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MYCOBACTERIAL INFECTIONS AND HIV

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Mycobacterial infections are important complications of HIV disease. In the past decade, the emerging HIV pandemic has resulted in dramatice increases in illness caused by mycobacteria. In particular, the HIV epidemic has contributed to resurgent tuberculosis in developed countries, exacerbations of hyperendemic tuderculosis in developing countries, and unprecedented numbers of patients with disseminated *Mycobacterium avium*–complex infections.

Mycobacterium tuberculosis

The overlap of HIV and *M. tuberculosis* infections has resulted in a number of significant interactions between these two pathogens. Epidemiologic data indicate that HIV infection is increasingly common in populations with a high prevalence of *M. tuberculosis* infection. In the United States, for example, HIV is prevalent in injection drug users, people from racial and ethnic minority groups, and residents of inner cities, populations with historically high rates of tuberculosis[1]. The increased susceptibility of these coinfected individuals to developing active tuberculosis contributed to a 20% increase in tuberculosis morbidity in the United States between 1985 and 1992[2]. In developing countries where the prevalence of tuberculosis infection in adults may exceed 50%, the spread of HIV has caused sharp increases in tuberculosis case rates[3]. Substantial increases in tuberculosis morbidity have occurred in sub–Saharan African countries, Thailand, and in Latin American countries where HIV is prevalent. The World Health Organization estimates that the prevalence of HIV–related tuberculosis doubled worldwide between 1990 and 1995 (from 4% to > 8% of all cases), and will increase a further 65% by the year 2000[4]. As case rates of tuberculosis have increased as a consequence of the HIV epidemic, additional problems have emerged. Outbreaks of tuberculosis in HIV–infected individuals in hospitals or other congregate living facilities and multidrug resistant tuberculosis are problems that have assumed enormous proportions[5].

HIV infection profoundly alters host defenses against *M. tuberculosis*. In individuals with latent tuberculosis infection, the acquisition of HIV infection produces progressive loss of cell–mediated immunity which impairs containment of tubercle bacilli. A number of immunologic defects have been described in patients with HIV and *M. tuberculosis* infections, including impaired T–cell proliferation, decreased cytolytic responses, and reduced cytokine elaboration in response to mycobacterial antigen challenge. Patients with latent tuberculosis infection and HIV have a 2–10% annual risk of developing active tuberculosis[6)~9)]. The risk of reactivation rises and CD4 cell levels decline.

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The early natural history of *M. tuberculosis* infection is also greatly affected by HIV disease. Individuals with HIV infection who acquire new tuberculosis infections have an extraordinarily high rate of progressive, primary tuberculosis. In an outbreak of tuberculosis among HIV-infected residents of a residential facility in San Francisco, 38% of susceptible patients developed active pulmonary tuberculosis with an identical strain of *M. tuberculosis* (identified by restriction fragment length polymorphism analysis) within four months of exposure to the index case[10]. The rapid progression of tuberculosis infection to tuberculosis disease in individuals with HIV infection has resulted in numerous epidemics of tuberculosis in institutions such as hospitals, nursing homes, and prisons, as well as in community settings. Recent studies have shown that approximately 40% of tuberculosis cases in San Francisco and northern New York City are epidemiologically clustered, indicating recent transmission and primary disease[11)12)]. In both settings, HIV infection was significantly associated with clustering of tuberculosis cases.

While HIV has a major effect on the natural history of tuberculosis, there is also evidence that tuberculosis may affect the course of HIV disease. Activation of CD4 lymphocytes by tuberculosis enhances susceptibility to HIV infection *in vitro*, and HIV-infected CD4 cells stimulated by mycobacterial antigens have enhanced *in vitro* HIV replication[13]. Cytokine elaboration by lymphocytes and macrophages in patients with tuberculosis and HIV, in particular tumor necrosis factor and interleukin-2, may upregulate HIV expression[14]. Preliminary studies indicate that HIV viral load is increased in patients with active tuberculosis and HIV infection. Thus, prevention of tuberculosis in HIV-infected persons may prevent AIDS-related morbidity in addition to tuberculosis.

The clinical features of tuberculosis in individuals with HIV infection may differ considerably from those seen in patients without HIV infection[15]. In patients with higher CD4 cell counts (e.g.,> 300), tuberculosis may be more typical, with pulmonary disease predominantly and upper lobe infiltrates, with or without cavitation[16]. As CD4 cell levels decline, tuberculosis in the HIV-infected patient is more likely to be disseminated, both within the lung and throughout the body[17]. The pulmonary presentation of tuberculosis in these patients may mimic *Pneumocystis carinii* pneumonia, with diffuse interstitial infiltrates and/or alveolar infiltrates. Hilar adenopathy and lower lobe infiltrates are found in patients with progressive, primary tuberculosis. In advanced HIV disease, extrapulmonary tuberculosis is more common. Sites of extrapulmonary involvement that are most prevalent are lymph nodes, the urinary tract, meninges, and blood and bone marrow. Mycobacteremia is not unusual, particularly in patients with CD4 cell counts< 100. The diagnosis of tuberculosis in the HIV-infected patients requires a high index of suspicion and the utilization of appropriate diagnostic tests. Acid fast smears of respiratory secretions or tissue samples is useful, in that positive smears are strongly predictive of tuberculosis, even in populations where *M. avium*-complex is more common. Rapid diagnostic methods, such as radiometric culture systems, nucleic acid amplification, or other novel techniques are necessary to establish a timely diagnosis. Presumptive therapy for tuberculosis is often necessary while diagnostic studies are underway.

Treatment of tuberculosis in patients with HIV infection is extremely effective when begun promptly[18]. Early mortality from untreated or undertreated tuberculosis has ranged from 5 to 18 percent of patients in various series. When patients with HIV-related treatment are treated with rifampin-based regimens, clinical responses are gratifying and similar to tuberculosis patients without HIV infection. Several recent studies have indicated that short course regimens (i.e., six months treatment) are highly successful, with low relapse rates[19]. Moreover, therapy given under direct supervision is associated with better outcomes and longer survival[20]. Use of thiacetazone in place of rifampin in developing counrties has been

associated with a high rate of serious cutaneous toxicities, and responses to thiacetazone-based regimens are poorer than to rifampin-based regimens[21)22)].

Resistance to antituberculosis agents is a growing problem that has been exacerbated by the HIV epidemic[23)24)]. While the molecular mechanisms of isoniazid and rifampin resistance were only recently elucidated, the manner in which drug resistance occurs in patients has long been known[25)~27)]. Inappropriate exposure to antituberculosis drugs, through patient non-adherence or physician mistake, promotes emergence of innately resistant strains of *M. tuberculosis*[28)]. The magnitude of drug resistant tuberculosis has grown substantially in recent years, particularly in the United States. In New York City, the prevalence of drug resistance in tuberculosis isolates from April 1991 was approximately 33%, while multidrug resistance (resistance to isoniazid and rifampin) was detected in 19% of isolates[24)]. Outbreaks of multidrug resistant tuberculosis were reported in hospital patients and prison inmates in New York, Florida and other locations, primarily in HIV-infected individuals. Case fatality rates have approached 80% in these outbreaks. Control of multidrug resistant tuberculosis has required enormous investments in tuberculosis treatment programs and institutional infection control programs. With the emergence of multidrug resistant tuberculosis, the United States Centers for Disease Control and the American Thoracic Society have recommended that the initial treatment of active tuberculosis consist of at least a four drug regimen, and that therapy be supervised unless adherence to treatment is assured[29)]. Treatment of multidrug resistant tuberculosis is frequently unsuccessful, even in immunocompetent patients, underscoring the importance of prevention of this complication[30)].

Prevention of tuberculosis in HIV-infected persons can be achieved with isoniazid chemoprophylaxis. Several studies have demonstrated the effectiveness of isoniazid preventive therapy. Pape and colleagues showed that isoniazid preventive therapy reduced the risk of both tuberculosis and death in HIV seropositive Haitian adults[31)]. The benefit of preventive therapy was only apparent in tuberculin skin test positive patients, although the number of anergic patients was too small to draw firm conclusions. The Centers for Disease Control and Prevention recommend that isoniazid preventive therapy be given to PPD-positive, HIV seropositive persons who do not have evidence of active tuberculosis. The role of prophylaxis in anergic patients remains controversial. Prospective studies are underway to determine whether preventive therapy is efficacious in such individuals. Alternatives to isoniazid prophylaxis are under study also. The combination of rifampin and pyrazinamide given for two months is extremely effective in the murine model of chronic tuberculosis[32)]. One study has suggested that this regimen is active in HIV-infected, PPD-positive adults, and a larger study is still ongoing[33)]. Other alternatives include short courses of rifampin, rifabutin, or the combination of isoniazid and rifampin[34)].

Mycobacterium avium-Complex

Disseminated *M. avium*-complex infection is an increasingly common complication of HIV[35)]. While prior to the AIDS epidemic disseminated *M. avium*-complex infections were extremely rare, tens of thousands of cases have occurred in the United States alone among AIDS patients[36)]. Common signs and symptoms of disseminated *M. avium*-complex include fever, sweats, weight loss, diarrhea, malaise, hepatomegaly, anemia, and elevated liver enzymes. The diagnosis of disseminated *M. avium*-complex is usually made by isolation of organisms from blood or bone marrow cultures. *M. avium*-complex may be restricted to the lymph nodes, gastrointestinal tract or the lungs in occasional patients.

Several risk factors for disseminated *M. avium*-complex have been identified. The most important predictor of subsequent disseminated *M. avium*-complex is low CD4 lymphocyte count[37)38)]. Several prospective studies have shown that as CD4 counts fall to $< 100/mm^3$, the annual incidence of *M. avium*-complex bac-

teremia rises substantially[39]. For patients with CD4 counts $< 50/mm^3$, the risk of *M. avium*–complex bacteremia is between 10 and 20 percent per year. Prior colonization of the respiratory and gastrointestinal tracts increase the risk of disseminated *M. avium*–complex significantly, but most patients with *M. avium*–complex bacteremia never show evidence of colonization[40], Recent data suggest that genetic susceptibility to *M. avium*–complex infection may be related to the HLA B35 haplotype[41]. The role of other genes in host resistance to *M. avium*–complex and other mycobacterial infections in humans is not clear.

The pathogenesis of *M. avium*–complex infections in patients with HIV is not precisely understood. Exposure to the organism presumably occurs from ingestion of contaminated water or food. Colonization of the gastrointestinal or respiratory systems ensue, and seeding of other organs, such as lymph nodes, may also occur. Subsequent dissemination develop when cell mediated immunity has been ablated by HIV progressive infection. For some time it has been hypothesized that *M. avium*–complex bacteremia is an "overflow" phenomenon, with organisms spilling into the blood from heavily infected organs. Several recent studies suggest that bacteremia precedes dissemination, however, and transient bacteremia with less severe clinical disease may be present in 10–15 percent of patients[42]. An autopsy study of patients with previous mycobacteremia showed that evidence of *M. avium*–complex in organs was found in 50 percent of patients who died within one month of being bacteremic but in > 90 percent of patients who died more than six months after developing bacteremia[43].

Because disseminated *M. avium*–complex infection is a predictable late complication of HIV disease, chemoprophylaxis is desirable. Rifabutin, a semisynthetic rifamycin S derivative, was shown in two placebo–controlled trials to reduce the incidence of *M. avium*–complex bacteremia in AIDS patients with CD4 counts $< 200/mm^3$ by 50 percent[44]. The United States Public Health Service has recommended that lifelong rifabutin preventive therapy be offered to HIV–infected patients with CD4 counts $< 100/mm^3$ [45]. Rifabutin given at a dose of 300 mg daily was well tolerated in the clinical trials, though there have been recent reports of uveitis in patients treated with rifabutin in higher doses[46]. Concomitant use of fluconazole or clarithromycin increases serum rifabutin levels and may result in a greater risk of this toxicity. Failure of rifabutin prophylaxis does not appear to select for drug–resistant *M. avium*–complex organisms. A recent, unpublished study suggests that clarithromycin is also effective in preventing *M. avium*–complex bacteremia in patients with HIV infection, though selection of resistant organisms may occur[47].

Treatment of disseminated *M. avium*–complex in patients with AIDS has been daunting, as many standard antimycobacterial agents have been found to have minimal activity against this pathogen. Four to five drug combination regimens have shown moderate to good effect in some studies[48][49]. The extended spectrum macrolides clarithromycin and azithromycin have been shown to have superior activity against *M. avium*–complex disease in several studies. Clarithromycin at doses of 500 to 2000 mg twice daily significantly reduces levels of bacteremia and is associated with clinical improvement. Lower doses of clarithromycin are better tolerated and may be associated with better survival. Use of clarithromycin alone for the treatment of *M. avium*–complex bacteremia is associated with high rates of emergence of resistant organisms. Azithromycin also reduces the level of bacteremia, and its use as monotherapy similarly results in emergence of drug–resistant disease[50]. The United States Public Health Service Task Force recommends that combination therapy for disseminated *M. avium*–complex should consist of clarithromycin or azithromycin with at least one other antimycobacterial agent. Other agents with known activity against *M. avium*–complex are ethambutol and rifabutin[51]. Other drugs also used include ciprofloxacin, amikacin, rifampin, and

clofazimine. Recently, interferon gamma has been shown to be active in controlling disseminated *M. avium*-complex infections in patients without HIV[52]. The efficacy of interferon gamma in AIDS patients is not known.

Other Mycobacteria

Patients with HIV infection are susceptible to a number of other mycobacterial infections, though these are less common than tuberculosis or *M. avium*-complex. *M. kansasii* infections generally mimic tuberculosis, presenting in severely immunocompromised HIV-infected patients with cavitary or diffuse pulmonary infiltrates[53]. Bacteremia, osteomyelitis and soft tissue infections are also seen. Treatment with isoniazid, rifampin and ethambutol for 18 months is recommended. *M. genavense* causes disseminated disease in advanced immunodeficiency, with bacteremia and other organ involvement[54]. The organism grows poorly in liquid media and cannot be cultured on solid media. It is detectable by amplification of genomic sequences by the polymerase chain reaction. Formal studies of treatment for *M. genavense* infections have not been conducted, but anecdotal information suggests that regimems active against *M. avium*-complex are also effective for this organism. *M. hemophilum* may cause skin and soft tissue infections in AIDS patients, and case reports of infections with *M. fortuitum, M. chelonei,* and *M. xenopi* have appeared.

REFERENCES

1) CDC. HIV/AIDS epidemic : the first ten years. MMWR. 1991 ; 40 : 357-369.
2) Cantwell MF, Snider DE, Jr., Canthen GM, et al. : Epidemiology of tuberculosis in the United States, 1985-1992. JAMA. 1994 ; 272 : 535-539.
3) Harries AD : Tuberculosis and human immunodeficiency virus infections in developing countries. Lancet. 1990 ; 335 : 387-390.
4) Raviglione MC, Snider De, Jr., Kochi A : Global epidemiology of tuberculosis, morbidity, and mortality of a worldwide epidemic. JAMA. 1995 ; 273 : 220-226.
5) CDC. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected person-Florida and New York, 1988-1991. MMWR. 1991 ; 40 : 585-591.
6) Selwyn PA, Hartel D, Lewis V, et al. : A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989 ; 320 : 545-550.
7) Selwyn PA, Sckell BM, Alcabes P, et al. : High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. JAMA. 1992 ; 268 : 504-509.
8) Moreno S, Baraia-Etxaburu J, Bouza E, et al. : Risk for developing tuberculosis among anergic patients infected with HIV. Ann Intern Med. 1993 ; 119 : 194-198.
9) Allen S, Butungwanayo J, Kerlikowske K, et al. : Two-year incidence of tuberculosis in cohorts of HIV-infected and uninfected Rwandan women. Am Rev Respir Dis. 1992 ; 146 : 1439-1444.
10) Daley CL, Small PM, Schecter GF, et al. : An outbreak of tuberculosis with accelerated progression among persons infected with human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. N Engl J Med. 1992 ; 326 : 231-235.
11) Small PM, Hopewell PC, Singh SP, et al. : The epidemiology of tuberculosis in San Francisco : a population-based study using conventional and molecular methods. N Engl J Med. 1994 ; 330 : 1703-1709.
12) Alland D, Kalkut GE, Moss AR, et al. : Transmission of tuberculosis in New York City. An analysis by DNA fingerprinting and controversial epidemiologic methods. N Engl J Med. 1994 ; 330 : 1710-1716.
13) Toosi Z, Vjecha M, Amir-Tahmasseb M, et al. : Enhanced susceptibility of blood monocytes from patients with pulmonary tuberculosis to productive infection with human immunodeficiency virus type 1. J Exp Med. 1993 ; 177 : 1511-1516.
14) Wallis RS, Vjecha M, Amir-Tahmasselo M, et al. : Influence of tuberculosis on HIV :

enhanced cytokine expression and elevated Beta-2 microglobulin in HIV-1-associated tuberculosis. J Infect Dis. 1993 ; 167 : 43-48.
15) Chaisson RE, Schecter GF, Theuer CP, et al. : Tuberculosis in patients with the acquired immunodeficiency syndrome : clinical features, response to therapy and survival. Am Rev Resp Dis. 1987 ; 136 : 570-574.
16) Theuer CP, Hopewell PC, Elias D, et al. : Human immunodeficiency virus infection in tuberculosis patients. J Infect Dis. 1990 ; 162 : 8-12.
17) Jones BE, Young SM, Antoniskis D, et al. : Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Resp Dis. 1994 ; 148 : 1292-1297.
18) Small PM, Schecter GF, Goodman PC, et al. : Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. N Engl J Med. 1991 ; 324 : 289-294.
19) Holt E, Cantave M, Johnson M, et al. : Johns Hopkins University, Baltimore, MD, and Centers for Development and Health, Cite Soleil, Haiti. Efficacy of supervised, intermittent, short course therapy of tuberculosis in HIV infection. Abstract No, WSB 09-4. IXth International Conference on AIDS, Berlin, June 7-11, 1993.
20) Alwood K, Keruly J, Moore-Rice K, et al. : Effectiveness of supervised intermittent therapy for tuberculosis in HIV-infected patients. AIDS. 1994 ; 8 : 1103-1108.
21) Nunn P, Kibuga D, Gathua S, et al. : Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. Lancet. 1991 ; 337 : 627-630.
22) Hawken M, Nunn P, Gathua S, et al. : Increase recurrence of tuberculosis in HIV-1 -infected patients in Kenya. Lancet. 1993 ; 342 : 332-337.
23) Bloch AB, Cauthen GM, Onorato IM, et al. : Nationwide survey of drug-resistant tuberculosis in the United States. JAMA. 1994 ; 271 : 665-671.
24) Frieden TR, Sterling T, Pablos-Mendez A, et al. : The emergence of drug-resistant tuberculosis in New York City. N Engl J Med. 1993 ; 328 : 521-526.
25) Zhang Y, Heym B, Allen B, Young D, Cole S. The catalase-peroxidase gene and isoniazid resistance of *mycobacterium tuberculosis*. Nature. 1992 ; 358 : 591-593.
26) Telenti A, Imboden P, Marchesi F, et al. : Detection of rifampicin-resistance mutations in *mycobacterium tuberculosis*. Lancet. 1993 ; 341 : 647-650.
27) Bloom BR, Murray CJL : Tuberculosis : commentary on a reemergent killer. Science. 1992 ; 257 : 1055-1064.
28) Mahmoudi A, Iseman MD : Pitfalls in the care of patients with tuberculosis : Common errors and their acquisition of drug resistance. JAMA. 1993 ; 270 : 65-68.
29) American Thoracic Society. Treatment and prevention of tuberculosis in adults and children. Am J Respir Crit Care Med. 1994 ; 149 : 1359-1374.
30) Goble M, Iseman MD, Madsen LA, et al. : Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med. 1993 ; 328 : 527-532.
31) Pape JW, Jean SS, Ho JL, et al. : Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet. 1993 ; 342 : 268-272.
32) Lecouer HF, Truffot-Pernot C, Grosset JH : Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. Am Rev Respir Dis.1989 ; 140 : 1189-1193.
33) Halsey N, Coberly J, Atkinson J, et al. : Twice weekly INH for TB prophylaxis. Abstract No. PB0681. Tenth International Conference on AIDS, Yokohama, Japan, August 7-12, 1994.
34) Ji B, Truffot-Pernot C, Lacroix C, et al. : Effectiveness of rifampin, rifabutin, and rifapentine for preventive therapy of tuberculosis in mice. Am Rev Respir Dis. 1993 ;

148 : 1541–1546.
35) Hoover DR, Saah AJ, Bacellar H, et al. : Clinical manifestations of AIDS in the era of pneumocystis prophylaxis. N Engl J Med. 1993 ; 329 ; 1922–1926.
36) Horsburgh CR Jr. : *Mycobacterium avium*–complex infection in the acquired immunodeficiency syndrome. N Engl J Med. 1991 ; 324 : 1332–1338.
37) Chaisson RE, Keruly J, Richman DD, et al. : Incidence and natural history of *Mycobacterium avium*–complex disease in advanced HIV infection treated with zidovudine. Am Rev Respir Dis. 1992 ; 146 : 285–289.
38) Nightingale SD, Byrd LT, Southern PM, et al. : Incidence of *mycobacterium avium–intracellulare* complex bacteremia in human immunodeficiency virus–positive patients. J Infect Dis. 1992 ; 165 : 1082–1085.
39) Horsburgh CR Jr, Metchock B, Gordon SM, et al. : Predictors of survival in patients with AIDS and disseminated *Mycobacterium avium*–complex disease. J Infect Dis. 1994 ; 170 : 573–575.
40) Chin DP, Hopewell PC, Yajko DM, et al. : *Mycobacterium avium*–complex in the respiratory or gastrointestinal tract and the risk of *M. avium*–complex bacteremia in patients with human immunodeficiency virus infection. J Infect Dis. 1994 ; 169 : 289–295.
41) Cameron PU, Mallal SA, Witt C, et al. : MHC ancestral haplotypes containing HLA–B8 and B35 are associated with different patterns of HIV–1 disease progression and complications. Second National Conference on Human Retroviruses and Related Infections. January 29–February 2, 1995, Washington, DC. Session Number 43. Paper Number 247.
42) Kemper CA, Havlir D, Bartok AE, et al. : Transient bacteremia due to *Mycobacterium avium*–complex in patients with AIDS. J Infect Dis. 1994 ; 170(1) : 157–164.
43) Torriani FJ, McCuthan JA, Bozzette SA, et al. : Autopsy findings in AIDS patients with *mycobacterium avium*–complex bacteremia. J Infect Dis. 1994 ; 170 : 1601–1605.
44) Nightingale SD, Cameron DW, Gordin FM, et al. : Two controlled trials of rifabutin prophylaxis against *Mycobacterium avium*–complex infection in AIDS. N Engl J Med. 1993 ; 329 : 828–833.
45) Masur H and the U.S. Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium*–complex. Recommendation on prophylaxis and therapy for disseminated *mycobacterium avium*–complex disease in patients infected with the human immunodeficiency virus. N Engl J Med. 1993 ; 329 : 898–904.
46) Schafran SD, Deschenes J, Miller M, et al. : Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin and ethambutol. N Engl J Med. 1994 ; 330 : 438–439.
47) Pierce M, Lamarca A, Jablonowski H, et al. : A placebo controlled trial of clarithromycin prophylaxis against MAC infection in AIDS patients. In program Addendum, 34th ICAAC, Orlando, Florida, October 5, 1994.
48) Hoy J, Mijch A, Sandlum M, et al. : Quadruple–drug therapy for *Mycobacterium avium intracellulare* bacteremia in AIDS patients. J Infect Dis. 1990 ; 161 : 801–805.
49) Kemper CA, Meng T–C, Nussbaum J, et al. : Treatment of *Mycobacterium avium* complex bacteremia in AIDS with a four–drug oral regimen : rifampin, ethambutol, clofazimine, and ciprofloxacin. Ann Intern Med. 1992 ; 116 : 466–472.
50) Young LS, Wiviott L, Wu M, et al. : Azithromycin for treatment of *mycobacterium avium–intracellulare* complex infection in patients with AIDS. Lancet. 1991 ; 338 : 1107–1109.
51) Sullam PM, Gordin FM, Wynne BA, et al. : Efficacy of rifabutin in the treatment of isseminated infection due to *mycobacterium avium*–complex. Clin Infect Dis. 1994 ; 19 : 84–86.
52) Holland SM, Eisenstein EM, Kuhns DB, et al. Treatment of refractory disseminated nontuberculosis mycobacterial infection with

interferon gamma. A preliminary report. N Engl J Med. 1994 ; 330 : 1348–1355.
53) Levine B, Chaisson RE. *Mycobacterium kansasii* : a cause of treatable pulmonary disease associated with advanced human immunodeficiency virus (HIV) infection. Ann Intern Med. 1991 ; 114 : 861–868.
54) Bottger EC, Teske A, Kirschner P, et al. : Disseminated "*Mycobacterium genavense*" infection in patients with AIDS. Lancet. 1992 ; 340 : 76–80.