increases in HCV RNA accompanied progressive immunodeficiency during a 10–20-year period and were correlated with aspartate aminotransferase levels and evidence of hepato-megaly, liver injury, and failure.\(^{248–251}\) Despite this overall increased incidence of HCV-related liver injury and mortality in HIV-infected hemophiliacs,\(^{245}\) HCV infection is not an independent determinant of mortality in nonhemophiliacs with AIDS,\(^{240}\) probably because these patients have high mortality rates from other AIDS-related opportunistic illnesses.
In summary, there does not seem to be an increase in prevalence or severity of HAV infection associated with HIV infection. HBV infection in HIV disease is associated with increased levels of HBV DNA but no apparent increase in severity of liver disease or independent effect on mortality. HCV infection may be associated with increased viral replication and more severe liver disease, especially in HIV-infected hemophiliacs.

Neoplasms. Neoplasms may be first diagnosed in the liver. Non-Hodgkin’s lymphoma, also referred to as large cell or Burkitt’s lymphoma depending on the histology, presents in extranodal sites in the majority of cases in those with HIV infection. It may appear at any stage of HIV disease, although it usually occurs in the later stages of immunodeficiency. In a large series of patients with HIV-associated non-Hodgkin’s lymphoma, 9%–16% had a primary presentation in the liver.\(^{252,253}\) The most common presentation is abnormal liver test results (elevated alkaline phosphatase levels, often with jaundice) and hepatomegaly. Fever is inconsistent. Abdominal computed tomography almost always shows one or multiple mass lesions. Prognosis depends primarily on the stage of immunocompromise rather than the lymphoma itself.\(^{252}\)

Kaposi’s sarcoma, which occurs most frequently in homosexual men, is a multicentric neoplasm derived from lymphatic endothelial cells.\(^{254}\) Hepatic Kaposi’s sarcoma has been detected on liver biopsy or autopsy in 14%–49% of patients,\(^{194,201,255}\) although it is rarely evident clinically. Interestingly, the prevalence of Kaposi’s sarcoma seems to be decreasing.\(^{256}\) Its occasional presence in HIV-negative homosexual men has suggested that it may arise from a transmissible agent, and recent studies identifying herpes virus–like DNA in Kaposi’s sarcoma tissue supports this possibility.\(^{257,258}\)

Drug-induced disease. In any patient with signs or symptoms of hepatobiliary disease, drug-induced liver abnormalities are important to consider because they are so readily treatable by drug withdrawal in most cases. Sulfonamides in particular have been associated with adverse reactions requiring alternative agents in >50% of patients in one series.\(^{259}\) Typical manifestations include fever, rash, leukocytosis, eosinophilia (occasional), and transferase level elevations.\(^{259}\) Antimycobacterial drugs have also been linked to severe liver disease.\(^{260}\) In some patients, antiretrovirals, particularly zidovudine and didoxynosine, have been associated with severe, sometimes fatal hepatic failure\(^ {261-264}\) in conjunction with marked steatosis. The basis for this lesion seems to be mitochondrial toxicity with impairment of mitochondrial DNA synthesis.\(^{265}\) Survival is possible if the syndrome is recognized early and the offending agent promptly withdrawn.\(^{260}\) Other agents associated with hepatotoxicity include pentamidine\(^ {258}\) and acetaminophen.\(^ {262}\) An additional form of iatrogenic liver injury attributable to iron overload has been described in patients who have received multiple transfusions.\(^ {198,266}\) In patients with HIV infection, the heightened sensitivity to drugs combined with the frequent use of concomitant medications suggest that any agent should be considered hepatotoxic, including alcohol, nonprescription medications, and herbal remedies.

Miscellaneous. In a small study, amyloidosis was observed in 5 of 12 patients with AIDS and a history of injection drug use.\(^ {267}\) All had hepatomegaly, and none had underlying myeloma or plasma cell dyscrasia. In these patients, it is unclear whether the lesion represents a complication of HIV disease or of injection drug use alone.

HIV itself may infect hepatocytes and Kupffer cells. Several studies have identified the virus within Kupffer cells (hepatic macrophages) and occasionally within hepatocytes using immunocytochemistry or in situ hybridization.\(^ {268-271}\) The findings have been complemented by evidence of infection of human Kupffer cells and sinusoidal endothelial cells in culture,\(^ {272,273}\) probably via CD4 cell receptors.\(^ {274}\) A study quantitating HIV-1 DNA in human liver showed a broad range of DNA concentrations in different patients, with some samples from patients with AIDS lacking HIV-1 DNA by PCR.\(^ {275}\) No correlation was evident between HIV-1 RNA levels and histological liver injury.\(^ {271}\) The demonstration of HIV in liver has two major implications. First, as the largest macrophage population in the body, Kupffer cells represent a major potential reservoir of virus; this must be considered in designing antiretroviral strategies. Second, active HIV infection of hepatic macrophages might lead to impaired cellular function, which could explain the increased rate of systemic enteric bacteremia in some patients with HIV infection.\(^ {273}\)

Nonspecific histopathologic findings have been frequently described in autopsy and liver biopsy series. These include granulomas (without organisms), Kupffer cell hyperplasia (which may reflect direct HIV infection), steatosis, portal inflammation, focal necrosis, bile stasis, or congestion.\(^ {194,276}\) Such findings rarely have clinical significance.

Clinical Manifestations of Biliary Disease

AIDS cholangiopathy. Disorders of the biliary tract in patients with HIV infection consist predominantly of the syndrome known as AIDS cholangiopathy.\(^ {277-280}\) This abnormality resembles ductular changes of sclerosing cholangitis and is characterized by intrahepatic and/or extrahepatic duct strictures. The most com-
mon cholangiographic pattern is diffuse (intrahepatic and extrahepatic) sclerosing cholangitis in combination with papillary stenosis.\textsuperscript{278,281–283} Less commonly, there may be isolated intrahepatic sclerosing cholangitis, papillary stenosis, or long extrahepatic strictures.\textsuperscript{281} Clinically, the presentation is variable, although right upper quadrant pain accompanied by an elevated alkaline phosphatase level is the most common manifestation. Liver biochemical test results may be normal.\textsuperscript{278,282} Interestingly, jaundice is very unusual,\textsuperscript{278,280,282,283} suggesting that complete ductal obstruction is rare. AIDS cholangiopathy has been more commonly reported in homosexual men than in other transmission categories. A significant proportion of patients may harbor ductal changes that are clinically silent, as shown in a study of patients who had CMV viremia but no abdominal symptoms.\textsuperscript{284} When using endoscopic retrograde cholangiopancreatography (ERCP) as the gold standard, ultrasonography or computed tomography have an approximately 75\%–87\% sensitivity in detecting ductal disease,\textsuperscript{278,280} implying that the syndrome cannot be excluded definitely using these latter two imaging studies. The etiology is usually related to a specific infection (cryptosporidiosis, microsporidiosis, CMV), neoplasm, pancreatic disease, or possibly some other process or immune mechanism. One study from France has reported an extremely high frequency of biliary microsporidiosis in affected patients,\textsuperscript{285} whereas other studies from the United States and France have more commonly identified cryptosporidium or CMV.\textsuperscript{279,281,286} particularly in patients with involvement of large intrahepatic ducts.\textsuperscript{283} The presence of AIDS cholangiopathy does not seem to affect survival.\textsuperscript{287}

**Acalculous cholecystitis.** Acute calculus cholecystitis occurs as a late-stage complication when opportunistic infections are more likely.\textsuperscript{288} Common findings include thickening of the gallbladder wall; radioisotope imaging with 2,6-dimethylphenylcarbamoylmethylimidodiacetic acid usually shows cystic duct obstruction.\textsuperscript{288} Cholecystectomy is curative, although associated sclerosing cholangitis of the bile ducts may subsequently become clinically evident. Histopathologic examination of the gallbladder will frequently identify an opportunistic pathogen such as CMV, cryptosporidiosis, microsporidiosis, or *Isospora belli*. Gallstones may also be detected.\textsuperscript{288–290} Rare cases of lymphomatous or nodal biliary obstruction have been reported.

**Liver Chemistry, Noninvasive Imaging, and ERCP**

As in all patients, the magnitude and pattern of liver test abnormalities in those with HIV infection can help distinguish cholestatic from hepatocellular lesions but taken alone do not indicate a specific diagnosis. Marked elevations of serum alkaline phosphatase levels are particularly common, having been reported in 17\% of 90 consecutive patients with AIDS in one series.\textsuperscript{291} The majority of these patients had no identifiable biliary or hepatocellular disease, although liver biopsy and ERCP were not performed in all patients. In one large series,\textsuperscript{194} the mean serum alkaline phosphatase level among patients with AIDS cholangiopathy was 600 (normal value < 115). As noted above, the serum bilirubin levels are usually normal so that jaundice from cholangiopathy alone is extremely unusual.\textsuperscript{280,282,285} Alternatively, marked elevation of alkaline phosphatase levels in the absence of ductal pathology may indicate the presence of MAC\textsuperscript{194} or some other disseminated infection or malignancy.

Noninvasive imaging is an important tool in evaluating hepatobiliary pathology. In one large series of HIV-infected patients undergoing abdominal ultrasonography, abnormalities were detected in 264 of 399 ultrasonography studies.\textsuperscript{292} Typical findings included gallbladder and biliary duct abnormalities (n = 80), hepatosplenomegaly (n = 337), and hepatomegaly (n = 77). Associated abnormal liver biochemistries were present in 270 patients. The frequency of abnormalities detected in this series increased substantially during a 10-year period (from 1984 to 1994); it is uncertain whether this represents increased prevalence of abnormalities, increased experience of the ultrasonographer, or technological improvements in imaging. Computed tomographic scanning is also useful in evaluating hepatobiliary abnormalities.\textsuperscript{293} In particular, lesions attributable to lymphoma\textsuperscript{294} and large pelvic spaces\textsuperscript{212} are usually well visualized. Focal lesions attributable to MAC may occasionally be detected by either computed tomography or ultrasonography,\textsuperscript{295} although this infection is usually diffuse. No studies have directly compared the sensitivity and specificity of noninvasive techniques in detecting hepatobiliary disease. Liver-spleen scintigraphy rarely adds additional information.\textsuperscript{296}

In patients with AIDS cholangiopathy, noninvasive imaging (ultrasonography, computed tomography) plays an important role in diagnosis, although this approach is less sensitive than ERCP (see above). In the patient with biliary dilation shown by noninvasive imaging studies, ERCP may be appropriate to diagnose AIDS cholangiopathy, exclude other disorders, and provide the opportunity for therapeutic intervention such as sphincterotomy, stenting, or biopsy, depending on the lesion.

In assessing the use of liver biopsy, at least three issues must be considered: the probability of making a specific diagnosis, the probability of identifying a lesion not iden-
tified by other diagnostic methods, and the probability of making a diagnosis for which therapy will improve the patient’s quality of life or survival. Retrospective data are emerging that address these issues, but no study has prospectively assessed the impact of liver biopsy on patient outcomes.

According to most reports, percutaneous liver biopsy will uncover one or more specific abnormalities in the majority of patients when undertaken to evaluate fever, hepatomegaly, and/or abnormal liver biochemistries.\(^{194,196,298}\) In a study of HIV-infected patients who were injection drug users,\(^ {196}\) liver biopsy was helpful in the evaluation of fever of unknown origin. Several difficulties arise, however, in evaluating liver biopsy data from retrospective studies. First, the indications and frequency of performing liver biopsy have evolved considerably during the 15 years since AIDS was first described. Whereas biopsy was commonly performed when the AIDS epidemic began, it is now performed less frequently. Second, other diagnostic methods have been refined, and we have a greater appreciation of the spectrum of hepatobiliary disease. A clear example is the recognition of bacillary peliosis hepatis as a specific infection, which might obviate the need for biopsy if diagnosed by skin or blood culture. Third, it is possible that liver biopsies are now performed later in the course of HIV infection, when it is more likely that a specific diagnosis will be uncovered.\(^ {297,298}\) Fourth, the spectrum of abnormalities will differ among different transmission categories. For example, the prevalence of HCV in injection drug users is much greater than in homosexual men.

Liver biopsy rarely uncovers a lesion not previously identified in other tissues. In one study,\(^ {194}\) only 2 of 26 biopsy specimens revealed a new diagnosis (1 of CMV and 1 of lymphoma). For diagnosing fever of unknown origin, liver biopsy may have special value if other methods such as bone marrow biopsy and blood cultures are nondiagnostic. In a prospective study of 24 patients undergoing liver biopsy that had unexplained fever and increased alkaline phosphatase or \(\gamma\)-glutamyl transferase levels, a microbiological diagnosis was made in 13 (54%), in 9 of whom MAC was found.\(^ {299}\) Liver biopsy seems to be more sensitive than bone marrow biopsy in diagnosing MAC infection.\(^ {200}\) Thus, when MAC is suspected and blood and bone marrow cultures are negative, liver biopsy may enable a prompt diagnosis.

No reliable data exist that specifically address how often findings from liver biopsy lead to improved quality of life or survival. However, this is not likely to be a frequent occurrence given the low probability of uncovering new diagnoses. Moreover, enthusiasm for uncovering unrecognized pathogens or neoplasms is tempered by the realization that many are untreatable, especially in late-stage HIV infection. Similarly, biopsy is not likely to be useful in HCV infection if HIV disease is advanced, because patients with low CD4 counts are unlikely to respond to interferon alfa (see below).

Despite reports to the contrary,\(^ {300,301}\) no comprehensive evidence suggests that complications from liver biopsy are more likely in patients with HIV infection, provided that coagulation parameters are normal. Concern persists, however, about the possibility of hemorrhage from vascular lesions such as Kaposi’s sarcoma\(^ {302}\) or peliosis hepatis.

A valuable alternative to Klatskin or Menghini needle biopsy for focal lesions is directed fine-needle aspiration. This technique greatly reduces the risk of hemorrhage and can be directed to specific abnormalities using computed tomography or ultrasonography guidance. It is particularly useful to diagnose primary hepatic lymphoma, where it was successful in 22 of 24 patients in one series.\(^ {303}\) Laparoscopy may also be helpful to perform a biopsy on focal hepatic lesions as well as to identify associated peritoneal disease.\(^ {304}\)

**Treatment**

**Liver disease.** The therapy of hepatobiliary disease in HIV-infected patients depends on at least three factors: (1) specific findings of culture, biopsy, or imaging studies; (2) extent of the patient’s immunocompromise; and (3) presence and severity of other infections or neoplasms. The treatment of opportunistic infections involving the liver is similar to that for other sites. The focus here is on the use of interferon in viral hepatitis.

The value of interferon alfa for treating chronic HBV or HCV infections in patients with HIV is debatable, primarily because these infections are rarely a cause of morbidity or mortality in this setting. Before considering therapy, the goal must be defined. For patients with HBV who are \(e\) antigen positive, a reasonable goal might be seroconversion to \(e\) antigen negative status, but only if this clearly translates into prolonged survival. However, the data needed to address this issue are lacking. Moreover, responsiveness to interferon in patients with chronic HBV carriage is lower in HIV infection. Wong et al.\(^ {305}\) reported that a response (defined as loss of HBV DNA and \(e\) antigen and appearance of anti-\(e\) antibody) to interferon in patients with HBV infection was one fifth as likely in those coinfected with HIV compared with those who were HIV seronegative. These results are similar to those reported by Marcellin et al.\(^ {306}\) For chronic HCV infection, the likelihood of response seems to be greatest in those who are not severely immunocompromised.\(^ {307,308}\) However, treatment is most clearly indicated...
when HCV replication increases, which occurs in the late stages of HIV infection when other opportunistic life-threatening infections develop. Thus, treatment with interferon alfa is least likely to be helpful when it is needed most. Optimal dosing and duration of therapy in this setting are not established. Use of interferon alfa in patients coinfected with HBV and HIV is not indicated, except within the context of clinical trials. As with HBV, no study has shown that treating HCV with interferon improves the patient’s quality of life or prolongs survival. Given that HCV does not seem to adversely influence survival in HIV-infected patients without hemophilia, the need for treatment is less clear.

**Biliary tract diseases.** Papillary stenosis associated with AIDS cholangiopathy can be effectively treated by endoscopic sphincterotomy, and this approach should be considered in the symptomatic patient because pain is improved in most patients. Nevertheless, controlled trials of sphincterotomy or stenting for papillary stenosis are lacking. In two series totaling 22 patients with abdominal pain and papillary stenosis, sphincterotomy resulted in complete relief of pain. However, in another series of 21 patients, pain relief occurred in only 9. After sphincterotomy, progressive elevation of alkaline phosphatase levels continues in most of these patients, reflecting ongoing intrahepatic biliary disease. In some patients, stenosis may reoccur, necessitating repeat ERCP. There is no evidence to support the use of sphincterotomy in the patient with intrahepatic sclerosing cholangitis who has a normal common bile duct.

Acalculous cholecystitis can be a surgical emergency, or it may result in chronic progressive symptoms. In otherwise stable patients, cholecystectomy is indicated and is remarkably well tolerated. In patients too ill to tolerate open surgery, laparoscopic cholecystotomy, cholecystostomy, or minilaparotomy may be feasible. If the clinical evidence supports CMV infection as an underlying etiology, empiric administration of ganciclovir or foscarnet may be considered before definitive therapy.

**Diagnostic Evaluation of Hepatobiliary Disease: An Approach**

In general, the diagnostic workup should be similar to the immunocompetent host. A suggested approach is summarized in Table 5. Mild elevations in liver chemistry test results (<2 times the upper limit of normal) in an asymptomatic patient may warrant no specific evaluation. Elevation of the transferase levels may indicate hepatitis and should be evaluated with hepatitis serologies and consideration of drug-induced disease. All prescription and nonprescription drugs should be considered potentially hepatotoxic and stopped, if possible, before or concurrent with additional evaluation. Marked elevation of serum alkaline phosphatase levels usually indicates an infiltrative disorder (neoplasm, infections) or cholangiopathy. In this setting, evaluation should depend on the clinical features. In a patient with systemic symptoms and hepatomegaly, computed tomography is probably the preferred test because adenopathy can be appreciated and mass lesions are better delineated. The presence of mild hepatomegaly in the absence of significant liver test abnormalities, right upper quadrant pain, or systemic symptoms demands no specific evaluation. Computed tomography and ultrasonography are especially useful in guiding fine-needle aspiration or biopsy of focal lesions. Abdominal ultrasonography should be the test of choice when cholangiopathy is suspected, such as in a patient with right upper quadrant pain and elevation of the serum alkaline phosphatase level. If biliary duct dilation is detected, particularly of the common bile duct, ERCP is appropriate because sphincterotomy or stenting may be helpful. In the jaundiced patient without clinical evidence of hepatitis, CT may be the preferred test to evaluate for mass lesions or adenopathy. Liver biopsy rarely uncovers new unrecognized disease. Biopsy may be most useful in those patients with persistent fever in whom other less invasive methods have not uncovered a treatable lesion.

**Conclusions**

In HIV-infected individuals, abnormal liver test results, jaundice, or hepatomegaly can develop as a result of hepatic parenchymal disease, biliary lesions, or both. More than one abnormality is not unusual, particularly in late-stage HIV infection. The spectrum of potential causes for liver or biliary disease are dependent on the

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**Table 5. An Approach to the Evaluation of Hepatobiliary Disease in Patients With HIV Infection**

<table>
<thead>
<tr>
<th>Elevated transferase levels</th>
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<tbody>
<tr>
<td>Hepatitis serologies</td>
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<tr>
<td>Exclude drug-induced hepatitis</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase levels</td>
</tr>
<tr>
<td>Step 1: Abdominal US or CT; US is preferred to evaluate bile ducts; CT preferred if mass lesion suspected</td>
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<tr>
<td>Step 2: ERCP; consider if bile ducts are dilated</td>
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<tr>
<td>Step 3: Liver biopsy; consider if US and CT are negative</td>
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<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Asymptomatic with minimal biochemical abnormalities: follow Symptomatic</td>
</tr>
<tr>
<td>Step 1: if elevated transferase levels, see above if elevated alkaline phosphatase levels, see above</td>
</tr>
<tr>
<td>Step 2: consider cultures of blood or bone marrow before proceeding to liver biopsy</td>
</tr>
</tbody>
</table>

CT, computed tomography; US, ultrasonography.
stage of immunocompromise. However, the liver is rarely the only site of involvement due to infection or neoplasm, so that evidence of infection in other sites may obviate the need for invasive hepatic evaluation. Liver or biliary disease is rarely the cause of death in patients with HIV infection. As such, reasonable end points apart from survival must be defined before considering treatment. These may include relief of symptoms (pain, fever, jaundice) or improved quality of life.

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