PROSPECTIVE STUDY OF PULMONARY COMPLICATIONS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

P R O T O C O L

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Immunodeficiency Virus Infection

Protocol Summary

This study seeks to provide information concerning the pulmonary diseases that occur as a result of infection with the human immunodeficiency virus (HIV). The primary objective of the study is to determine the frequency and types of lung diseases that occur in persons with HIV infection and to describe the course and outcome of these disorders. These diseases or abnormalities may be either secondary to the immunologic abnormalities caused by the virus (opportunistic processes) or the result of the HIV infection itself.

The study will be based in seven Clinical Centers (six in the United States and one in Europe) and will be a prospective, longitudinal evaluation of a cohort of seropositive persons and seronegative control subjects. Seropositive subjects will be stratified into two groups defined by the number of circulating CD-4 cells (≥400 per microliter, <400 per microliter) and the presence or absence of "pre-AIDS" conditions. Evaluations of these three groups will enable identification of the lung diseases that occur at various stages of HIV disease. The "background" prevalence/incidence of various diseases and abnormalities that are related to demographic, environmental, or lifestyle factors, rather than HIV infection, will be determined by evaluation of the seronegative group.

Evaluations will be conducted at regular intervals and when predefined symptoms occur. Screening and diagnostic studies that are of proven value in detecting AIDS-associated lung diseases will be used. Tests will be performed in a uniform manner using standardized techniques among all Clinical Centers. Subjects will be followed for between 3 and 4 years (one year recruitment period and 3 year period of observation) or until death.

As a substudy, the effect of early detection of P. carinii pneumonia on subsequent morbidity and mortality will be evaluated. Seropositive subjects will be allocated at random to either "routine" (testing at 12-

month intervals) or "intensive" (testing at 3-month intervals) evaluations.

Data from all components of the study will be transmitted by all Clinical Centers to a single Coordinating Center. The Coordinating Center will maintain all study-wide data files, will monitor performance of each of the centers, and will coordinate a quality control program that will ensure uniformity of data quality.

Appropriate statistical techniques will be applied in the analysis of data relevant to the various questions being asked.

A variety of carefully designed safeguards will ensure the confidentiality of subject records.

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Protocol

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1. Introduction

It is increasingly apparent that the concept of the "acquired immunodeficiency syndrome" (AIDS) presents a very limited and incomplete picture of the manifestations of human immunodeficiency virus (HIV) infection. Rather, it is more valid from both clinical and epidemiologic points of view to think in terms of "HIV disease", a designation that encompasses the full range of both primary and secondary effects of HIV infection.

Current data indicate that infection with HIV, once established, persists. Although there is a several year period of latency between infection and the onset of symptoms that are clearly attributable to HIV, it appears that there are ongoing, progressive effects on host immune responsiveness. These effects are measurable in part as a decrease in the number of circulating helper T lymphocytes (T-4 or CD-4 cells). The reduction in immune response sets the stage for a variety of opportunistic diseases, some of which are currently considered to be AIDS-defining and mark the end-stages of HIV disease. The point at which opportunistic illnesses occur is probably determined by the interactions of a number of factors, including the status of nonimmunologic host defenses, exposure to or previous infection with specific pathogens, the virulence of these pathogens, and the effects of HIV infection, to name a few. Because of the complexity of these interactions there is no "threshold" before which opportunistic diseases are not seen and beyond which they occur with predictable frequency. Thus, it is likely that, although the frequency and severity of disorders associated with HIV disease occur in crescendo fashion as the end-stages of the infection approach, HIV plays a role in the causation of disease all along the course of the infection.

In addition to the secondary opportunistic processes associated with HIV disease, HIV itself may primarily cause symptoms and organ system dysfunction that contribute to the spectrum of illnesses. Examples of diseases resulting directly from HIV infection include acute "seroconversion" illness, dementia, myelopathy, peripheral neuropathy, and, perhaps, lymphadenopathy and gastrointestinal disease.

Because, as described in Section 3, the lungs are the most frequent sites of AIDS-defining diseases, it is logical to assume that

there may be pulmonary involvement, either primary or secondary, at any point in the course of HIV disease. Although much is known about the pulmonary disorders associated with AIDS, there are very important deficiencies in the available information. These deficiencies are due in large part to clinicians and investigators focusing on those disorders that serve to define AIDS or that occur in patients who have AIDS. There is little or no information that systematically identifies the pulmonary disorders that occur at all stages of HIV disease or that describes the course patients follow after the diagnosis of a lung disease has been established.

2. Primary and Secondary Objectives

The primary objective of this study is to determine the prevalence, incidence, and types of lung diseases that occur in persons in selected HIV transmission categories with and without HIV infection and to describe the course and outcome of these disorders.

Within the context of the primary objective there are several secondary objectives that this study seeks to achieve. These are subsidiary to the primary objective but have importance in their own right.

The secondary objectives are as follows:

1. To identify demographic, clinical, and immunologic and other laboratory variables that are associated with the subsequent diagnosis of specific HIV-related lung diseases;
2. To describe the clinical, radiographic, and pulmonary physiologic, immunologic, and other laboratory variables that are associated with specific HIV-related lung diseases at the time the disease is diagnosed;
3. To determine if there is a difference in the prevalence/incidence of identified pulmonary disease, respiratory symptoms, chest radiographic abnormalities, and rates of decline in pulmonary function in subjects with HIV infection compared with these same variables in subjects from the same HIV transmission categories who do not have HIV infection;

4. To measure the frequency with which HIV-related lung diseases are present in HIV-infected persons who do not have symptoms;

5. To compare survival, days in hospital and functional status in subjects who have had lung diseases diagnosed as a result of intensive screening or evaluation of respiratory symptoms with subjects who have had the same diseases diagnosed as a result of routine screening tests or evaluation of respiratory symptoms.

Appendix 1 lists the questions that the primary and secondary objectives seek to answer together with the variables that will be analyzed and the analytic methods to be used.

3. Background

3.1 Natural history of HIV infection

Substantial evidence now suggests that HIV infection is persistent and generally progressive, producing clinical illness (AIDS or AIDS-related conditions-ARC) in at least a majority of seropositive persons within five years from the time of seroconversion (1). Reported rates of progression to AIDS have been variable. In the San Francisco City cohort 30% of seropositive homosexual or bisexual men developed AIDS at a median of 5 years from the time of seroconversion (1). Goedert and coworkers (2) showed 3 year actuarial progression rates of 34% and 17% in cohorts of homosexual men in New York and Washington whereas Polk and associates (3) reported a crude 15 month progression rate of only 3.2% in a multicenter study of homosexual and bisexual men. One cohort of hemophiliacs showed an 18% rate of progression at 6 years after seroconversion (4). More recently, Moss and associates (5) reported a 3 year actuarial progression rate to AIDS of 22% with an additional 19% developing ARC.

Data from several of these same studies describe indicators that serve to predict the risk of progression to AIDS and, thus, are markers for the stage of HIV disease. In all studies a lower number of circulating CD-4 lymphocytes on enrollment was correlated with an increased rate of developing AIDS. Additionally, a progressive reduction in CD-4 cells was highly associated with the risk of AIDS. Direct relationships with risk of AIDS have been found with beta 2

microglobulin concentration and HIV P-24 antigenemia, and inverse relationships detected with the level of HIV antibody, hemoglobin concentration, and platelet count (3,4,5,6,7). Clinical predictors of progression have also been identified and include the presence of thrush (oral candidiasis) hairy leukoplakia, constitutional symptoms (unexplained fever and weight loss) and persistent unexplained diarrhea.

Particularly noteworthy were the findings by Moss and associates (5) that in the men in their cohort who did not develop AIDS or ARC there, nevertheless, was a progressive decrease in the absolute number of CD-4 cells during the 3 year period of observation. The median CD-4 counts in this subgroup fell from a baseline value of 626 to 428 cells per microliter at the end of 3 years in rather even decrements of approximately 65 to 70 cells per year. This observation is indicative of the chronic progressive nature of HIV disease during a time when it is subclinical.

In all of these natural history studies the occurrence of AIDS, or in some instances ARC, was the outcome of interest. There were no data collected concerning diseases that occurred before the AIDS- (or ARC-) defining condition was diagnosed nor was there continued follow-up after an AIDS diagnosis except to establish dates of death and survival times (8). Thus, by design these studies leave an important void in our understanding of HIV diseases--what happens between the time of HIV infection and the occurrence of AIDS. Given the frequency of pulmonary involvement when AIDS is diagnosed, it is logical to assume that, during the long "latent" period between infection and AIDS, HIV-related lung diseases occur with increased frequency.

3.2 Overview of pulmonary complications of HIV infection

It is well-established that the lungs are the most frequent site of secondary involvement in patients with the acquired immunodeficiency syndrome (AIDS) and that respiratory failure is a common cause of death (9,10,11). Since AIDS was first reported in 1981, Pneumocystis carinii pneumonia has been the most frequent AIDS-defining diagnosis and has been increasing in relative frequency since that time (9). In addition to P. carinii pneumonia a broad range of pulmonary infections, as well as neoplastic and idiopathic diseases, have been reported in patients with HIV infection. As shown in Table 1, some of

Table 1

CURRENTLY RECOGNIZED HIV-RELATED LUNG DISEASE[1]

A. Pulmonary Infections Diagnostic of AIDS
   1. *Pneumocystis carinii* pneumonia
   2. Pulmonary toxoplasmosis
   3. Pulmonary strongyloidiasis
   4. Bronchopulmonary candidiasis
   5. Pulmonary cryptococcosis
   6. Disseminated histoplasmosis or coccidioidomycosis involving lung
   7. Disseminated *Mycobacterium avium* complex or *M. kansasii* involving lung
   8. Cytomegalovirus pneumonia
   9. Herpes simplex pneumonia

B. HIV-Related Pulmonary Infections
   1. Tuberculosis
   2. Nocardiosis

C. Presumed HIV-Related Pulmonary Disorders
   1. Pyogenic bacterial pneumonia
   2. Lymphoid interstitial pneumonitis
   3. Nonspecific interstitial pneumonitis

D. AIDS-Related Pulmonary Neoplasia
   1. Kaposi's sarcoma
   2. Non-Hodgkin's lymphoma

1/ From Ref 11.

these processes serve to define AIDS when they occur in the absence of other causes of immune compromise (and in some instances, when HIV seropositivity is identified). Other of the listed diseases are thought to be associated with HIV infection but are not AIDS-defining. Presumably each of these disorders is related to the immunologic abnormalities produced by HIV infection or is a direct effect of HIV, although the precise pathogenetic mechanisms are poorly understood.

The brief review that follows presents our current understanding of some of the pulmonary diseases that have been noted to occur within the context of HIV infection. Although a substantial amount of information is available concerning some of the disorders associated with AIDS, much less is known about conditions that occur earlier in the natural history of HIV infection (before a diagnosis of AIDS) or subsequent to an initial AIDS-defining pulmonary complication. Moreover, because a variety of interventions directed toward specific pathogens and toward HIV itself are now used commonly, it is likely that the frequency and spectrum of pulmonary complications will be changing in the next few years.

3.3 Pneumocystis carinii pneumonia

Pneumonia caused by P. carinii, either alone or with Kaposi's sarcoma, has served as the index diagnosis in approximately 64% of patients with AIDS and it is estimated that an additional 20% of patients who have had other index diagnoses will subsequently develop P. carinii pneumonia (9). Moreover, 30 to 35% of persons who have had one episode will have at least one subsequent episode (12). Given these percentages, the total number of episodes of P. carinii pneumonia occurring in HIV-infected persons is extremely large, probably exceeding the reported number of patients with AIDS.

Prior to the AIDS epidemic P. carinii pneumonia was diagnosed mainly by open lung biopsy (13). Because of the large number of patients requiring diagnostic studies and because of the morbidity and costs associated with open lung biopsy, this approach was obviously not feasible in the context of AIDS. During the course of the AIDS epidemic, evaluation of patients with respiratory complaints has become progressively less invasive. Relatively early in the epidemic, transbronchial lung biopsy (TTB) performed through a fiberoptic

bronchoscope was found to be a sensitive means of diagnosing P. carinii pneumonia and other opportunistic infections (14,15). Subsequently, bronchoalveolar lavage (BAL) was also shown to be quite sensitive for P. carinii and was associated with fewer complications than TBB (16,17). More recently, examination of sputum induced by inhalation of hypertonic saline has been determined to be useful as a first diagnostic study in selected patients suspected of having P. carinii pneumonia (18,19).

Other tests, including bronchial brush biopsy and transthoracic needle aspiration (TNA) biopsy, have been evaluated for diagnosing P. carinii and other opportunistic processes but have not been found to be superior to TBB and BAL (10,20). Brush biopsy has a lower sensitivity, and TNA has an unacceptable rate of complications when used in patients with diffuse infiltrative diseases. However, in evaluating focal lesions, TNA is of value.

Because even these relatively noninvasive studies carry some risk and discomfort, a variety of screening tests have been used to identify patients for whom specific diagnostic tests are indicated. In addition to chest radiography, pulmonary function tests and gallium lung scans have been reported to be sensitive to the presence of pulmonary disorders, especially P. carinii pneumonia, in patients with AIDS (21,22,23). When abnormal, these tests provide an objective indicator of lung disease, thereby corroborating symptoms reported by patients.

These same screening studies are also of value in following the course of P. carinii pneumonia, tending to return toward normal after treatment (24). However, diagnosis of second and further episodes may be confounded by residual abnormalities on chest films, pulmonary function tests, and to a lesser extent, gallium scans. In addition, P. carinii has been found to persist in lung-derived specimens from patients who have been treated successfully (25,26), thus making the diagnosis of subsequent episodes problematic.

There are three drug regimens that are of proven efficacy in treating P. carinii pneumonia: trimethoprim-sulfamethoxazole (TMP-SMX), pentamidine, and trimethoprim-dapsone. TMP-SMX and pentamidine are of equal efficacy and have equal rates of adverse reactions (27). Mortality rates for first episodes of P. carinii treated with either agent are approximately 20% and adverse reactions occur in nearly 50%.

Trimethoprim-dapsone has been used only in patients with mild to moderate forms of the disease and, consequently, reported mortality rates in patients treated with this combination are much lower, as are the rates of adverse reactions (28).

Data reported by Brenner and associates (29) have shown a lower short and long term mortality rates for patients diagnosed with P. carinii pneumonia after July 1985 compared with patients diagnosed before that date. There was no difference in the drug regimens used during the two periods. These investigators attributed this finding to earlier detection of the disease, at a stage when it was more responsive, in the patients treated after July 1985.

Because of the relatively poor rate of success and the high frequency of adverse reactions to TMP-SMX and pentamidine, alternative regimens are being investigated. Pilot trials have reported success using pentamidine aerosol, trimetrexate with and without sulfadiazine, and difluoromethylornithine (30,31,32). The potential roles of these regimens in treating P. carinii pneumonia remain to be defined.

Prevention of P. carinii is also an area of active investigation. Fischl and colleagues (33) have reported that TMP-SMX given prophylactically to HIV-infected persons not only reduced the frequency of P. carinii pneumonia but also significantly prolonged life. Similarly, preliminary data from Leoung and coworkers (34) and Feigal and associates (35) strongly suggest that aerosol pentamidine is effective in decreasing the incidence of P. carinii pneumonia in selected groups of patients with HIV infection. As with experimental therapies for P. carinii pneumonia, the role, general applicability, and impact of these preventive regimens have not yet been defined.

In addition to specific prophylaxis for P. carinii, the antiviral agent, azidothymidine (AZT), also decreases the incidence and severity of P. carinii pneumonia in selected groups of HIV-infected persons (36). It might be anticipated that more widespread use of AZT will in itself decrease the overall frequency of P. carinii pneumonia.

3.4 Mycobacterial Diseases

3.4.1 M. avium complex

Early in the course of the AIDS epidemic it was recognized that a nontuberculosis mycobacterium, M. avium complex, was isolated

frequently from patients with AIDS (37). Data from the Centers for Disease Control indicate that disseminated M. avium complex infection has been reported at the time of AIDS diagnosis in 4.5% of patients (9). Commonly the organism is isolated from blood and/or bone marrow (37). The lungs are involved less frequently (10), Autopsy series have suggested that as many as 53% of patients with AIDS have M. avium complex, usually isolated from multiple organs, at the time of death (38).

The infection is characterized histologically by huge numbers of organisms within involved tissues with there being little or no inflammatory response. This observation is perhaps a reflection of the fact that M. avium complex infection tends to be diagnosed late in the course of AIDS, when the immunosuppression is far advanced.

Data from Demopulous and coworkers (39) suggest that M. avium complex infections do not influence the overall course of AIDS, at least in terms of median survival. However, these investigators found that there was an increased blood transfusion requirement in patients with disseminated M. avium complex.

The role of M. avium complex in causing lung disease in patients with AIDS is not clear. Although M. avium complex may be isolated from lung-derived specimens, the functional and prognostic implications of this have not been determined.

Treatment of M. avium complex infections is especially problematic even in nonimmunosuppressed hosts. In patients with AIDS a variety of drug regimens have been used but success has been infrequent (38). Most patients who have had M. avium isolated from blood have continued to be bacteremic and at autopsy multiple organs have contained organisms in spite of aggressive chemotherapy.

3.4.2 Tuberculosis

Tuberculosis is also recognized as an opportunistic disease in patients with HIV infection (40,41,42). Given the nature of the defect in cell mediated immunity caused by HIV infection, the occurrence of tuberculosis in persons infected with both M. tuberculosis and HIV is predictable. Current information indicates that tuberculosis tends to occur relatively early in the course of HIV infection, presumably

because of the greater pathogenicity of M. tuberculosis compared with P. carinii or M. avium complex. Thus when tuberculosis occurs it commonly is the first symptomatic evidence of immunosuppression. For this reason, in populations at risk for infection with both HIV and M. tuberculosis the incidence of tuberculosis may serve as a useful epidemiologic indicator for the prevalence of HIV infection.

Epidemiologic data suggest that tuberculosis is much more likely to occur among groups of HIV-infected persons in which there is a high prevalence of tuberculous infection. Such groups include intravenous drug users and persons from parts of the world where tuberculosis is highly prevalent (43). It is likely that tuberculosis is the dominant HIV-related opportunistic disease in Central and Eastern Africa (44). However, there are no data either from the United States or developing countries that adequately describe the prevalence of tuberculosis among HIV-infected groups. A retrospective evaluation of intravenous drug users in New York City showed that 4.3% of those infected with HIV developed tuberculosis in a 2 year period whereas there were no cases among HIV seronegative drug users (43). These data, however, could not be assumed to be representative because of the retrospective nature of the evaluation and the population examined.

Also in New York City, matching of AIDS and tuberculosis case registers showed that 5% of adult and adolescent AIDS patients diagnosed from 1981 through 1985 had tuberculosis. In San Francisco, matching of the two case registries for the same time period showed that 2% of patients with AIDS had tuberculosis (42). Each of these studies may be misleading in that patients were identified by their having AIDS rather than HIV infection. Thus, a substantial amount of tuberculosis associated with HIV infection in persons who had not yet progressed to AIDS could have been overlooked.

Tuberculosis in the setting of HIV infection is of considerable importance for several reasons. First, it is the only one of the common HIV-associated diseases that can be transmitted to persons not infected with HIV, thus worsening the overall tuberculosis epidemiologic situation. Second, tuberculosis (as opposed to M. avium complex infection) is easily treated (45). Third, if a person is identified as being infected with both HIV and M. tuberculosis, tuberculosis is probably preventable by treatment with isoniazid (46).

The clinical presentation of tuberculosis in persons with HIV infection depends in part on the degree of immunosuppression. Early in the course of HIV infection the manifestations of tuberculosis are rather typical (45). Persons with more advanced HIV disease tend to have atypical presentations with multiorgan involvement, no cavitation on chest film, and tuberculous bacteremia (42). The tuberculin skin test response also varies with the degree of immunosuppression and, thus, is still useful in diagnosing tuberculous infection at least early in HIV disease. The diagnosis of tuberculosis depends on the identification of M. tuberculosis in specimens from involved organs. Sputum smears and cultures are of value since the proportion of HIV-infected patients who have positive smears and cultures is essentially the same as nonHIV-infected patients who have pulmonary tuberculosis (41,45).

In general, patients with tuberculosis and HIV infection respond well to standard antituberculosis treatment. However, available data suggest that rates of adverse reactions during treatment and relapse after treatment may be increased compared with nonHIV-infected patients (42,47). Current recommendations are that patients be treated for a minimum of 9 months or 6 months after sputum conversion has occurred (46).

3.4.3 Other nontuberculous mycobacteria

Small numbers of patients with disease caused by nontuberculous mycobacteria other than M. avium complex have been described. Disseminated M. kansasii has been reported at the time of diagnosis of AIDS in 0.2% of patients. Disseminated disease caused by M. xenopi and M. gordonae have also been reported. Because of the small numbers of cases, the clinical manifestations of these infections and the response to therapy are not well described.

3.5 Fungal Infections

Cryptococcus neoformans, Coccidioides immitis and Histoplasma capsulatum are the three most common fungal pathogens to involve the lungs in patients with HIV infection. Cryptococcosis is the fourth most common opportunistic infection in patients with AIDS, occurring in 6 to 13% of patients, often as the presenting illness (48). Although the central nervous system is involved most commonly, the lungs are the next

most frequent site of disease, either alone or as part of a disseminated process. The lung disease may present as focal masses or nodules, lobar pneumonia, or interstitial pneumonia. Pleural effusion may also occur with or without lung parenchymal involvement.

The diagnosis of pulmonary cryptococcosis is established by microscopic identification or culture of the organisms in lung tissue, BAL or sputum. The infection may be strongly suspected when there is an undiagnosed lung disease and the serum cryptococcal antigen is positive; however, the frequency of antigen detection in patients with isolated lung involvement is not well defined.

Amphotericin B is the treatment of choice for cryptococcosis. The optimal duration is not known and the rate of response of pulmonary disease is not described. Relapse after treatment is terminated seems very common. For this reason maintenance therapy with amphotericin B given 3 times a week is recommended.

Both histoplasmosis and coccidioidomycosis occur in disseminated form in patients with AIDS (49). Because both H. capsulatum and C. immitis are endemic to specific areas, diseases caused by these organisms are far more common in these areas. However, because both diseases usually occur as recrudesences of previously acquired infections, they may be diagnosed long after a person has left an endemic area.

The lungs are nearly always involved in disseminated histoplasmosis and coccidioidomycosis. This involvement may produce diffuse or focal infiltration on the chest film with intrathoracic adenopathy seen commonly. Diagnosis is established by microscopic identification and/or culture of the organism from lung-derived specimens. Serologic tests appear to be less reliable in patients with AIDS than in non-immunocompromised patients.

As with cryptococcosis, amphotericin B is used for treating for both histoplasmosis and coccidioidomycosis. However, lasting cure is uncommon and lifelong suppressive therapy with either amphotericin B or ketoconazole is probably indicated.

Fungal lung infections other than those caused by C. neoformans, H. capsulatum, and C. immitis have been very unusual. Although oral candidiasis occurs in a large percentage of patients with

AIDS and other opportunistic infections, the lungs are rarely involved. A few patients with disseminated aspergillosis have been reported, but the disease is less common than would be expected from its frequency in other immunosuppressed patients.

3.6 Bacterial Infections

Although the dominant immunologic abnormality caused by HIV infection is a reduction in cell-mediated immunity, B-cell defects also occur and result in impairment of humoral immunity. As a consequence there is an apparent predisposition to more frequent and more severe infections with certain pyogenic bacteria, particularly S. pneumoniae and H. influenzae (50,51). The frequency of pyogenic bacterial pneumonia in HIV-infected persons has not been well-defined. Polsky and associates (51) reported that 10% of pneumonias in AIDS patients at Memorial-Sloan Kettering Hospital were bacterial, mainly S. pneumoniae and H. influenzae. In the only prospective study reported, Selwyn and colleagues (52) found that 14 of 159 (9%) HIV seropositive heroin addicts developed bacterial pneumonias in a 12 month period compared with 6 of 277 (2%) seronegative addicts. Again, these pneumonias were primarily due to S. pneumoniae and H. influenzae.

Other bacterial agents have also been reported to cause lung infections in HIV-infected patients, although their frequency and the relationship to the HIV infection is not clear. These include S. aureus, B. catarrhalis, Legionella species, M. pneumoniae and Corynebacterium equi.

The presentation of bacterial pneumonia in HIV-infected patients tends to be similar to the presentation in nonHIV-infected persons (50). However, the pulmonary involvement tends to be more severe and bacteremia is common. The diagnosis is established in the usual manner by isolating the organism from lung-derived specimens or blood.

Treatment with antibacterial agents is probably associated with rates of success similar to those seen in nonimmunocompromised patients. However, relapse or multiple episodes seem to be common. The effectiveness of pneumococcal vaccine in HIV-infected persons has not been evaluated, but failures have been reported.

3.7 Viral Infections

Infection with cytomegalovirus (CMV) is extremely common in patients with HIV infection and can result in a variety of clinical illnesses, including pneumonia. Although CMV is frequently isolated from lung derived specimens, its role in causing lung disease either alone or as a coinfection is not well defined (10,11,53). In patients with P. carinii pneumonia the isolation of CMV or the finding of CMV inclusion bodies does not seem to be of significance in terms of altering the course of the P. carinii pneumonia (53). There are, however, patients who have objective evidence of progressive lung disease in whom only CMV is identified, who respond to treatment with ganciclovir, and, thus, appear to have CMV pneumonia. Clinically and radiographically these patients present in a similar fashion to P. carinii pneumonia or other opportunistic infections.

Other viruses have been isolated from lung-derived specimens and have been thought in some instances to account for lung disease. These have included herpes simplex type I, adenovirus, and Epstein-Barr virus.

3.8 Miscellaneous Infections

Small numbers of patients with lung disease caused by other organisms have been reported. These include Strongyloides stercoralis, Toxoplasma gondii, and Nocardia species. It is likely that strongyloides is more common in areas where the parasite is endemic, but its true frequency is not known.

3.9 Neoplastic lung diseases

The recognition of an unusually high frequency of Kaposi's sarcoma was the first clue to the AIDS epidemic, and this tumor continues to be a common index diagnosis as well as the most frequent AIDS-associated malignancy. Other malignancies that are clearly related to HIV include primary central nervous system lymphoma, and high-grade B-cell lymphoma (54). Squamous cell carcinomas of the oral cavity and anus and Hodgkin's lymphomas are thought perhaps to be associated with HIV and there is speculation that squamous cell carcinoma of the lung, squamous cell carcinoma of the esophagus, and melanoma also may be associated (54).

Kaposi's sarcoma is multicentric and most prominently involves the skin, but virtually any organ system may be involved. The frequency with which pulmonary involvement occurs is not known but, generally, lung disease is present in patients who have extensive cutaneous lesions. The radiographic presentation of Kaposi's sarcoma may be identical to that of opportunistic infections; however, the presence of pleural effusions and intrathoracic adenopathy suggest the diagnosis. Visualization of typical endobronchial lesions at bronchoscopy is diagnostic (55). Biopsy of these lesions may be difficult and may not show typical cellular abnormalities.

It is generally thought that patients with pulmonary Kaposi's sarcoma have a very poor prognosis but the natural history is not defined. Response to chemotherapy is usually poor, although some patients have transiently improved with aggressive treatment (56).

B-cell lymphomas in patients with HIV infection may involve pleura, intrathoracic lymph nodes, and lung parenchyma. Pulmonary parenchymal involvement may take the form of solitary or multiple mass lesions or, rarely, interstitial infiltration.

The overall response to treatment of HIV-associated B-cell lymphomas is not as good as seen in nonHIV-infected patients. In the report by Ziegler and coworkers (57) the major determinant of prognosis seemed to be the status of the HIV infection at the time treatment was started. The specific response of the pulmonary component is not described.

3.10 Idiopathic Lung Diseases

Two patterns of histologic abnormalities have been noted in patients with what is presumed to be an HIV-related lung disease in whom no specific etiology is detected. These have been termed lymphoid interstitial pneumonia (LIP) and nonspecific interstitial pneumonia (NIP) (58,59).

Lymphoid interstitial pneumonia has been previously noted to occur in association with immunodeficiency states and autoimmune disorders, although its pathogenesis in these situations is not known. This disorder seems to be more common among children with HIV infection and serves as an AIDS-defining condition in children less than 14 years of age who have a positive HIV serology.

LIP is characterized histologically by lymphocytic infiltration of lung parenchyma with formation of peripheral lymphoid aggregates. Fibrosis may also be present. Because the diagnosis is based on finding a specific histologic pattern, lung tissue is necessary to define the process. Transbronchial biopsy may be adequate for diagnosis, but open biopsy is more likely to show the typical histologic abnormalities.

The natural history of LIP in the setting of HIV infection is not known but it appears that spontaneous improvement may occur. Response has also been related to corticosteroid therapy.

Nonspecific interstitial pneumonitis was reported to be the diagnosis in 38% (41/110) of AIDS patients with pneumonitis described by Suffrendi and associates (59). This histologic pattern is characterized by diffuse alveolar damage, increased numbers of intraalveolar macrophages, alveolar hemorrhage and occasional lymphoid aggregates without any pathogens being identified. In 28 of the 41 patients, possible causes, including drug therapy and previous episodes of pneumonitis, were identified whereas in 13 there was no evident alternative explanation for the condition. In general, the abnormalities on chest film were less severe than those found in patients with P. carinii pneumonia with 50% of the patients having normal chest films. In most of the patients the disease was either stable or showed spontaneous improvement but the natural history was not defined. It is speculated that both LIP and NIP are caused by unidentified viruses such as cytomegalovirus, Epstein-Barr virus or HIV itself. Although HIV has been cultured from lung specimens in patients with LIP and NIP, proof of the etiology is lacking (60,61).

Also unexplained is the finding by Gullion and coworkers (62) of a lymphocytic alveolitis (defined as > 15% lymphocytes on BAL) in 27 (59%) of 46 HIV-infected subjects who had no respiratory symptoms, normal chest films and no lung infections or neoplasia. The mean percentage of lymphocytes was greater in symptomatic patients and in patients with radiographic abnormalities. Respiratory symptoms were consistently present when the proportion of lymphocytes was greater than 35%. Overall, 88 (72%) of 122 HIV-infected individuals without evidence of infectious or neoplastic lung disease had a lymphocytic alveolitis. These data suggest that the lungs may be involved early in the course of HIV infection and produce both symptomatic and asymptomatic processes.

Additional, albeit more inferential, information concerning idiopathic processes in HIV-infected persons was provided by Shaw and associates (63). These investigators found that the transfer factor for carbon monoxide was normal in HIV seropositive patients with no respiratory symptoms (this group included patients with lymphadenopathy) but that patients with symptomatic HIV infection apparently not involving the lungs (ARC, nonpulmonary Kaposi's sarcoma and other symptomatic processes) had abnormal values. As with the findings on BAL described by Gullion and coworkers, these observations suggest early asymptomatic lung involvement associated with HIV infection without identifiable secondary processes.

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4. Rationale

As reviewed previously, the lungs are known to be the most frequent site of secondary involvement in patients with AIDS, and there is compelling evidence that nonAIDS-defining conditions such as tuberculosis and pyogenic bacterial pneumonias occur with increased frequency in the presence of HIV infection. Moreover, the studies of Gullion and associates (ref 62, Section 3) suggest that there are pulmonary abnormalities detectable by BAL in "healthy" asymptomatic HIV seropositive persons. No etiology for the lymphocytic alveolitis described by these investigators was identified, but it was speculated that it may have been caused by HIV.

The report by Shaw and coworkers (ref 63, Section 3) of abnormalities in pulmonary function detected in patients who had no respiratory symptoms but who had otherwise symptomatic HIV infection also is suggestive of the presence of an as yet unappreciated pulmonary disorder (or disorders) associated with HIV infection. Patients with CDC class IV A, B, C2 and E HIV-related disease (e.g., nonpulmonary) had a mean value for the carbon monoxide transfer factor that was significantly lower than the value for asymptomatic HIV seropositive subjects. Again, because no specific disease could be diagnosed the investigators speculated that these findings might be due to HIV itself.

In neither study was there longitudinal evaluation of the patients to describe the evolution of their findings or to determine if a specific lung disease was eventually diagnosed.

The reports of both LIP and NIP also suggest that there are pulmonary diseases associated with HIV infection that might be due to HIV itself. Again, the natural history of these processes has not been elucidated and the implications of finding LIP and NIP for the eventual course of HIV disease have not been determined.

A prospective longitudinal evaluation of a cohort of persons with HIV disease at various stages in its evolution as described in this protocol can identify the spectrum of pulmonary disorders associated with HIV infection and describe their "natural" history. Both screening and diagnostic studies that are of proven value in the evaluation of patients who are suspected of having HIV-related pulmonary disorders will be applied in a uniform manner according to predefined criteria.

By so doing the findings will be comparable among the centers participating in the study and, thus, will provide a much broader picture of the full range of lung disorders in a variety of HIV transmission categories and geographic areas than currently exists. Designing the study cohort to include persons in the major HIV transmission categories should enable determination of differences in the relative and absolute frequencies of lung diseases in these groups.

Continued use of standardized pulmonary evaluations and careful clinical follow-up will provide a description of the patient's course after a lung disease has been diagnosed and will identify the disorders that occur subsequent to an initial pulmonary disease. Within the context of the study the utility of tests to identify second and subsequent episodes of P. carinii pneumonia will be determined.

The subjects in the cohort will be characterized by clinical features and immunologic tests that previous epidemiologic studies have shown to be predictive for the subsequent development of AIDS. Correlation of the results of these tests with pulmonary abnormalities will enable identification of variables that are associated with or predictive of specific lung disorders.

As noted in Section 3, it is likely that the spectrum of lung diseases associated with HIV infection will change as antiviral therapy and various preventive treatments for P. carinii pneumonia and tuberculosis become more widely applied. Having a prospective surveillance system in place in which a uniform series of diagnostic studies is applied in a defined manner over a period of several years should serve to identify changes in the absolute and relative frequencies of the lung diseases associated with HIV infection.

Although the existing data strongly suggest a broader range of lung diseases associated with HIV infection than is currently recognized, it is not clear that infection with HIV is the only determining factor in all instances. It is possible that the apparent increased incidence of processes such as pyogenic pneumonias, tuberculosis, lymphocytic alveolitis, etc. may be related to "lifestyles" or practices such as intravenous drug use, inhalation of nitrates, or other as yet unidentified factors. For example, it is well established that both intravenous and inhalational drug use cause lung

disease. Thus, establishing associations between HIV infection and the various nonAIDS-defining lung diseases necessitates evaluation of persons from HIV transmission categories who do not have HIV infection.

Inclusion of an HIV seronegative control group not only enables comparisons of the incidence of various lung diseases, but also provides inferential information concerning the possibility of HIV itself causing lung disease. If there is an excess prevalence of respiratory symptoms, radiographic findings and abnormalities in pulmonary function tests that cannot be attributed to identifiable lung diseases, one inference would be that HIV itself was causing the findings. Such an observation would provide the rationale for a more specific directed study seeking to answer the question, "Is HIV a direct cause of lung disease?".

The potential value of screening asymptomatic HIV seropositive subjects for the presence of P. carinii is of great interest to both investigators and clinicians. For example, Brenner and associates (ref 29, Section 3) found improved short and long term survival in patients with P. carinii pneumonia that was diagnosed after July, 1985 compared with survival in patients diagnosed before that date. They attributed the improvement to earlier diagnosis, at a time when the disease was less severe. However, this would not explain improved long term survival, and, it is possible that lead-time bias accounted for the apparent increased longevity. Alternatively, early treatment may minimize the impact of P. carinii pneumonia on the overall course of the HIV disease. The present study seeks to evaluate this latter possibility by intensively screening a randomly selected subset of subjects and comparing subsequent morbidity and mortality with these variables in a routinely evaluated group.

Clearly, new information leading to a broader understanding of the pulmonary diseases that are associated with HIV infection would be of major importance with relevance to both clinical and epidemiologic aspects of HIV disease. Both predictors and patterns of pulmonary diseases will be identified, enabling more accurate empiric diagnoses and earlier therapy. The data will also be useful in planning for long term management of patients and assessing the magnitude and types of resources necessary in the future. As with most natural history studies, questions will be raised that can then be addressed more specifically by targeted studies.

5. Study Design

This study is designed to identify the lung diseases that occur in patients with all stages of HIV infection and to describe the "natural history" of these processes. Patients will be managed with current standard or approved experimental care, thus, the course described will be that of the treated process, not the true natural history. To accomplish this objective a cohort of subjects with HIV infection and an HIV seronegative control group will be prospectively evaluated in six centers in the United States and one in Europe. Seropositive study subjects will be stratified into two groups: Group A subjects will consist of persons who have not had symptoms or diseases likely to be associated with HIV infection as specified in Table 2 and will have $\geq$ 400 CD-4 cells per microliter; Group B subjects will be identified by having either clinical findings or $<$ 400 CD-4 cells per microliter or both. Seronegative control subjects (Group C) will be enrolled concurrently. Screening and diagnostic studies will be applied in a uniform fashion at predetermined intervals, and when symptoms or findings suggestive of lung disease are noted. Each subject will be followed for between three and four years (depending on date of entry) or until death and data describing the course and outcome of pulmonary processes will be collected over the full duration of the study. All data will be collected on standard forms and will be transmitted to the Coordinating Center (CC) where studywide computer files will be maintained.

Stratification of seropositive study subjects by level of CD-4 cells and the presence or absence of HIV-related clinical manifestations will provide a spectrum of severity of HIV infection and consequently lower and higher risks of developing HIV-related lung diseases. It is anticipated that Group A subjects will be more likely to manifest pulmonary disorders that do not serve to define AIDS (Table 1), that occur earlier in the course of HIV infection, and that may be underappreciated by most clinicians. Examples include pyogenic bacterial pneumonias and tuberculosis. In addition, it is primarily in this group that evidence of lung disease that might be caused by HIV itself will be sought.

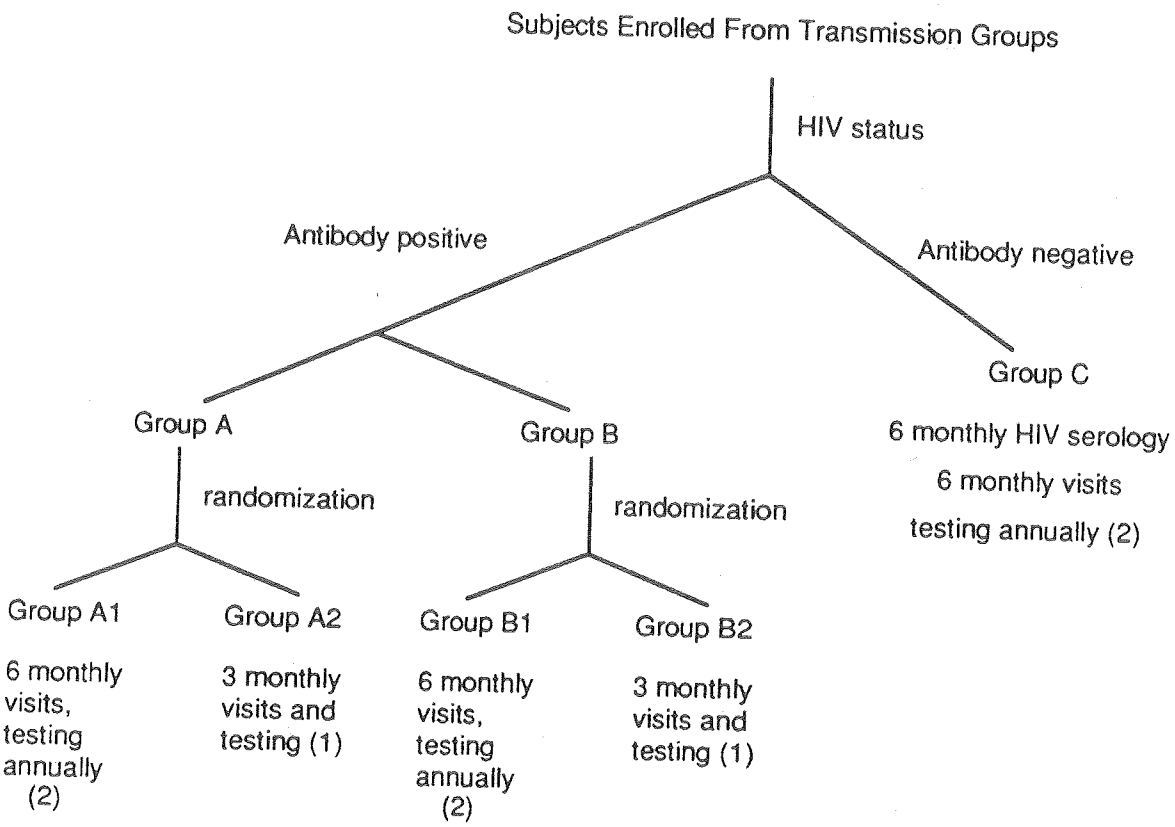
Group B subjects, as indicated by their having clinical or laboratory findings indicative of more severe immunosuppression (Table 2), will be at greater risk of developing HIV-associated, often AIDS-defining, lung diseases. It is anticipated that studies of individuals in Group B will serve to determine the natural history of the AIDS-defining processes and to describe the diagnostic features of second and subsequent episodes of P. carinii pneumonia. Because it is estimated (from the data of Moss et al) that approximately 5% of Group A and 20% of Group B patients will develop an AIDS-defining condition each year, in most instances P. carinii pneumonia, a specific group of subjects with existing AIDS will not be recruited.

Inclusion of an HIV-seronegative control group will be necessary to determine if diseases and abnormalities in pulmonary function that are anticipated in Groups A and B are related to the HIV infection or may be caused by lifestyle or other factors independent of HIV infection. Group C will be composed of homosexual/bisexual men and intravenous drug users and will be matched by age, race, and sex with Groups A and B. Homogeneity of transmission group distribution and matching characteristics between Group C and Groups A and B will be continuously monitored by the Coordinating Center with appropriate feedback to the Clinical Centers.

To determine the feasibility and impact of early diagnosis of P. carinii pneumonia subjects in Groups A and B will be assigned at random to equal size groups for either "intensive" (3 month intervals) or "routine" (12 month intervals) testing. Figure 1 describes the group assignments and follow-up intervals.

Figure 1

Group Assignments and Follow-up



(1) Intensive evaluation with history, physical examination and testing every 3 months.

(2) Routine evaluation with history and physical examination every six months and testingevery 12 months. (See Table 6 for list of tests.)

Definition of Study Groups

Group A: HIV seropositive. No symptoms or findings attributable to HIV. CD-4 cells ≥ 400 per microliter.

Group B: HIV seropositive. Either clinical manifestations attributable to HIV within the past 6 months (thrush, hairy leukoplakia, fever >38° C persisting > 2 weeks, involuntary weight loss > 10% of baseline, or diarrhea persisting >1 month) or CD-4 cells < 400/microliter or both.

Group C: HIV seronegative homosexual/bisexual men or intravenous drug users.

6. Anticipated Problems

There are a number of substantial problems, common to studies of persons with HIV infection, that confront this study. A major problem is the lack of information that quantifies the incidence/prevalence of the various pulmonary diseases associated with HIV infection. Accurate, representative data exist only for P. carinii pneumonia. Thus, the only disease upon which estimates of necessary sample size can be made is P. carinii pneumonia. To further compound this problem, it is likely that with wider use of antipneumocystis preventive therapy and AZT the incidence of the disease will decrease.

Very limited retrospective data suggest that the incidence of tuberculosis in HIV-infected intravenous drug users in New York is approximately 2% per year, but this proportion could not be applied to the study cohort as a whole. Similarly, limited data are available for bacterial pneumonias in intravenous drug users. Again, however, it likely would be misleading to apply these data to the study cohort.

As a consequence of these problems, part of the primary object of the study is to determine the incidence of the various diseases and to ascertain if a shift in their absolute and relative frequencies is occurring.

It is also possible, especially if the incidence of P. carinii decreases and subsequent mortality and morbidity decline, that the sample size will be too small to detect differences between the

intensive and routine groups. Given the practical limits on the size of the cohort this problem may prove to be insoluble. However, failing to achieve this secondary objective will not detract in a major way from the overall value of the study.

A second important problem relates to the lack of control of therapy for subjects in the study. It would be neither ethical nor practical for the study to control or limit therapies that are applied to study subjects. This includes both standard and alternative treatments. The study is not designed to serve as the source of primary care for subjects in the cohort. Moreover, because of the multiplicity of clinical trials in which HIV-infected patients participate, it is possible that the evaluation of course and outcome of the various diseases will be influenced by variations in effectiveness of therapy. The magnitude of this potential effect is not known. However, efficacies of current therapies for P. carinii pneumonia are nearly equivalent and experimental therapies are expected to be at least as effective as standard regimens.

Similarly, the lack of control over therapy will confound the interpretation of the results of comparing the intensive versus the routine groups. Again, however, the near equivalence of treatment regimens should enable valid conclusions to be derived. Essential to accomplishing this part of the study is ensuring that all information related to treatment, course and outcome be collected accurately and completely.

Also anticipated to present a problem is the cohort's (especially intravenous drug abusers) compliance with study procedures. However, the centers contributing the largest number of intravenous drug users also have extensive experience in dealing with this difficult group. Procedures designed to maintain compliance are detailed in Section 7.1.7.

7. Methods

7.1 Study Population

7.1.1 Composition of cohort

The cohort will consist of three groups of subjects (Table 2): Group A, HIV seropositive subjects who have ≥ 400 CD-4 cells and no

clinical manifestations of HIV infection; Group B, HIV seropositive subjects with < 400 CD-4 cells and/or clinical manifestations of HIV infection; and Group C, HIV seronegative homosexual/bisexual men and intravenous drug users.

Each Clinical Center will recruit a study population that is approximately representative of the HIV transmission categories in their locales. The categories include homosexual/bisexual men, intravenous drug users, and seropositive women who have no risk factors other than sexual contact with presumed HIV infected men. For purposes of analysis, each transmission category will be examined separately.

Target quotas have been established for the study as a whole and for each Clinical Center. Table 3 shows the transmission category quotas for each of the eight centers. The apportioning of subjects among the three groups (A, B, C) and transmission categories will be monitored by the Coordinating Center, and the Clinical Centers will be guided in recruitment to reach their quotas. Because the study is not intended to be population-based, no attempt is made to enroll a truly representative group or a predetermined number of consecutive subjects.

Table 3

Target Quotas for HIV Transmission Categories by Center

	H/B(1)	IVDU(2)	Partners(3)	Total
New York	130	60	10	200
Newark	0	190	10	200
Detroit	140	40	20	200
Chicago	180	10	10	200
San Francisco	170	20	10	200
Los Angeles	180	10	10	200
Frankfurt	150	40	10	200
	950	370	80	1400

(1) H/B = Homosexual/Bisexual men

(2) IVDU = Intravenous drug user

(3) Partners = Seropositive female sexual partners of HIV infected men

7.1.2 Inclusion criteria

1) Membership in an HIV transmission category: homosexual/bisexual men, intravenous drug users, seropositive female partners of presumed HIV infected men.
2) Willing to have HIV antibody status determined.
3) Willing to have evaluations for symptoms or findings suggestive of pulmonary disease performed in one of the Clinical Centers.
4) Willing and able to provide informed consent.
5) Willing to be informed of HIV antibody status as required by Federal regulations.

7.1.3 Exclusion criteria

1) Younger than 18 years
2) Presence of a nonHIV-related process likely to affect survival
3) Judged unwilling or unable to cooperate with the study protocol
4) Use of immunosuppressive therapy (Table 4) within the past six months
5) Presence of an underlying disorder that makes future use of immunosuppressive therapy likely
6) Lung disease that may interfere with evaluations (Table 4)
7) Presence of pulmonary symptoms at baseline evaluation (Table 4) either new symptoms or a worsening of chronic symptoms
8) Current or previous AIDS-defining diseases (Subjects who meet all inclusion criteria and have no exclusion criteria yet have an AIDS-defining disease diagnosed on the initial evaluation will not be excluded.) (Table 4)
9) (Applies only to female partners of HIV infected men) Receipt of blood or blood products or intravenous drug use in past 10 years

NonHIV-related processes likely to interfere with four-year survival include incurable neoplastic diseases, and severe cardiac, liver and renal disease. Such illnesses not only reduce the likelihood that the patient will complete the study, they also represent Table 4

Excluding Conditions and Therapies

1. Immunosuppressive therapy within previous 6 months.
   - Corticosteroids (systemic administration of >15 mg prednisone or equivalent amount of other preparation for >14 days)
   - Cytotoxic agents
   - Antimetabolites Cyclosporin

2. Lung diseases that may interfere with evaluation
   - Pneumonia, any cause, within 3 months
   - Invasive pulmonary fungal infection diagnosed within the past 12 months or continuing to receive treatment for such infection
   - Pulmonary mycobacterial disease diagnosed within the past 12 months or continuing to receive therapy for the disease
   - Diagnosed diffuse fiberoptic lung disease or sacroidosis.

3. Respiratory symptoms
   - Unexplained cough that persists for more than five days
   - Unexplained breathlessness progressive over ≥ five days or severe ≥ one day

4. AIDS-defining diseases (MMWR 1987;37:45) (Appendix 10)

Items 1-12	Section I-B	CDC definition
Items 1-12	Section II-A	CDC definition
Items 1-7	Section II-B	CDC definition

Note: Potential study subjects who at the time of initial evaluation are excluded because of any of the exclusions listed above (1-3), except fibrotic lung disease or sarcoidosis may be reevaluated for study entry after an appropriate time interval.

considerable confounding factors in the interpretation of diagnostic studies and natural history data.

Circumstances decreasing the likelihood or capability to adhere to the protocol include the presence of advanced dementia or active psychosis, past history of poor compliance with medical regimens, recent criminal behavior, and plans to relocate during the study period.

The administration of immunosuppressive therapy, including systemic corticosteriods, antimetabolites, cytotoxic agents, and radiation therapy would cause unacceptable confounding of the results because of their potential for direct pulmonary toxicity and their predisposing towards pulmonary infection.

Inclusion of individuals with current or previous AIDS-defining diseases would greatly diminish the study's ability to characterize the early natural history of pulmonary complications. It is anticipated that sufficient numbers of subjects will develop pulmonary complications during the course of the study that the later stages of the natural history can be evaluated adequately.

The presence of current lung diseases would confound the interpretation of many of the evaluations designed to determine if HIV-associated lung disease is present.

7.1.4 Sample size

The determination of sample size was based on: 1) guidelines initially provided in the RFP regarding the total number of subjects to be studied; 2) estimated rates of drop-outs; and 3) the precision that can be achieved in making estimates of key data desired for the study. Each of the 7 Clinical Centers will enroll at least 200 subjects during the first year of the study. All subjects who meet the definition of drop-out within the first 12 months of enrollment will be replaced, hence, the study population will total 1,400 at the end of month 21. Table 5A shows the expected numbers of subjects to be enrolled in the 1st year for the entire study by clinical subgroup and transmission category.

Table 5A

NUMBER OF STUDY SUBJECTS BY CLINICAL STATUS AND TRANSMISSION CATEGORY TO BE RECRUITED

	A	B	C	Total
H/B(1)	405	405	140	950
IVDU(2)	155	155	60	370
Partners(3)	40	40	0	80
Total	600	600	200	1400

(1) H/B - Homosexual/Bisexual males

(2) IVDU - Intravenous Drug Users

(3) Partners - Seropositive female sexual partners of HIV infected men

The distribution of subjects entered into the study will be monitored by the Coordinating Center with quotas fixed for the subjects in the two HIV seropositive groups and the seronegative group. These relative proportions will be the same for each Clinical Center. The number of subjects from each transmission category will also be monitored by the Coordinating Center and reported periodically to the Clinical Centers. The proportion of patients in each transmission category for the entire study is based on a compilation of estimates for the relative proportion of subjects to be recruited at each Center as shown in Table 3.

The target quotas by study group for each Clinical Center are Group A-85, Group B-85, Group C-30.

Rates of lost to follow-up from several cohorts of HIV seropositive intravenous drug users and gay men have ranged from approximately 12% to 20%. Because most losses are expected to occur in the first year (and these will be replaced), it is anticipated that a total of 1,231 patients will be maintained in the cohort (lost to follow-up rate = 12%). The sample size/precision calculations were based on a total sample size of 1,231. Table 5B shows the anticipated numbers remaining for analysis at completion of the study.

Table 5B
NUMBER OF STUDY SUBJECTS BY CLINICAL STATUS AND TRANSMISSION CATEGORY TO BE ANALYZED

	A	B	C	
H/B	356	356	124	836
IVDU	136	136	53	325
Partners	35	35	0	70
Total	527	527	177	1231

The relative numbers of patients to be recruited in each of the clinical subgroups was adjusted in order to obtain reasonable precision estimates for several questions listed in Appendix 1.

In designing the sample, it has been assumed that a sufficient number of subjects from Groups A and B will go on to develop pulmonary complications. Data from Moss et al (Ref 5, Section 3) indicate that approximately 5% of asymptomatic HIV seropositive persons with > 400 CD-4 cells will develop an AIDS diagnosis in each year of observation. In nearly all instances (at least recently) the AIDS-defining diagnosis was P. carinii pneumonia. In patients with findings indicative of more severe immunosuppression, the annual incidence of an AIDS diagnosis (again usually P. carinii pneumonia) was 20%. The incidence of other HIV associated pulmonary processes has not been well quantified, thus there are not sufficient data upon which to base sample size calculations.

The sample size of the study is adequate to estimate the prevalence rates of major pulmonary complications (i.e., P. carinii pneumonia) with reasonable precision, to compare those rates to the background rates among controls, and to provide information about rates in the major transmission categories. The sample is also adequate to estimate and compare the lung function parameters, in terms of DLCO, for Groups A, B, and C and the major transmission categories. In addition, the design will permit adequate comparison of long term prognosis (i.e. mortality) between those intensively studied and those studied in a routine manner. Details of the precision calculations for the above-mentioned parameters are given in Appendix 3.

7.1.5 Recruitment strategies

Study subjects will be recruited from various sources, depending on the Clinical Center and the transmission category to be recruited. Based on the potential sources as delineated below, flyers, brochures, posters, and contact with study personnel will publicize the program. Professional staff at potential reference sources will be briefed about the program and requested to provide information to their clients. Publicity at the Clinical Centers will encourage professional staff to bring potential recruits to the attention of the investigators for inclusion in the cohort. Freestanding clinics or drug treatment programs will be approached by the investigators to ensure that their staff are aware of the project. Other referrals of potential subjects will come from advertisements and press coverage of the activities under the contract. Recruitment strategies for each center are detailed in Appendix 4.

The following is a composite listing of the sources of subjects compiled from the Clinical Centers.

Existing hospital clinics, services and programs: Sexually Transmitted Disease Clinic, Tuberculosis or Chest Clinic, Infectious Diseases Clinic, Pediatric Clinic, AIDS Clinic.

Hospital Consultation Services: Pulmonary Disease Service, Infectious Disease Service.

Existing cohorts: ATEU, CSG, MACS, other established cohorts (having the advantage of demonstrated motivation and commitment already generated by the subject).

Gay community events: Various events may be held by gay men's health associations and similar groups. Support is often requested from local agencies and personnel can be assigned to participate in the event and to convey information concerning the study.

HIV testing sites: Centers that provide voluntary anonymous testing for HIV antibody.

The private practices of physicians who see large numbers of HIV infected persons.

Methadone Treatment Programs and other drug programs (advantage in commitment of subjects to continued care in participation treatment program.)

Individuals responding to word of mouth or media-generated publicity about the project (advantage of subject generated interest in the program).

7.1.6 Enrollment

Potential subjects will be approached and introduced to the study either at the Clinical Center or at the source of referral by one of the investigators and/or program coordinator. After providing a thorough description of the study and obtaining informed consent, an initial interview will be obtained by the investigator and/or coordinator. A physical examination, and initial laboratory examinations (chest film, blood studies, pulmonary function tests and sputum induction) will be performed at the Clinical Centers. A preliminary determination of the subject's category may be made at the initial visit, however, random assignment to the routine (A1,B1) or intensive (A2,B2) follow-up groups will be provided by the Coordinating Center after CD-4 counts are known. The subject will be advised of his/her schedule of visits after the subgroup has been determined.

Subjects who, during the first 12 months after their enrollment, do not appear for evaluation in spite of at least three telephone or mail reminders during a three month period will be replaced by new enrollees. For any subject who does not return for scheduled evaluations, efforts will be made to ascertain his/her status at each of the originally scheduled intervals so long as he/she is not confirmed to be dead.

At the time study enrollment is being considered if the subject agrees the subject's care provider should be contacted, informed of the study, and his/her cooperation sought to ensure that all pulmonary diagnostic evaluations are performed in the Clinical Center.

7.1.7 Management and retention of the cohort

Each Clinical Center will develop its own administrative structure for managing the cohort and for retaining study subjects. In developing this structure and for all contacts with study subjects, confidentiality will be of paramount importance. Each Clinical Center will determine a study name and address that does not indicate the nature of the project. In addition, because of possible unauthorized mail-opening, any communications will be worded so as to not reveal the

nature of the appointment or other indicated contact. Telephone messages will be similarly cryptic.

The major means of ensuring the continued cooperation of study subjects will be personal contact with individuals on the study staff. Frequent telephone communication with the subjects will inform and remind them of scheduled visits. The contact person will be easily accessible to the subjects by telephone and will facilitate their interactions with other study personnel and, where possible, with the subjects' sources of care. Patients will receive reminders by mail before visits and notes after each visit. Other forms of contact such as newsletters and social gatherings may also serve to foster compliance and to provide the study with a "face". The study Executive Committee (See Section 14) will review each center's plan for fostering compliance and will review data on missed visits that will be provided by the Coordinating Center.

Study personnel should be able to provide useful services to subjects. Such services might include referrals to various community support organizations, welfare agencies, and discussions of HIV-related therapies. In addition, compliance enabling devices may be of considerable benefit. Examples include provision of taxi fares or other means of transportation, scheduling visits at times convenient for the subject (such as after work hours), and having an easily accessible site for conducting the evaluations. In some instances paying an honorarium for each visit may improve subject cooperation.

Contact with heroin addicts who are in methadone treatment programs will be facilitated by developing close liaisons with the treatment program personnel. Hiring of "street-wise" interviewers and outreach workers will also serve to maintain compliance for this group.

Compliance will also be achieved by maintaining regular contact with the subject's primary physicians if the subject agrees. At the time of enrollment in the study the subject's primary physician will be provided with a written summary of the protocol and a schedule of follow-up visits. After each visit a summary of the results of the evaluation will be sent to the physician (with the subject's authorization).

7.2 Clinical Evaluations

All clinical evaluations will be performed in the Clinical Centers using uniform methods described in detail in Appendix 5. Each center will comply with the study quality control program (Section 10), thereby ensuring that results will be comparable among the centers.

7.2.1 Initial visit and assessment

The initial visit and assessment will be conducted as soon as possible after identification and recruitment of the subject, determination that he/she meets study criteria, and obtaining informed consent. During the initial visit, study procedures will be explained in detail. The symptoms that will prompt an evaluation will be reviewed carefully and the patient will be instructed to contact the Clinical Center should he/she note such symptoms. In addition to the discussion each subject will be given a card with a summary of the symptoms that should prompt a visit, the phone number of the Clinical Center and the names of the contact person, Principal Investigator, Study Coordinator and other relevant personnel.

The specific evaluations to be performed at the initial assessment include the following (methods described in Appendix 5):

1) History and physical examination;
2) Performance status;
3) Frontal and lateral view chest films;
4) Pulmonary function tests;
5) Hemoglobin, hematocrit, white blood cell, differential and platelet counts, erythrocyte sedimentation rate;
6) SMA 20 automated blood chemistry panel including serum lactate dehydrogenase;
7) HIV antibody test (previously known positive results from a qualified laboratory will be accepted);
8) Serum specimens to be frozen at -70°C for subsequent analyses (Appendix 8);
9) Determination of lymphocyte subsets (helper/inducer, cytotoxic/suppressor and mature circulating T cells);
10) Skin testing using tuberculin and mumps antigens (read by study staff or other qualified professional staff at 48 to 96 hours) (Appendix 9);

11) Induced sputum examined for P. carinii and mycobacteria (Group B only). Abnormalities detected during the initial assessment will be evaluated as described in the diagnostic algorithms, Section 7.2.7.

7.2.2 Frequency of follow-up evaluations

All subjects in Groups A and B will be assigned at random by the Coordinating Center to receive either routine (subgroups A-1 and B-1 and Group C) or intensive (subgroups A-2 and B-2) follow-up evaluations. Randomization will be accomplished at the Coordinating Center by a computer generated series of random numbers unique to each Clinical Center. Thus, there will be approximately even numbers in the subgroups in each Clinical Center as well as in the cohort as a whole.

7.2.3 Scheduled follow-up evaluations

Table 6 shows the evaluations to be performed and their frequencies in each of the groups. During these evaluations a modified history and physical examination will be done and the same series of laboratory tests as performed in the initial evaluation (except induced sputums) will be obtained. For purposes of data analysis subjects will be considered as belonging to the group to which they were originally assigned. Subjects in Groups A-1, B-1 and C who develop an HIV-related pulmonary process will continue to be followed at the same intervals except that pulmonary function tests will be performed every 6 months. HIV seronegative controls (Group C) will be followed at the same intervals as Groups A-1 and B-1. The schedule for Group C subjects who become HIV seropositive will not change.

7.2.4 Diagnostic evaluation of symptoms or findings suggestive of lung disease

All diagnostic evaluations will be performed in the Clinical Centers and will follow the algorithms devised for purposes of the protocol (Section 7.2.7). The diagnostic evaluation may be triggered by the occurrence of symptoms (noted either at the time of a scheduled evaluation or between evaluations) or by chest radiograph detected on scheduled screening examinations. Standard methods to be used for each of the studies are described in Appendix 5. All data will be recorded on standard forms.

The symptoms that will trigger an evaluation include:

Table 6
Schedule of Interval Laboratory Studies

Frequency of studies (months)
(See text for definitions of group)

Study	Group A-1(1)	Group A-2	Group B-1(1)	Group B-2	Group C(1)	1-month F/U (all groups)(2)
History Performance status	6	3	6	3	6	+
Physical Exam	6	3	6	3	6	+
CBC/Diff, platelets	6	3	6	3	6	+
ESR/SMA	6	3	6	3	6	+
Absolute CD-4, CD-8, CD-3(4)	6	3	6	3	6	+
Serum Bank	6	3	6	3	6	+
HIV Ab(3)	Entry	Entry	Entry	Entry	6	0
Induced Sputum	Entry	Entry	Entry	Entry		
Skin tests	12	12	12	12	12	0
PFT	12	3	12	3	12	+
CXR (PA/Lat)	12	3	12	3	12	+

(1) Subjects enrolled in Group A-1 or B-1 who later develop an HIV-related pulmonary complication will continue the same schedule, except PFT's will be performed every 6 months. The schedule of evaluations for Group C subjects who seroconvert will not change.
(2) "+" = test performed.
(3) Omit if documented positive prior to study entry.
(4) May be omitted if performed within the three months prior to visit.

1) unexplained cough that persists for more than five days; 2) unexplained breathlessness (progressive over ≥ 5 days or severe ≥ 1 day); or 3) unexplained new onset of documented fever (≥ 38°C oral ≥ 5 days). As a part of the orientation and at each routine clinic visit, each study subject will be alerted to these symptoms and instructed to contact the study office should they develop. For each of these symptoms, if a reason other than a possible HIV-related pulmonary process can be found (e.g., asthma), the evaluation will not proceed. If the subject has fever with localizing extrapulmonary symptoms (e.g., diarrhea) and no pulmonary symptoms, the evaluation will not proceed, and the subject will be referred to the primary physician. Any diagnoses resulting from such an episode will be entered at the subsequent visit on the Interval Visit Questionnaire.

Symptom Evaluation: When symptoms are reported the subject will be scheduled for a Symptom Evaluation Visit. These evaluations may be performed either on an inpatient or outpatient basis depending on the severity of symptoms and logistics of the evaluation.

The symptom evaluation visit will include:

1. Interval Visit Questionnaire.
2. Physical examination. The physical examination will be the same as that performed for the routine visits. The methods for procedures 3 through 7 are described in Appendix 5.
3. Chest radiograph (frontal and lateral views). If a radiographic abnormality is found, further evaluation will proceed as outlined in Section 7.2.7. Patients with cough and/or shortness of breath and no radiographic findings will have pulmonary function tests performed. Patients with fever but no specific pulmonary symptoms and normal chest films will be referred to their primary physicians and scheduled for a one month follow-up visit.

Based on the results of the history, physical examination, and chest radiograph, the physician investigator may make the clinical decision that the subject has acute bronchitis and elect to empirically treat the patient with antibodies or simply observe him/her without proceeding to the items listed below. Otherwise, the following sequence of studies will be done:

4. Pulmonary function tests (lung volumes, expiratory flows and the single breath diffusing capacity for carbon monoxide (DLCO)).

Abnormalities in pulmonary function such as airways obstruction, or bronchitis, may account for the patient's symptoms. The subject will be scheduled for a one month follow-up visit.

If in a symptomatic patient other abnormalities are not detected, the next step will be lung imaging using ^{67}Gallium citrate.

5. ^{67}Gallium citrate imaging

Lung imaging using ^{67}Ga citrate will be performed in symptomatic subjects with normal chest radiographs and in whom other pulmonary function abnormalities do not account for the symptoms. Subjects having pulmonary parenchymal uptake of the isotope will be evaluated with sputum induction. If there is no pulmonary ^{67}Ga uptake, the diagnostic evaluation will not proceed further, and the subject will be scheduled for a one month follow-up visit.

6. Sputum induction All patients who have symptoms and an abnormality on chest film (as specified in Section 7.2.7), or ^{67}Ga scan will have sputum induced.

7. Bronchoscopic procedures

All patients who have sputum induced and who do not have a pathogen identified will undergo bronchoscopy. Bronchoscopy will be performed within two weeks of the symptom evaluation visit.

8. Blood studies

All subjects who require additional evaluation because of chest radiographic abnormality, or abnormal GA scans will have the following blood tests:

T-cell subset determination (if not done within 3 months)
Complete blood count and differential, ESR SMAC (with LDH)
Serum to be frozen at -70°

Chest Radiograph Abnormalities: Chest radiographic abnormalities may be discovered during symptom evaluation visits or scheduled clinic visits in subjects with or without associated symptoms.

Radiographic abnormalities will be categorized as follows:

1. diffuse process (including diffuse infiltration of any pattern, multiple ill-defined densities, multiple nodules or masses)
2. focal interstitial pattern
3. focal consolidation;
4. pleural effusion;
5. intrathoracic adenopathy;
6. focal cavity lesions;
7. solitary masses or nodules;

If a chest radiographic abnormality is noted, comparison with any available previous chest radiographs will be made. If the abnormality can be documented on radiographs performed ≥ 6 months previously, and is currently unchanged or has been evaluated previously and is unchanged, the evaluation will not proceed unless there are new symptoms.

If an abnormality is found on the film of an asymptomatic subject who has no old films the evaluation may proceed directly or a second film may be obtained one month later and if there is no change the evaluation need not proceed.

The specific evaluations to be performed will depend on the kind of abnormality noted and on the clinical circumstances. The diagnostic approaches to be used for the most common kinds of abnormalities are shown in Section 7.2.7.

Pulmonary Function Abnormalities: Pulmonary function abnormalities may be identified during scheduled or symptom evaluation visits in symptomatic and asymptomatic subjects with or without chest radiograph abnormalities.

1. Subjects with chest radiographic abnormalities will be evaluated as outlined in Section 7.2.7.
2. When a subject develops an AIDS defining or AIDS associated pulmonary diagnosis (e.g., PCP, bacterial pneumonia, etc.), the subject will have a one month follow-up DLCO which will constitute the new baseline DLCO. Further, if a 20% drop in the DLCO generated an invasive diagnostic work-up that resulted in no definitive

diagnosis to explain the reduced DLCO, then the new (lower) DLCO will constitute a new baseline for that subject.

Asymptomatic subjects with abnormal spirometry will not require further diagnostic evaluation because airways obstruction have not been features of AIDS-related lung disease. The subject and the primary physician will be notified so that treatment (e.g., bronchodilators) can be started if appropriate. Any treatment that has been started will be recorded on the subsequent Interval Visit Questionnaire.

7.2.5 Follow-up after a non-diagnostic evaluation of suspected pulmonary disease

If the evaluation does not provide a diagnosis and the clinical course is stable or improving, the patient will be observed. If he/she is severely ill or rapidly deteriorating further evaluation will be undertaken as determined by the clinical circumstances. All subjects who undergo a diagnostic evaluation for suspected pulmonary complications will return for a follow-up one month after hospital discharge for inpatients or one month after the symptom evaluation visit for outpatients.

Patients will be instructed to call the study office if they feel there is no symptomatic improvement after one week or sooner if they feel the symptoms are worsening. Patients who appear unreliable or ill will be telephoned by a member of the study team as frequently as needed to determine their progress until stable or improving.

Subjects who do not have symptoms or whose symptoms are improving will return for a one month follow-up visit. If the chest radiograph and pulmonary function tests demonstrate no deterioration the subject will revert to the routine protocol.

If the symptoms worsen or do not improve, the subject will return before the one month follow-up visit for a repeat physical examination, and chest radiograph. If the chest radiograph abnormality is worse, the patient will be considered to have deteriorated. Patients with documented deterioration will undergo repeat sputum induction, bronchoscopy and/or open lung biopsy. If no deterioration is documented, the subject will continue to be monitored by telephone calls and reevaluated as needed until deterioration, stability or improvement

is noted. After the one month follow-up clinic visit, stable and improved patients will revert to the routine study protocol.

7.2.6 One month follow-up visit

In addition to follow-up after evaluations for suspected pulmonary complications, one month follow-up visits will be scheduled for subjects with: 1) fever, no respiratory symptoms, and a normal chest radiograph; 2) respiratory symptoms, a normal chest film, and normal 67Ga scan; 3) respiratory symptoms, and other abnormalities in pulmonary function that account for the symptoms; or 4) one month after hospital discharge for subjects admitted with respiratory symptoms; 5) one month after the symptom evaluation visit for outpatients if respiratory symptoms persist; or 6) one month after start of therapy for lung diseases.

For all of the above (numbers 1-6), the one month follow-up visit will include:

1. Interval visit questionnaire. In addition, information from relevant medical records will be abstracted.
2. Physical examination. The physical examination will be the same as that performed for routine visits and will be recorded on the same form.
3. Pulmonary function tests (lung volumes, expiratory flows and DLCO).[2]
4. Chest radiographs (standard frontal and lateral views).[3]
5. Blood tests. All subjects who had blood tests performed at the symptom evaluation visit will have the following blood tests:

   T-cell subset determination (if not done within 3 months of the visit).

   Complete blood count and differential, ESR, SMAC panel (including LDH).

   Serum to be frozen at -70°.
6. Obtain induced sputums for PCP and AFB for all subjects diagnosed with PCP or infection with M. tuberculosis (not

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2/ If the PFTs and chest film were normal at the symptom evaluation visit and the symptoms have resolved, these evaluations do not need to be repeated at the one-month follow-up visit.

3/ Same as footnote 2.

atypical mycobacteria) and analyze the sputum for both PCP and M. tuberculosis q one month until the subject is negative for the organism originally identified (either PCP or M. tuberculosis).

At baseline, a one month follow-up visit will be scheduled for subjects with: 1) DLCO <75% at the initial visit; and/or 2) abnormal chest film at the initial visit. The one month evaluation will include only a repeat of the abnormal test (DLCO and/or chest film). If the abnormality is stable or improved no further evaluation will be performed. If it is worse then evaluation will proceed.

A one month follow-up visit can substitute for a routine assessment if it is done ± 3 months for Groups A-1 and B-1 or ± 1 month for Groups A-2 and B-2 from the date of scheduled studies and tests are complete. This may in some cases require that in addition to the usual one month follow-up studies HIV antibody, skin test and sputum induction may be performed.

7.2.7 Diagnostic algorithms

The following algorithms will be used in the diagnostic evaluations of patients with symptoms or findings:

7.2.8 Procedures for Obtaining Clinical Data From Facilities Outside of the Clinical Centers

Although participants must agree, as a condition of entry into the study, to be evaluated at a Clinical Center in the event of possible pulmonary complications, it is likely that some participants will undergo evaluation at facilities other than the Clinical Centers. In order to retrieve data from such evaluations, the following procedures will be used:

1. Participants will sign a release of information form at the time of initial enrollment into the study. This will be used subsequently to obtain medical records for review if necessary.
2. Participants will be given an identification card with the Clinical Center's number. They will be instructed to inform any nonstudy physician/caregiver to contact the Clinical Center as soon as possible in the event that a possible pulmonary complication arises.

Figure 2

Evaluations of Radiographic Abnormalities - Focal Consolidation

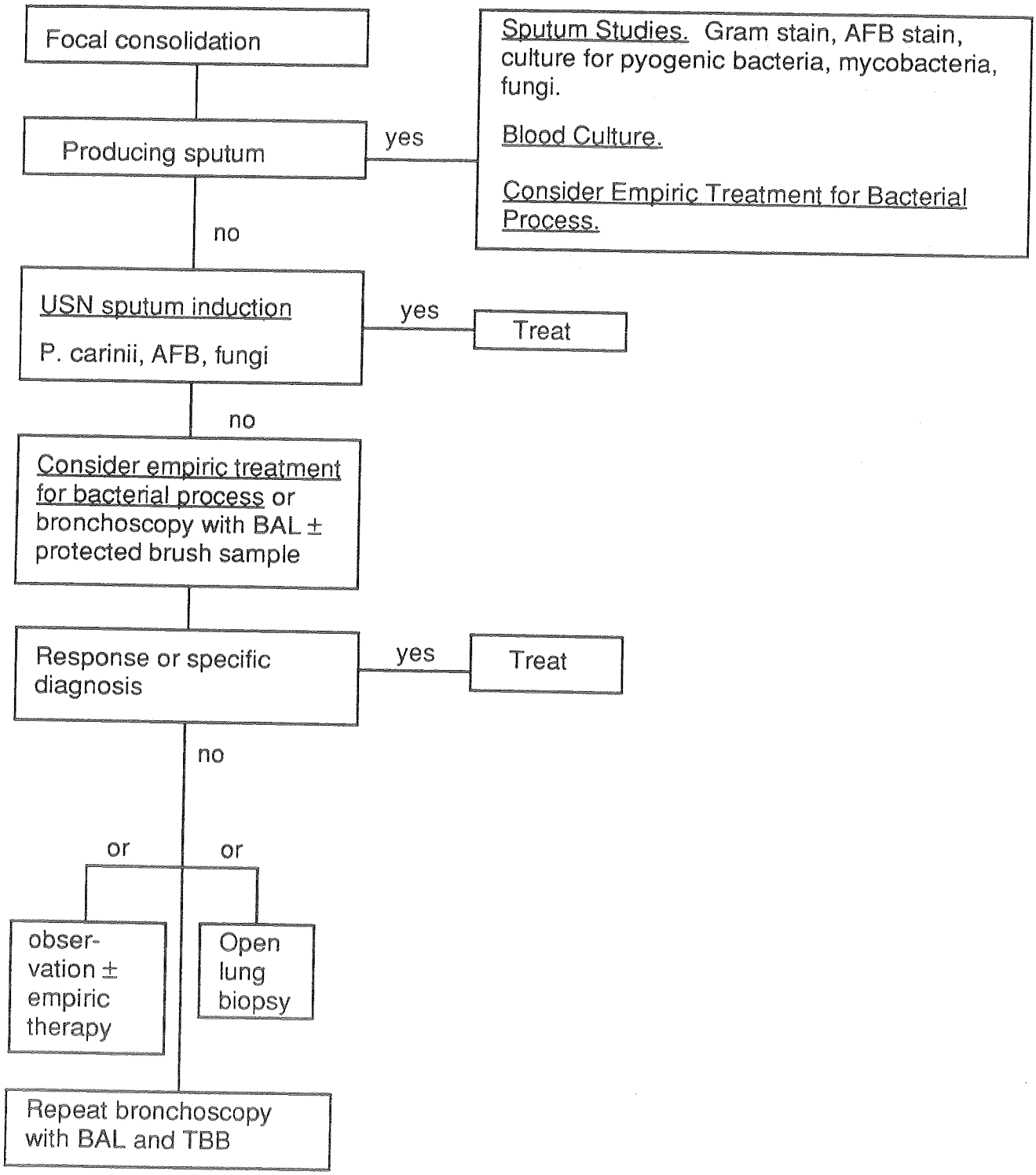


Figure 3
Evaluation of Radiographic Abnormalities - Pleural Effusion

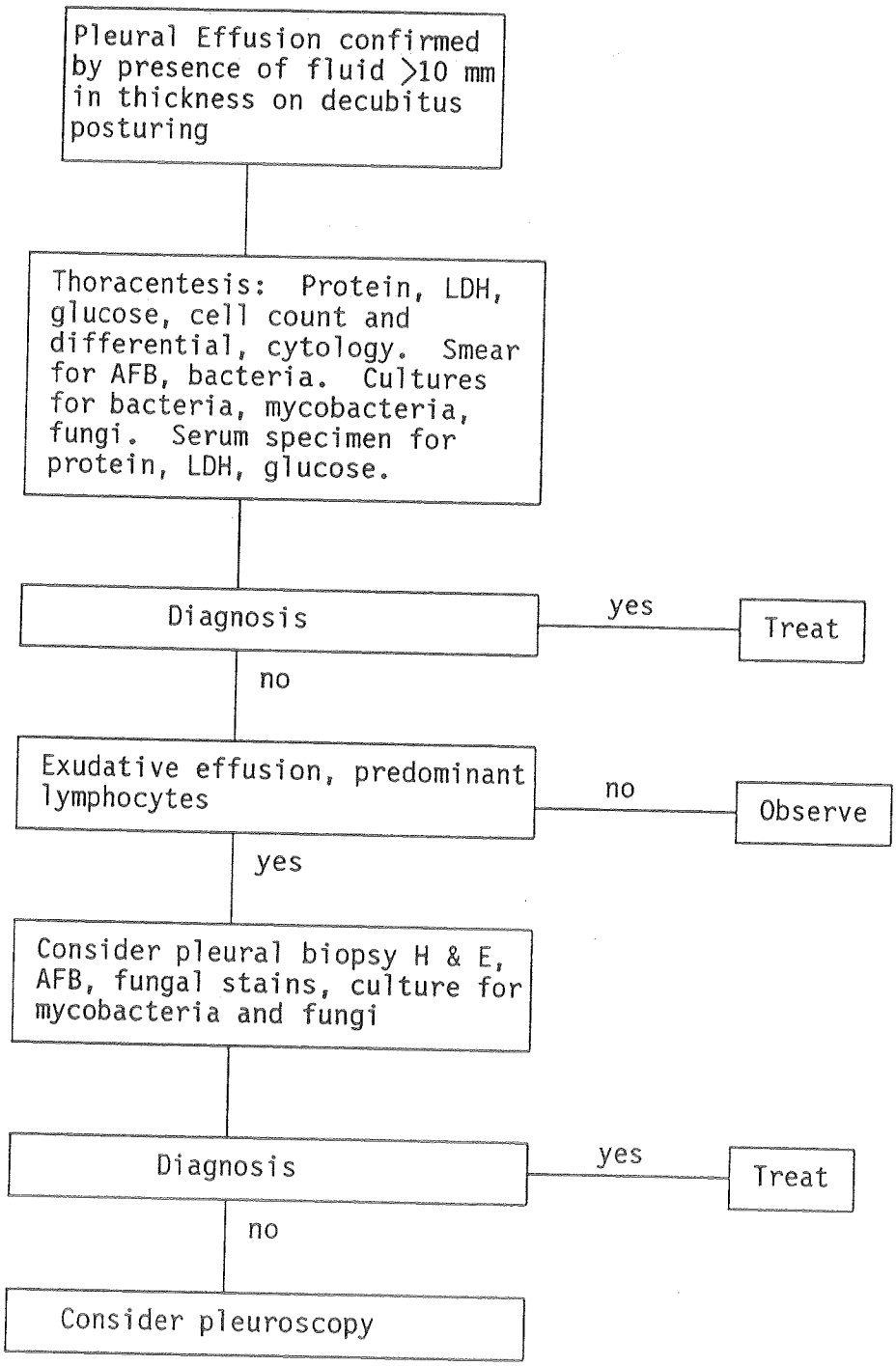


Figure 4

Evaluation of Radiographic Abnormalities - Intrathoracic Adenopathy

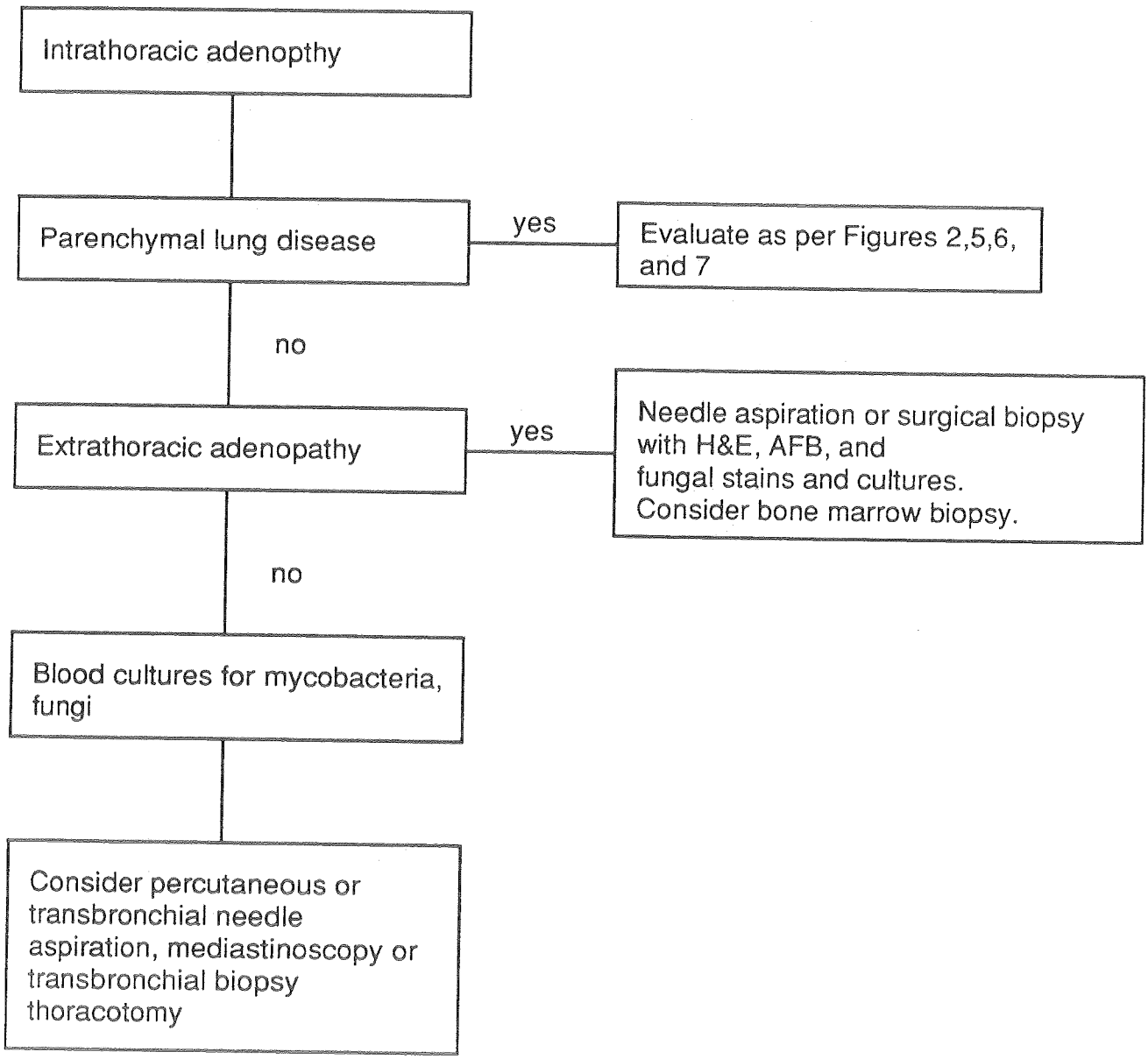


Figure 5

Evaluation of Radiographic Abnormalities - Cavitary Lesion

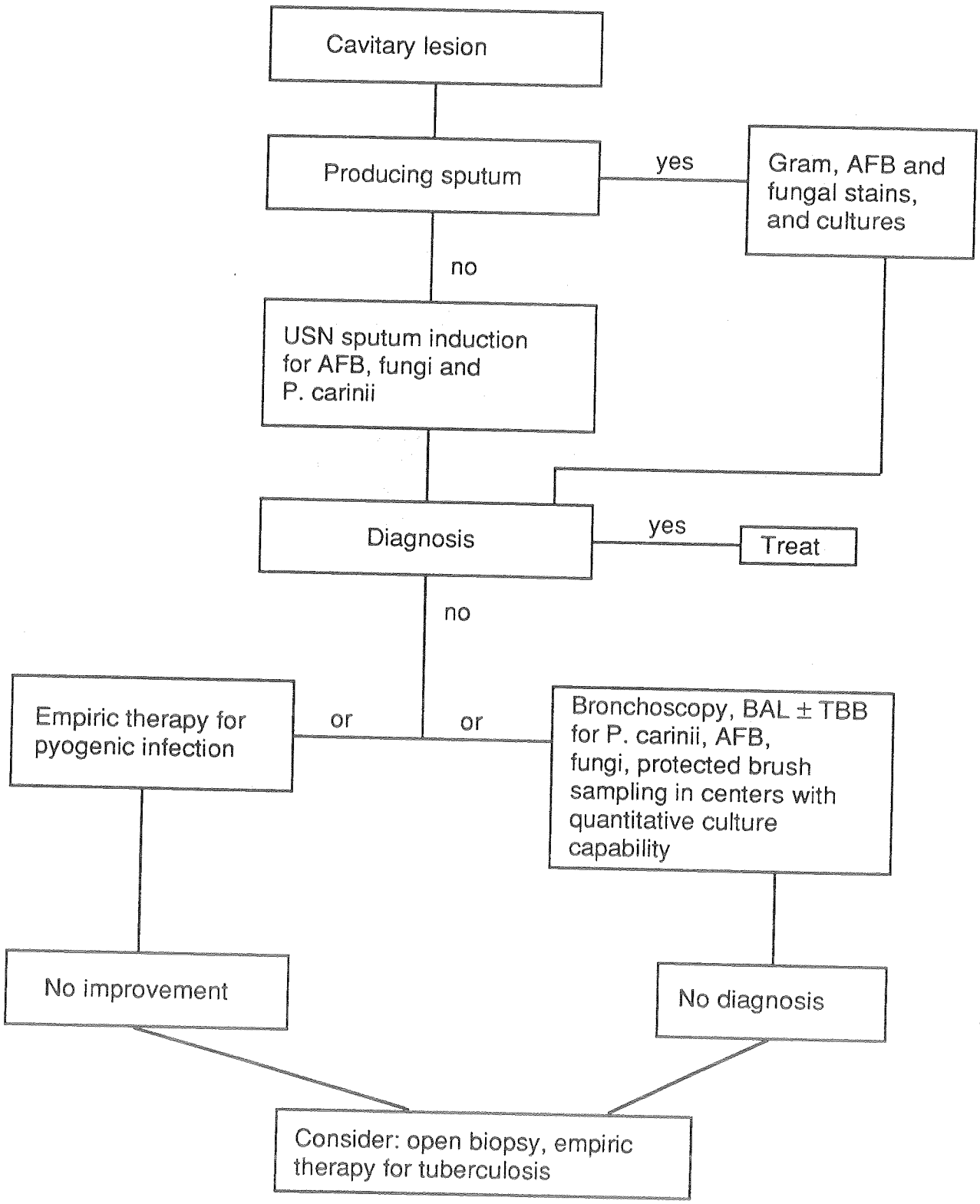


Figure 6

Evaluation of Radiographic Abnormalities - Mass Lesion or Solitary Pulmonary Nodule

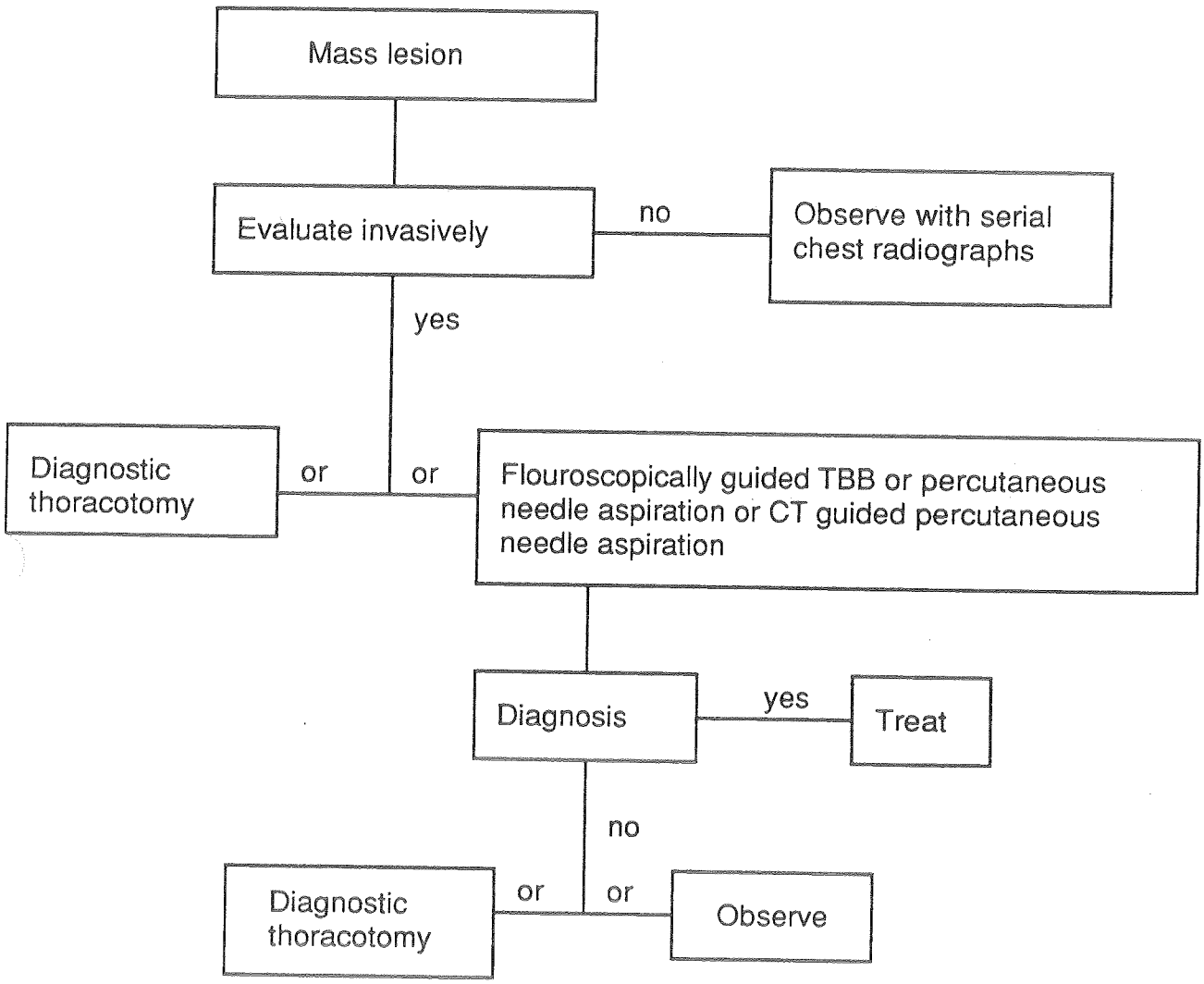
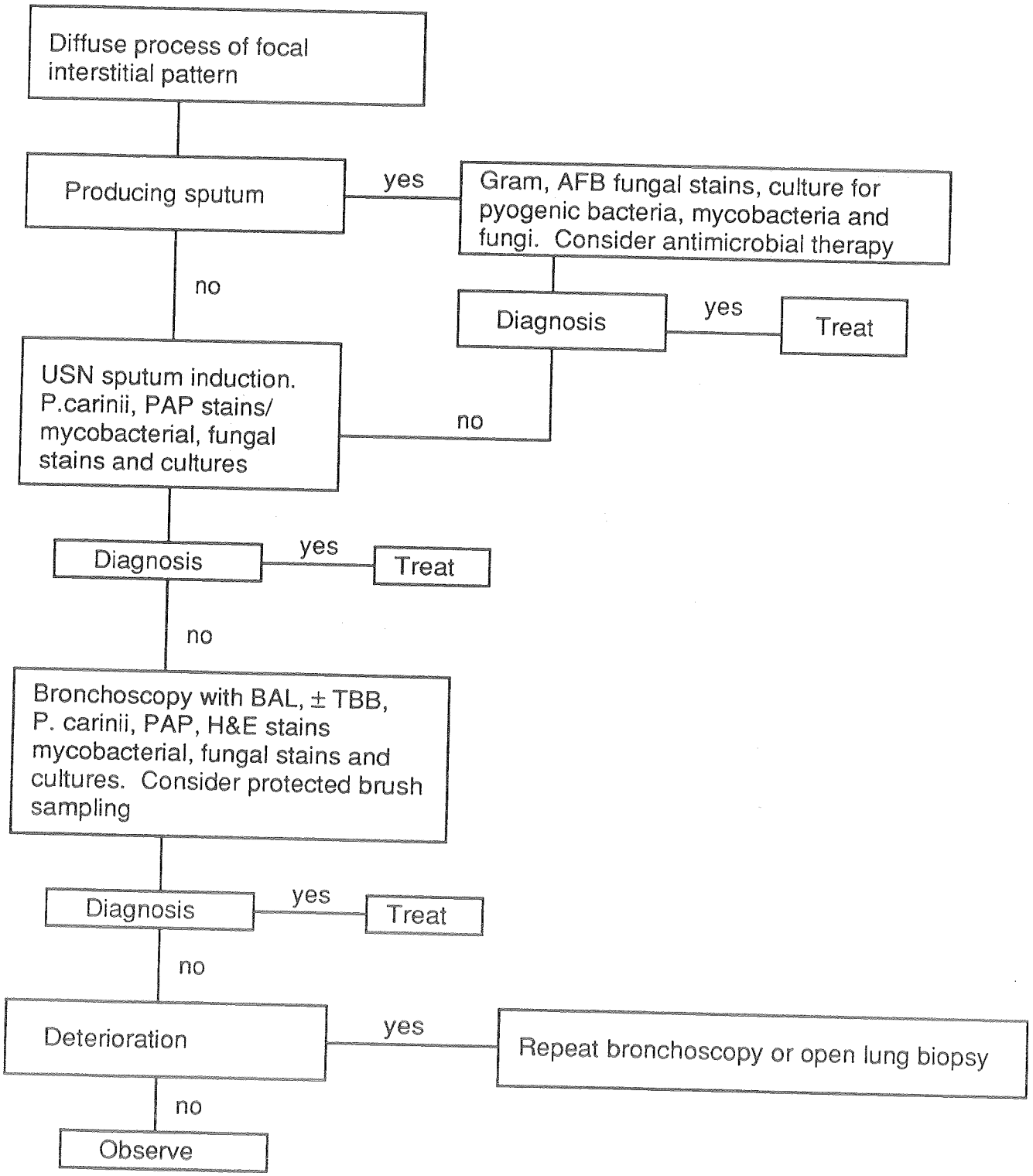


Figure 7

Evaluation of Radiographic Abnormalities - Diffuse Process of Focal Interstitial Pattern



3. When a nonstudy physician/caregiver contacts the center the study's purposes will be described and relevant procedures and algorithms explained. A request will be made that these be followed. Whenever possible center services and expertise should be made available to the noncenter physician.

4. Subsequent to the completion of the participant's evaluation, every effort will be made to obtain the relevant medical records. In addition, related chest radiographs, pathologic and microbiologic (e.g., stained sputum smears for P. carinii) specimens and pulmonary function data will be requested for review at the Clinical Center. Data gathered as the result of such a review will be entered after validation on the appropriate study forms and transmitted to the Coordinating Center.

8. Data Collection, Entry and Management

8.1 Introduction and Summary

The data will be initially recorded on study data forms. This approach has a number of advantages over direct data entry onto a microcomputer including the following:

- less obstruction to personal communication with the patient;
- less restriction on the logistics of where data can be collected;
- no disruption of data collection should a microcomputer break down; and
- allowance for keying a sample of forms at the Coordinating Center for quality control monitoring.

The data will be keyed at the Clinical Center using a microcomputer. This approach was chosen for several reasons. First, the power of a computer-based system used to detect and correct edit failures "on the spot" is expected to improve data quality. Second, obvious improvements in the timeliness of the data and of error resolution exist with such a system since several subsequent data processing steps are eliminated and the number of instances in which it is necessary to query the study site for resolution of errors on the

data file will be reduced. The potential for generating a database in a more timely fashion is of utmost importance for this study. In studying subjects with HIV infection, it is anticipated that the changes that will occur in their prognosis will require frequent evaluation of the accumulating database so that the need for changes in the study can be made as expeditiously as possible. This type of data entry system will also facilitate the timely assignment of study participants to the "routine" or "intensive" follow-up groups. Third, the hardware and software used for data entry can also be used for clinic management functions such as scheduling visits and report generation.

At the convenience of the data coordinator at the Clinical Centers, data will be keyed under the control of the data entry software. Although keyed at the convenience of the Clinical Center, keying should be completed as soon as possible after a subject's visit, preferably on the same day. Any errors detected by the data entry software or by the more complex editing which will be done at the CC subsequently, will be easier to resolve when needed information is more readily available. Each completed data form will be retained at the clinic in a subject folder and kept current with any revisions to the database. These files will be kept in a locked cabinet with access only the Principal Investigator and Study Coordinator.

Periodically the clinics will be instructed to send copies of the data forms of randomly selected patients to the CC for central keying and comparison to the database records. It is anticipated that the needed frequency of this quality control measure will be relatively high early in the study and diminish as the study progresses, when most problems with data collection and processing procedures have been resolved.

The CC will assign its own ID numbers to study subjects. This is preferable to using a Clinical Center number. The ID assigned by the CC has the advantage of eliminating duplications between Clinical Centers, identifying the Clinical Centers and original category of subject, and containing one digit designated as a check digit. The check digit is used as an internal check on the validity of the ID number and safeguards against many types of errors, including single digit transcription errors. Accurate identification is an obvious

necessity in development of a database with multiple inputs per individual over time.

The Clinical Centers will maintain the linkage between the CC assigned IDs and the subject identification. This linkage file will be protected against access by CC and by unauthorized personnel in Clinical Centers. The CC will not maintain on its database any information, such as medical record number or social security number, that can be used to identify the subject.

8.2 Data entry operations and software

The CC will develop a data entry program for each of the study forms, using a general purpose form system. The data entry package will be the Research Triangle Institute Form System (RTIFS), a product developed in-house and owned by RTI. This system is currently the only known system that supports the required ID check digit routines.

Basic features of the data entry software that will be used are:

- Field checks (only numeric data in numeric fields allowed);
- Required data item checks (data entry cannot proceed until a legitimated value is entered into that field);
- Range checks and/or valid value checks;
- Checks for legitimate date values;
- Within form logical consistency checks (e.g., proper data sequence for procedures reported in one form);
- Logical branching algorithms (e.g., if a procedure that is optional is not done, the data entry system will automatically skip over that section of the form);
- Check digit verification checks;
- Log of keying errors.

All skip logic, range checks, and consistency checks inherent in the form will be included in the form program. Also, included will be definitions of any required fields (fields for which a blank or "don't know" entry are considered inappropriate). Data entry personnel at the Clinical Center will not be able to override any of the restrictions programmed into the data entry software.

Double entry verification will not be used. Adequate quality control can be maintained without this expenditure of clinical personnel resources. The sample keying at the CC will alert staff of data entry problems that could lead to the necessity of double entry verification of certain forms.

During the course of the study, existing forms will be revised and, possibly, new forms will be developed. After the hard copies of these revised or new forms are produced, appropriate data entry programs will be produced. This programming will take only a few days, except for long, complicated forms. After the data entry programming is complete, hard copies of the revised or new forms will be sent to each Clinical Center. The new data entry programs will be placed on the Clinical Centers' microcomputer during the nightly transmission. Since for revised forms the old version of the data entry program for a form will be replaced by the newer version, the old hard copy forms can no longer be used. They should be discarded. In order to correlate the arrival of the new hard copy forms, the replacement of the data entry program, and the making of all modifications to existing production software at the CC, it may be necessary to postpone the keying of the revised forms for several days.

8.3 Data editing during keying

An important aspect of distributed data entry is that keying and initial editing of the responses are combined into a single process at the Clinical Centers where errors are best resolved. Internal checks will be built into the program to provide greater assurances that certain types of data recording errors (e.g., out-of-range, skip pattern failure, inappropriate multiple responses) do not occur.

If a key field (e.g., subject ID) is improperly specified during data entry, a flashing indicator message on the video screen will halt that data recording activity, identify the specification problem, and request the key field be checked and reentered. Failure to key a legitimate value into this field will preclude further data entry until the keyer resolves the problem.

During the entering of a nonkey field, range checks and other simple single record edits will be used to identify improperly specified fields. In the event that a variable range or other edit is violated,

the nonkey datum will be flagged and the keyer notified. The data keyer will be expected to double check the entered value. If the keyer enters a replacement value and that value passes the edit, the previously set error flag for that datum will be turned off. However, if the keyer finds that the originally entered value is not a keying error, and if other clinical personnel feel that no error was made in recording the value in the hard copy records, then the keyer will be able to reset the error flag to a new value indicating "this datum fails an edit but is correct."

While keying a form, if an error is noted in a previously keyed field, there are two ways for correcting the error. The first method is for the keyer to back up to the filed containing the erroneous value and change it. However, this method will erase values in all the fields that are backed through. The second method is to use the data review option of the data entry package. This method allows a specific case to be called up and to move to a specific item in the form in order to make a change to that field. In the first method, all edits are redone on the changed field, including any skip logic. The second method does all edits except for the skip logic. Therefore, the first method should be used if the field that needs to be changed is the gate question in a skip pattern or if only a few fields have entered passed the field to be changed. The second method should be used if a lot of fields must be backed over in order to reach the error (and no skip pattern is involved) or if the error is found after data entry is completed on the form.

Errors detected at the Clinical Center after the transmission of the data to the CC will be corrected through data entry of "change requests" at the clinic. The changes will be transmitted back to the CC where a database update feature will record the requests in the receipt control audit trail, update the record, edit the updated record, and incorporate the corrected record into the database.

8.4 Transmission to the Coordinating Center

Each microcomputer will have a built-in 1200 baud modem. Prior to transmission, the data will reside in single form specific files. RTIFS has been adapted to conform to a file naming convention that is supported by BLAST. At the end of the day the clinic staff will load

the communications environment by responding GOODIGHT (the computer will not be powered down). Following this, all subsequent transmission activities will be automatic.

During the evening hours, the BLAST communications package located on RTI's VAX will execute a program which continuously reads the system clock and calender and at predetermined times, dials phone numbers attached to the clinics' microcomputers. This will be scheduled in a precise polling order so that the scheduling of phone lines is a centralized operation. On connection to a specific clinic, the communications package will log into the microprocessor, locate the data, and transmit the data to the RTI machine. Any mail or other electronic messages designated for that site will be transmitted from the CC to the site. Messages will include success/failure and completion of the transmission, other computer generated messages regarding processing of previously transmitted data, routine reports, and any routine mail messages specific to that Clinical Center. At the end of the transmission, the communications package will terminate the phone connection and post a message on the screen for the data coordinator to read giving the results of the transmission, including any instructions for retransmission or failed transmissions.

Session transmission, including dialup, will require less than 3 minutes/center by transmitting the data nightly. The communications will be designed to be error-free. After every 128-or 256-character record transmitted, the sending and receiving computers will compare the record. If they do not agree, the record will be resent until it is correct or until a 10 minute window for transmission is surpassed. If the latter case, the center will be notified before the phone connection is terminated that transmission did not proceed properly.

8.5 Backup procedures for data entry files

Backup files of all newly keyed data will be automatically produced during the transmission session. After the transmission is complete, the original copy of the keyed data will be deleted. These backups will then be used if problems are discovered in the transmission of the original files.

The backup files will be accumulated over time. It will be necessary for the clinical staff to consolidate these files onto a

nonhard disk medium at appropriate intervals. The procedure will involve appending the newly keyed and transmitted data to a file containing all previously keyed data.

8.6 Subject visit summary records

Each Clinical Center will keep summary records of each visit of each study participant. These records will be useful in resolving discrepancies between the forms received at the CC and the forms keyed at the Clinical Center, and between expected forms received and actual forms received. These records will also help resolve discrepancies and inconsistencies that might develop in other files, such as a file containing information on serum collection and storage. Information to be recorded would include the tests and procedures that were conducted during the visit, what forms were completed and keyed, what specimens (e.g., serum, sputum) were collected, the amount collected, and where the specimens are stored. If these records are maintained on the microcomputer, the file could be used to give advanced notice of the subject's next visit.

8.7 Confidentiality

As part of their orientation training, all staff members at each Clinical Center will be thoroughly indoctrinated on the paramount importance of confidentiality and instructed that no information can be released about any subject without his/her permission. Access to records identifying subjects will be limited to staff members designated by the principal investigator at each center. Recruiting materials and other public information regarding the study will emphasize the inclusion of seronegative individuals in the study so that participation will not mark an individual as HIV seropositive.

Of the several independent data files maintained at each Clinical Center, only one, which will be used for study management, will contain identifying information. It will be maintained on floppy diskettes for use on the personal computer; the diskettes will be in the computer only during staff use and will not be resident. An electronic copy may be maintained in a study center mainframe in encrypted form and with sharply restricted access.

Data collection forms will be kept in locked files with restricted access. Identifying information of a personal nature such as

names, addresses, and particulars of the medical care provider can be removed from the data part of the form at the conclusion of collection and transmission of the data. For functions for which personal identification is irrelevant (e.g., laboratory, x-ray), identification will be confined to study numbers.

8.8 Data processing at the Coordinating Center

8.8.1 Initial processing

After the data have been transmitted to the CC, each record of new data will be checked using the same edits that were made by the data entry software. Discrepancies detected at this point may indicate inconsistencies in the edit specifications that have been programmed or possible software bugs. All discrepancies of this type will be resolved through interaction between the CC's data coordinator and Clinical Center staff.

After these edits are complete, the ID of each new subject will be checked to ensure that a duplicate ID has not been assigned. Also, all forms will be checked to see if duplicates have been received for a subject. A report of all ID and form duplicates will be prepared for transmission to the clinic at the next transmission.

Randomization will take place at this time. The results of any assignments will be returned to the centers at the next transmission.

8.8.2 Data editing

After the data have passed the initial processing edits, the more complex and longitudinal edits will be performed. As part of the editing process, reports will be produced for each Clinical Center and participant listing all data that need review for error resolution. These reports will be transmitted back to the Clinical Centers and resolution will be carried out jointly by Clinical Center staff and the CC's data coordinator. Data that are determined to be correct but still fail edit checks will remain flagged rather than be removed from the data files. Subsequent analysis of flagged data frequently points to the need to modify data collection procedures and/or edit specifications. In a similar manner the frequencies of edit errors in the early stages of the study will help determine the need for changes in the data collection procedures and/or edit specifications. Later analyses of these frequencies will provide a means of assessing clinic performances.

The number and complexity of edit checks depends on the number of data items collected, the complexity of the data collection protocol and the resources allocated to this activity. For the edit system to be effective, the Coordinating Center must communicate the problems with specific forms in a timely manner to Clinical Center personnel, and the problems must be corrected promptly.

8.8.3 Error resolution

The error resolution procedure will involve communicating the error symptoms to the Clinical Center for follow-up action. The monitoring system will continually remind the CC staff of any outstanding error resolution actions. All resulting data changes will be keyed at the clinics on "edit error resolution forms" that are designed specifically to accommodate these changes. These forms will provide an audit trail that includes Clinical Center ID, study participant ID, date, time, variable name, old field value, and new value. This approach not only documents all changes to the database, but also enables an ongoing analysis of the success/failure of data collection and data processing. The changes will be transmitted to the CC electronically. The new information will then be reedited and included in the database.

8.8.4 Transmission of data to the Clinical Centers

Periodically, the CC will transmit a subset of a Clinical Center's data in the database back to the center. This will allow the Clinical Center to retrieve subject data as it is needed. However, these data will be maintained only at the CC; i.e., any corrections, changes, or additions to the database will be made only by the CC staff on the main database. The Clinical Center data will be updated at the next transmission of the data to the center. The file on the Clinical Center's microcomputer will be completely replaced with a new file at each transmission.

8.9 Quality assurance procedures

The CC will monitor both the data collection and data processing activities at the Clinical Centers and the data processing tasks at the CC. This will be accomplished by the following procedures.

The CC will establish a database file which will describe the schedule for data acquisition for each participant enrolled in the study

and the status of their various data collection forms. This database will show: (1) when the CC can expect to receive the baseline data on a newly enrolled subject and when follow-up data should be received; (2) what forms should be collected after each visit and when the CC can reasonably expect to receive these data; (3) the date of receipt of various forms (keyed version) at CC; and (4) the edit related status of each form in CC's computer database. This file will be analyzed at regular intervals (initially once in two weeks, subsequently once a month) to monitor the status of data acquisition and to generate reports on overdue data and the status of participants relative to the study protocol. Other reports which will be generated include:

- Identification reports on new enrollees. This printout may be used by the Clinical Center for the purpose of verification;
- Identification reports on forms that have been transmitted to the CC and those forms that were expected by the CC but not received;
- Identification reports on forms that were transmitted to the CC and were missing critical data for the study;
- Identification reports of participant withdrawal information transmitted from the Clinical Centers; and
- Summary reports on forms with problems detected during edits.

These periodic reports will be designed to assist the study coordinators in the collection of data outlined in the protocol.

The CC will send a report message to the Clinical Centers each time data transmission is attempted. This message will indicate whether transmission was a success or a failure and will list the information (e.g., forms, mail messages, edit corrections, etc.) received at the CC. This will allow the site to immediately know whether all intended data were received at the CC.

The CC will monitor the study with respect to a number of aspects, including the following:

- baseline characteristics of the screened and recruited patients, transmission category, group assignment,
- subject accrual and retention,
- data acquisition,

- frequency of various pulmonary complications in the various transmission groups, and
- movement of patients from one category to the next.

The outcome of these monitoring activities will be periodically summarized and reported to the Clinical Centers, the Program Office and the Steering Committee.

9. Statistical Analysis

Because this is basically a natural history study rather than a randomized clinical trial, selection bias resulting from nonrandom assignment of patients to comparison groups of interest must be dealt with. When doing comparative analyses among patient groups of interest, it is important to be reasonably sure that the comparisons made are free from the influence of nuisance variables which are of no intrinsic interest in the analysis. This means that techniques must be available which will allow one to adjust the comparisons among patient groups of interest if there is evidence that there is an imbalanced distribution of risk variables for the outcome of interest among the groups being compared. The most elegant way to handle this analytic problem is to model the data with a statistical expression which expresses the outcome variable of interest (e.g., change in pulmonary function) as a function of the patient groups which are to be compared as well as the set of confounding variables for which adjustment is to be made.

Specific analytic plans which address the different questions related to the aims of the study are summarized in Appendix 1. These plans are generally of the regression model type with specification of: 1) the study groups to be analyzed (e.g., A, B, or C); 2) the predictive variables which will appear in the model; 3) confounding (nuisance) variables which will appear in the model; and 4) outcome variables which will be used in answering the specific questions. This information will not be repeated in this section but for illustrative purposes the specific questions related to the primary objective of the study and to the value of intensive screening will be discussed in some detail.

Question 1, which addresses the the primary objective of the study states, "What are the specific lung diseases that occur in HIV infected persons and what is their prevalence and incidence?" In order

to answer this question all HIV seropositive subjects (e.g., Groups A and B) will be included in the analysis. Possible predictor variables are HIV antibody status, stage of HIV infection, and HIV transmission category. Confounding variables are preventive treatment for infections, anti-HIV therapy, and immunosuppressive drugs. One of the principal outcome variables in this analysis will be presence or absence of P. carinii pneumonia. In order to calculate the prevalence of P. carinii pneumonia at, for example, 2 years into the study, a logistic regression model will be utilized which has the presence or absence of P. carinii pneumonia as the outcome variable and has the predictive and confounding variables as covariables. In this way, gross and adjusted odds ratios may be computed for the different subgroups of interest and the statistical equivalence of the magnitude of the gross or adjusted ratios may be assessed.

The second question in the primary objective concerns the association of various pulmonary diseases with subsequent morbidity and mortality. All seropositive subjects are to be part of this analysis and in this case P. carinii pneumonia will be one of the predictor variables. Confounding variables are transmission category, clinical and immunologic stage of HIV infection, and other coexisting diseases. One of the primary outcome variables for this analysis is mortality. In order to investigate the relationship of the presence or absence of P. carinii pneumonia on survival, a Cox regression model will be used in which mortality is the dependent variable and the presence or absence of P. carinii pneumonia is the predictive variable. The confounding variables above will appear as independent variables as well. In this analysis, comparisons will be made between the adjusted survival rates for those patients who developed P. carinii pneumonia versus those who do not over the course of the study.

Question 3 is, "What is the frequency with which multiple pulmonary diseases are present simultaneously and what are the common associations?" Again all HIV seropositive subjects will be used in this analysis and the major pulmonary diseases of interest will be P. carinii pneumonia, tuberculosis, mycobacterium avium complex infection, and cytomegalovirus infection. In order to discover associations which may exist among the different pulmonary diseases of interest, contingency

table analyses of 2 or higher dimensions will be constructed to assess statistically whether or not the different pulmonary diseases tend to occur together or whether they are basically independent. Chi-square tests for association will be appropriate in this situation. Simple adjustment for single confounding variables may be made by Mantel-Haenzel methods and more complicated adjustments will be done by loglinear modelling.

Question 12 is, "Does diagnosis of P. carinii pneumonia by intensive screening decrease both short-and long-term mortality?" All seropositive patients will be included in this analysis and the major comparison of interest will be the intensively screened patients versus those who have been randomized to routine evaluations. Since this is a randomized substudy, there is much less concern about selection bias than for the other questions of interest which involved nonequivalent groups. In this case the principal predictive variable of interest is intensive or routine screening and the outcome is short and long term mortality. Variables confounding the interpretation of the analysis include various forms of treatment which patient may be on. To explore question 12, Kaplan Meier survival curves (or Cox regression if covariables must be dealt with) will be computed and statistically compared. In the calculation of the curves it will be important to take the origins of the survival curve as the time of randomization in order to avoid length biased sampling. Additionally, based on back extrapolation of the slope of decline of CD-4 cell counts the approximate time of HIV infection can be estimated and used as the starting point for the curves.

If the answer to question 12 is "No", one may well wish to investigate the reasons for the lack of impact of the intensive effort. A logical inquiry in this regard is whether or not the lead time between onset of preclinical disease and symptoms is sufficient to permit a significant alteration of the disease process. In this regard, extensions to methodology of Zelen and Feinleib, [Biometrika, 1969, pp.601-614] may be useful in estimating the lead time from incidence and prevalence data from the intensive and routine study arms.

10. Quality Control

The Quality Control Subcommittee will monitor the performance of the Clinical Centers and Coordinating Center and report findings to the Steering Committee during the semiannual meetings. In addition, a quality control officer (other than the principal investigator) will be designated at each Clinical Center.

Specific programs will provide for quality control of: A) Clinical Center procedures; B) diagnostic procedures and laboratory tests; and C) Coordinating Center procedures.

10.1 Clinical Center Procedures

The proficiency of the Clinical Center staff will be assured by documentation of the initial orientation, review of performance with the principal investigator and co-investigators, and ongoing in-service training. Compliance with the study protocol will be determined by an on-site random review of subject records, log books, and other records. At the Coordinating Center, a review of a random sample of submitted data forms for completeness and accuracy will be periodically conducted. The following areas will be assessed during these random reviews:

1) enrollment and randomization procedures
2) adherence to the study protocol
3) adherence to the performance of the indicated diagnostic studies on subjects requiring symptom evaluation
4) completeness of data forms
5) adherence to minor study details.

10.2 Diagnostic Procedures and Laboratory Tests

10.2.1 Microbiology

For each laboratory providing microbiology services for the study, documentation of CAP annual certification and copies of the current CAP quality control record will be kept at the Coordinating Center, and reported to the Quality Control Subcommittee. If deficiencies are found they will be reviewed by the Quality Control Subcommittee.

10.2.2 Induced Sputum

Monitoring of the induced sputum specimens will be supervised by Dr. Keith Hadley at San Francisco General Hospital Microbiology Laboratory. Slides prepared in Dr. Hadley's laboratory will be sent to

each of the Clinical Centers for reading by the responsible laboratory personnel. Slides from each Center will be sent to San Francisco General Hospital for evaluation of quality of processing and comparison interpretations. Monitoring will be done annually. Records of performance of each laboratory will be kept at the Coordinating Center and reported to the Quality Control Subcommittee. Additional training will be provided for personnel not meeting quality control standards.

10.2.3 Chemistry and Hematology Blood Tests

All centers will perform the SMAC-20 panels, CBC, differential counts, platelet counts and ESR determinations using the usual quality control measures. Documentation of current CAP certification for each clinical laboratory performing these tests will be kept on record at the Coordinating Center. P-24 antigen and Beta 2 microglobulin determinations will be performed on batches of frozen serum in a central laboratory with a large experience and previous record of accuracy.

10.2.4 HIV Test

Each laboratory performing the HIV test will be responsible for quality control of technique and reagents, as well as for running standards quarterly and more often as needed. For laboratories participating in the CAP quality control program documentation of certification will be obtained.

10.2.5 CD-3, CD-4, and CD-8 Determinations

Each laboratory performing the determination will be responsible for quality control of instrumentation and reagents as outlined by the American Society for Histocompatibility and Immunogenetics Guidelines (Standards for Clinical Cytometry and Cell Surface Phenotyping, adopted November 1986). These laboratories will participate in the Flow Cytometry Quality Control Program sponsored by NIAID. A panel of unknown blood samples from HIV seropositive and HIV seronegative donors will be sent to each laboratory monthly for white blood cell count, differential, CD-3, CD-4, and CD-8 determinations. Analysis of results and differences among centers will be performed according to the Quality Control Program protocol. The Flow Cytometry Advisory Control Program will notify individual Clinical Centers if there are quality control problems, and will assist with problem solving. Records of performance will be kept at the Coordinating Center and regularly reported to the Quality Control Subcommittee.

10.2.6 Pathology

All fixed tissue and cytologic slides will be reviewed centrally by a pathology panel consisting of three pathologists from the Clinical Centers. Comparison with the original interpretation will be made by the Coordinating Center and a report will be issued to the Quality Control Subcommittee semiannually. Discrepancies in interpretation will be reported to the Clinical Centers and changes in the data records will be made according to a final consensus interpretation.

10.2.7 Pulmonary Function Tests

Quality control for pulmonary function tests will be based on determinations of reproducibility of test results within Centers, consistency of results among Centers and adequacy of testing procedures. Reproducibility of test results within each center will be assessed by repeated testing at three month intervals of one person who has no reason to have fluctuating lung function. At least two maneuvers for each of the tests will be performed for each of the subjects at each testing and results sent to the Coordinating Center. Consistency among centers will be evaluated in two ways. First, at least two site visitors will be the same for each round of visits and will be tested at each Clinical Center. At least two maneuvers will be performed and the results sent to the Coordinating Center for review by the Quality Control Subcommittee. Consistency among the Clinical Centers will also be assessed by monthly comparisons of mean data from each of the Centers. Mean values and statistical comparisons will be provided to each of the Clinical Centers each month. Centers having mean values for individual tests that are different from those for the group as a whole will be asked to check for possible sources of error and report the results to the Quality Control Subcommittee.

The adequacy of testing procedures will be determined by a review of adherence to the specified methods, including calibration and maintenance checks, observations of subjects being tested and review of raw data including spirographic tracings from randomly selected study subjects. Each of these evaluations will be performed at each site visit. All centers will be visited during the first six months of the study and at least annually thereafter.

10.2.8 Chest Radiographs

To monitor the consistency of radiographic interpretation among the Clinical Centers a representative sample of films taken during screening, follow-up and symptom evaluation visits will be circulated quarterly among the Clinical Centers for reading. In addition, a panel of radiologists from the participating Centers will review sample films submitted by each of the Centers periodically. The film will be evaluated for technical quality and interpretation. Comparison with the original interpretations will be made by the Coordinating Center and a report will be issued semiannually to the Quality Control Subcommittee.

10.2.9 Gallium Scans

All Gallium 67 scans and copies of the Gallium scan 67 forms (form G) will be sent to the nuclear medicine specialist who will do independent qualitative reading, and evaluate the quality of the scan. This information will be recorded on the QC Gallium 67 scan form (form QC-G). The QC Gallium 67 scan form will be sent to the QC coordinator who will enter the data. The scan and form G will be returned to the Center from which it originated.

10.3 Coordinating Center Procedures

Quality control at the Coordinating Center will be aimed at ensuring that data used in analysis and reporting are as free as possible from errors and inconsistencies. These procedures are described in detail in Section 8. Specific areas of concern include:

1) confidentiality of patient identification;
2) loss of data in transit (a log of received data will be compared with records kept at the participating Centers);
3) data entry;
4) machine editing;
5) report of errors/omissions to Clinical Centers, quality control subcommittee chairman, and NIH;
6) incorporating correction of errors into the database.

In order to asses the degree to which the Coordinating Center and the Clinical Centers adhere to quality control procedures, site visits to each Clinical Center and the Coordinating Center will be conducted once early in the study. Site visits will be conducted as needed thereafter. The site visit team will be composed of a

NHLBI/NIAID representative, a Coordinating Center representative, and a member from one of the Clinical Centers. Consultants may be added to the site visit team as needed.

11. Infection Control Procedures

Because of the cohort being studied, the potential for transmission of infectious agents must be considered. The primary concern is HIV but other agents (e.g., M. tuberculosis, hepatitis virus) also merit attention. Infection control procedures will be directed at personnel, at blood and secretions and at equipment which is subject to potential contamination.

General procedures will be consistent with those described in the Morbidity and Mortality Weekly Report for August 21, 1987 (vol 36, No. 25) and in Infection Control 1983; 4 (suppl):245-325. Specifically, all staff and other personnel having direct contact with study subjects will be instructed in the use of appropriate barrier precautions to prevent skin and mucous membrane exposure when contact with blood or body fluids of any subject is anticipated; hands and other skin surfaces will be washed immediately and thoroughly if contaminated; care will be urged in disposal of contaminated instruments such as needles, proper technique described and adequate disposal containers provided; universal blood and body fluid precautions will be taught and urged to all personnel within the Clinical Centers, including laboratory workers. Specimens will be transported in leak-proof containers and care will be taken to avoid contamination of the outside of the container. Laboratory and other work surfaces will be promptly decontaminated after any spill of blood or other body fluids and when work is completed. Standard sterilization and disinfection procedures for patient-care and diagnostic equipment will be used following each patient/subject contact. Personnel expected to have regular contact with blood or body fluids will be encouraged to receive Hepatitis B vaccination. This will be provided according to the procedures of the Clinical Centers. If a member of the study staff has a parenteral or mucous membrane exposure to blood or body fluids, they will be counseled regarding the risk of HIV infection and will be evaluated clinically and serologically as soon as possible by the local employee health service or comparable facility.

Exposed personnel will be advised to seek medical evaluation for any acute febrile illness occurring within 12 weeks of exposure. Seronegative staff will be retested 6 weeks after the exposure and approximately every three months for at least the next 6 months. Infection precautions for tuberculosis will be used when sputum induction is being performed. Tuberculin skin testing procedures will be established by the Clinical Centers and will reflect the potential for tuberculosis transmission at each Clinical Center.

12. Standards of Patient Care

All patients entering the study will provide informed consent. Should medical problems arise during the course of the study, patients will be encouraged to undergo treatment at the Clinical Centers. Although there is no attempt by the study to control treatment regimens, all subjects will be treated either according to established standards or under experimental protocols that have previously been approved by the local Institutional Review Boards.

13. Counseling of HIV Seropositive Subjects

Each Clinical Center will identify qualified counselors within their institution. All HIV seropositive study subjects will be questioned concerning the counseling he/she received at the time the test result was made known to the subject. Those who have been counseled inadequately will be referred to a counselor within the Clinical Center. Seronegative control subjects who seroconvert will be informed promptly (within 2 weeks of the test result) and will be referred for counseling. Detailed description of the counselling procedures are filed at the Coordinating Center.

14. Organization Structure

14.1 Introduction

The organizational components of this study include participating units and administrative units. The participating units are: individual Clinical Centers, a Coordinating Center, External Review Consultants, the National Heart, Lung, and Blood Institute, and the National Institute of Allergy and Infectious Diseases. The

administrative units are: a Policy and Data Safety Monitoring Board, a Steering Committee, an Executive Committee and working subcommittees established by the Steering Committee.

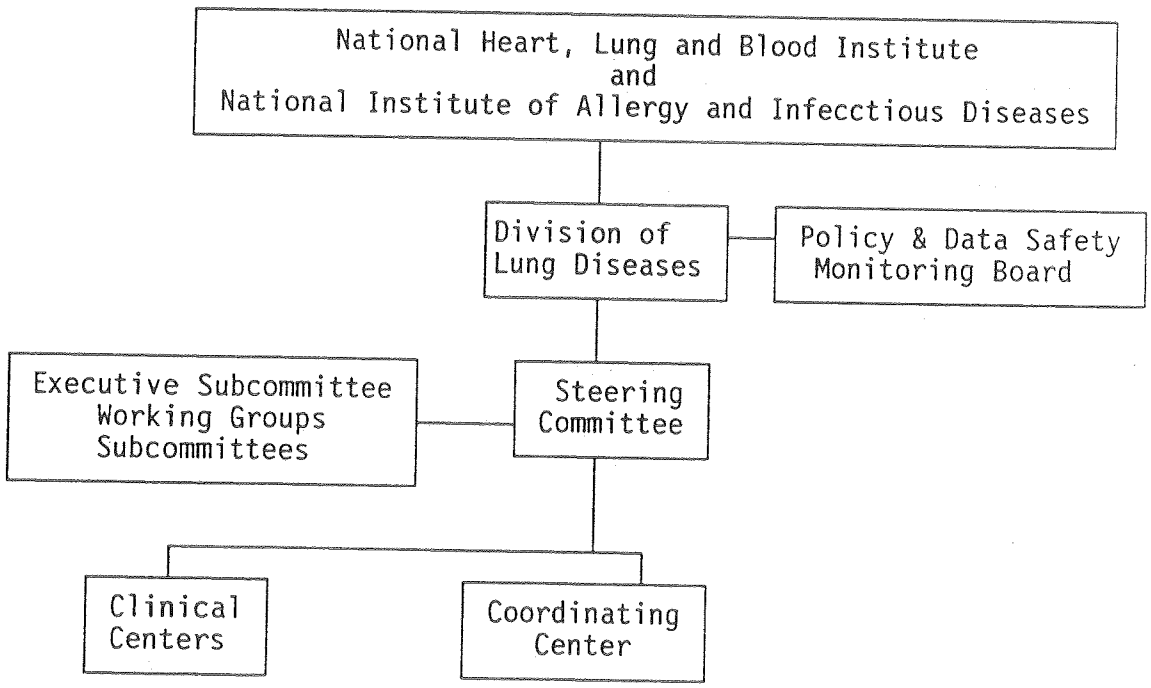
14.2 Participating Units

The duties and responsibilities of the participating units in this study are described below.

14.2.1 Clinical Centers

Each Clinical Center is responsible for recruiting the required number of patients, administering the clinical evaluation and diagnostic

Organizational Chart



tests as required by the study protocol, obtaining follow-up information, and collecting, recording and forwarding patient data to the Coordinating Center. The Principal Investigator from each Clinical Center will be a member of the Steering Committee and will be responsible for the ongoing conduct of the study. Clinical Center staffs will meet twice a month to review local study progress, report on work completed and bring up operational problems some of which may be brought to study-wide attention by the Clinical Center's Principal Investigator. The Principal Investigators have a forum for considering

study-wide problems in the Steering Committee and more immediately by conference telephone call. Conference telephone calls are planned for every second month except for those months when there is a Steering Committee meeting.

The Institutions participating in the study as Clinical Centers and their respective Principal Investigators are listed below.

1. University of California, San Francisco
   San Francisco, California
   Philip Hopewell, MD, Principal Investigator

2. Northwestern University
   Evanston, Illinois
   Jeffrey Glassroth, MD, Principal Investigator

3. Mount Sinai School of Medicine
   New York, New York
   Mark Rosen, MD, Principal Investigator

4. University of Medicine and Dentistry of New Jersey
   New Jersey Medical School
   Newark, New Jersey
   Lee B. Reichman, MD, Principal Investigator

5. University of California, Los Angeles
   Los Angeles, California
   Jeanne M. Wallace, MD, Principal Investigator

6. Henry Ford Hospital
   Detroit, Michigan
   Paul A. Kvale, MD, Principal Investigator

7. Klinikum J.W. Goethe University
   Federal Republic of Germany
   Michael Rust, MD, Principal Investigator

14.2.2 Coordinating Center

The Coordinating Center has a major role in the design, implementation, and execution of the study. The Coordinating Center will be represented on, and work under the direction of the Steering Committee. The staff of the Coordinating Center has the responsibility of collecting, editing, storing, and analyzing all data received from the Clinical Centers and the External Review Consultants. Among the specific functions of the Coordinating Center are:

1. To participate with the investigators in the development of the study protocol, forms, data reporting procedures, and the Manual of Operations.
2. To pretest the procedures for data recording, processing, and reporting.
3. To make random assignment of patient entry into the study.
4. To review and edit all data transmitted to the Coordinating Center.
5. To participate in the establishment and monitoring of quality control procedures.
6. To provide statistical analyses of all study data.
7. To check the completeness of records and periodically prepare performance reports to the Division of Lung Diseases and the participating Clinical Centers.
8. To analyze periodically the frequency of adverse side effects of the diagnostic procedures and to report this data to the Policy and Data Safety Monitoring Board.
9. To prepare interim technical and statistical reports for the Steering Committee.
10. To monitor patient recruitment at each Clinical Center.
11. To assist in the preparation of reports of the study for publication.
12. To provide administrative support to the program office in arranging the meetings of the study investigators.
13. To interact with the program office on all aspects of the study: design, conduct, monitoring progress and scientific inference.

The exact role of the CC will depend on the stage of the study. During the planning phase the CC investigators will participate in the

discussions on the design and conduct of the study and in the development of the study materials: protocols, manual of operations and study forms. They will assume a leadership role in developing and putting into operation the data processing systems and training Clinical Center personnel in the procedures for data collection, data keying and data transmission procedures specified by the protocol.

During the enrollment and follow-up phases the CC will be concerned with the collection and processing of the data specified by the protocol. The primary focus during this phase is to ensure that the data specified by the study protocol are collected and processed as accurately and reliably as possible within the resources. The CC will monitor the progress of the study and the quality of the data and will assist the Centers in finding solutions to operational problems (problems with data keying, data transmission, interpretations of the study protocol and study procedures). It will provide written and oral reports on important aspects of the study to NIH Program Office, the Clinical Center personnel, the Steering Committee and the Policy and Data Safety Committee. It will initiate corrective actions as the need arises.

The CC will also take a leading role in the statistical analysis of the study data and will provide assistance in the preparation of reports of the study for publication.

In the closeout phase phase of the study CC will assist the centers in closing out the study related files of the study patients.

The Coordinating Center staff will meet weekly to review study progress, report on assigned work and receive work assignments to fulfill the Coordinating Center specific functions.

Research Triangle Institute, Post Office Box 12194, Research Triangle Park, North Carolina 27709-2194 is the Coordinating Center for this study. Dr. Kenneth Poole is the Coordinating Center Principal Investigator for this project.

14.2.3 Institute Project Offices

The Division of Lung Diseases (DLD), National Heart, Lung and Blood Institute, and the AIDS Program (AP), National Institute of Allergy and Infectious Diseases, as sponsors of this study, are responsible for providing organizational, scientific, and statistical

direction to the study. The Scientific Project Officers are voting members of the Steering Committee and non-voting members of the Policy and Data Safety Monitoring Board. The Contracting Officer is responsible for all administrative and fiscal matters related to the award and conduct of the contracts.

14.3 Administrative Units

The participating units of the study are coordinated by the DLD, NIAID AIDS Program, the Policy and Data Safety Monitoring Board, and the Steering Committee.

14.3.1 Policy and Data Safety Monitoring Board

The Policy and Data Safety Monitoring Board acts in a senior advisory capacity to the DLD and AP on policy matters throughout the duration of the study. In addition, it periodically reviews study results and evaluates the study diagnostic procedures for beneficial and adverse effects.

The Board is composed of a chairman and additional voting members, who are appointed by the DLD and AP for the duration of the study. The Scientific Project Officers, as ex-officio members, are non-voting members of the Board. Board meetings are attended, when appropriate, by senior representatives from the Coordinating Center and the Chairman of the Steering Committee. Additional Board members or consultants may be appointed, if deemed necessary, by the DLD and AP in response to recommendations by the Board. No voting member of the Policy and Data Safety Monitoring Board may participate in the study as an investigator; however, other investigators from the Board member's institution will not be excluded from participating in the study. The Board will meet no less than twice a year.

Specific functions of the Policy and Data Safety Monitoring Board are:

1. To review and approve the study protocol, forms, and Manual of Operations.
2. To review and analyze the progress of the study, and to evaluation its relevance to the program goals.
3. To monitor the study diagnostic procedures for beneficial and adverse effects on the patient.

4. To make recommendations to the DLD and AP on major changes in the protocol, forms, or Manual of Operations.
5. To review and advise DLD and AP ancillary studies (with the possible effect on the main study being the major criterion).
6. To review the quality of the data.
7. To assist the DLD and AP in resolution of problems referred by the Steering Committee.
8. To make recommendations to the DLD and AP on any proposed early termination of the study because of failure to achieve recruitment goals or adverse or beneficial effects of any study procedure.
9. To recommend remedial measures or discontinuation of individual Clinical Centers which perform unsatisfactorily.

14.3.2 Steering Committee

The Steering Committee provides scientific direction to the study at the operational level. The voting members of the Steering Committee are one member from each Clinical Center and Coordinating Center, and the DLD and AP Project Officers. For practical reasons, all technical matters related to the study shall be directed through the DLD Program Office, NHLBI. Specific functions of the Steering Committee are:

1. To see that the program policy and protocol is carried out under the guidance of the DLD and AP Project Officers.
2. To review and analyze the progress of the program.
3. To make recommendations to the Policy and Data Safety Monitoring Board concerning changes in the protocol and Manual of Operations.
4. To review all proposed ancillary studies and to report all recommendations to the Policy and Data Safety Monitoring Board (the major criterion being the possible effect on accomplishing the objectives of the main study).
5. To monitor the performance of the individual Clinical Centers with regard to patient recruitment and patient follow-up studies.
6. To monitor the quality of data collected.

7. To be responsible for the presentation of the program results to the biomedical community.

The Steering Committee will meet no less than twice a year. Additional meetings of the Steering Committee will be held as necessary.

14.3.3 Executive Subcommittee

The Executive Subcommittee will meet as necessary between Steering Committee meetings to review interdisciplinary issues on the Steering Committee agenda. Voting members of the Executive Subcommittee are the Chairman, the Vice Chairman, the Principal Investigator of the Coordinating Center and the DLD and AP Project Officers. Specific functions of the Executive Subcommittee are:

1. To make recommendations to the Steering Committee
2. To assign to Working Groups
3. To review clinical science procedures for consistency.
4. To review data collection and interpretation.
5. To promote communication within centers.

15. Study Constitution

Article 1. Name

The name of this study group shall be the Pulmonary Complications of Human Immunodeficiency Virus Infection Study group.

Article 2. Objective

The objective of the Steering Committee for this group shall be to provide scientific and operational guidance in carrying out cooperative clinical studies.

Article 3. Members and Representatives of the Steering Committee

Section 1. The membership shall consist of representatives of the the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Allergy and Infectious Diseases (NIAID), the Coordinating Center, and hospitals or other clinical or research facilities, or of organized groups of such facilities that have been contracted by the NHLBI in response to RFPs NHLBI-HR-87-9 and NHLBI-HR-87-10, and collaborating European centers.

Section 2. Responsibilities of member institutions include adherence to the study protocol including maintenance and prompt submission of complete and accurate data.

Section 3. Each member institution shall be represented by the Principal Investigator or his/her designee. Such designee must have a major clinical or research responsibility with respect to studies of interest to the Committee. The Scientific Project Officers in charge of the study shall be representatives of the NHLBI and NIAID. The Principal Investigator of the Coordinating Center shall be the representative of the Coordinating Center.

Article 4. Officers

Section 1. The officers of the Committee shall be a Chairman, a Vice-Chairman, and a Secretary. The Chairman and Vice-Chairman shall be from different collaborating institutions. Each officer shall perform the duties specified by this constitution or by the Committee.

Section 2. The Chairman and the Vice-Chairman shall be appointed by the NHLBI/NIAID. The Coordinating Center shall serve as the Secretary.

Section 3. The Chairman shall determine the agenda for meetings, and preside over the Committee meetings. He shall appoint members to standing and ad hoc subcommittees with the approval of the Committee. The Vice-Chairman shall serve in the absence of the Chairman. The Secretary shall schedule meetings, notify members of meetings, record and distribute minutes of Committee meetings, keep and distribute protocols and other Committee documents, and maintain files of all Committee activities including files of scientific data.

Article 5. Executive Subcommittee

Section 1. The Executive Subcommittee shall be constituted of the Steering Committee Chairman and Vice-Chairman, the Principal Investigator of the Coordinating Center, and the NHLBI/NIAID Scientific Project Officers in charge of the project.

Section 2. The Executive Subcommittee shall be the governing body of the Steering Committee. It shall have general supervision of the affairs of the Steering Committee between its meetings.

Section 3. The Executive Subcommittee may act in meetings, by mail, or by telephone with written confirmation to the Chairman of each telephone vote.

Section 4. The Executive Subcommittee shall be subject to the order of the Steering Committee and none of its actions shall conflict with the actions taken by the Steering Committee.

Section 5. The Executive Subcommittee shall coordinate the Steering Committee meetings with the Policy and Data Monitoring Board.

Article 6. Meeting

Section 1. There shall be a regular meeting of the Steering Committee at least twice yearly.

Section 2. A quorum shall be constituted when there is one representative from five member institutions and at least one National Institutes of Health scientific project officer present.

Section 3. The deliberations of the Steering Committee shall be conducted in a parliamentary manner. Unless otherwise specified, all scientific decisions shall be taken based on a simple majority of those present and voting; provided a quorum is established.

Section 4. The Steering Committee may act in meetings, by mail, or by telephone, with written confirmation to the Chairman of each telephone vote.

Section 5. Special meetings of the Steering Committee shall be called by the Chairman, at the request of NHLBI/NIAID, or at the written request of a majority of its members.

Article 7. Consultants

The Steering Committee with the concurrence of NHLBI/NIAID may invite, as consultants, individuals whom it feels would contribute useful information to the Committee deliberations.

Article 8. Voting

Section 1. Each member institution shall have one vote concerning amendments to this Constitution, amendments to the protocols, and in all other matters.

Section 2. Each person appointed to a subcommittee (excluding consultants) shall have one vote.

Article 9. Subcommittees

Section 1. The Steering Committee may establish or abolish any subcommittee it determines to be in its best interest.

Section 2. The membership and the chairmanship of any subcommittee shall be determined by the Chairman with the approval of the Committee.

Section 3. No subcommittee shall present a report outside the Steering Committee unless it has been specifically authorized to do so.

Article 10. Design and Analysis Subcommittee

This subcommittee shall consider and make recommendations on the experimental design for the study. These considerations shall include sample size, randomization procedures, and stratification variables, as well as other design issues. It shall monitor the number of recruitments and make suggestions regarding methods for recruitment, follow-up and other matters which will help meet the objective of the study in more efficient ways. It shall develop plans for data analysis in collaboration with the Coordinating Center.

This subcommittee shall also deal with interpretations of diagnostic and endpoint criteria. It shall periodically review these criteria and recommend changes, if required, to the Committee.

Article 11. Laboratory and Quality Control Subcommittee

This subcommittee shall monitor the performance of the Clinical Centers and the Coordinating Center and report findings to the Committee. Information which would lend to the unblinding of the overall results of the Study shall not be reviewed by this subcommittee.

Article 12. Publications and Presentations Subcommittee

This subcommittee shall review all written and oral presentations on the design, progress, and results of the study including any ancillary studies. The subcommittee shall at a minimum follow DLD and AP guidelines on presentations and publications.

Article 13. Ancillary Studies Subcommittee

This committee shall review proposals for ancillary studies and make recommendations to the committee regarding these proposals.

Article 14. Publications

Section 1. The group shall present or publish from time to time the results of studies. Members and consultants are encouraged and urged to analyze and publish data based on the study, provided that they adhere to the DLD guidelines in Chapter XII.

Section 2. The Chairman, with the approval of the Executive Subcommittee, may designate and appoint members to a Writing Subcommittee for any study report. A Writing Subcommittee shall be automatically discharged when it submits its final report.

Section 3. There is likely to be a great variety of publication situations and degrees of appropriate acknowledgments for members and consultants, including the special requirements of some journals. Therefore, all papers for publication, abstracts, presentations at meetings, or other public distribution of results based on data for patients entered in the study must be sent to all members of the Publication and Presentation Subcommittee not less than two weeks prior to initial submission of the report. The Subcommittee shall decide (1) whether the scientific content of the paper and interpretation of the data are acceptable; (2) whether the contributions of members, representatives, and consultants are properly acknowledged; and (3) whether publication of the paper is in the best interest of the study. Each member of the Subcommittee shall notify the Chairman of the Subcommittee regarding his approval or disapproval of the report as submitted, with reasons for any disapproval and recommendations for changes. The Subcommittee Chairman shall then notify the principal author of the majority decision of the Subcommittee which may include approval, approval contingent upon specific revisions, approval with suggestions for revision and resubmission, or disapproval. In case the Subcommittee does not reach a majority decision, the matter will be deferred for decision by the Committee at its next meeting.

Section 4. Membership in the Steering Committee implies agreement to abide by these procedures for all publications based on study data. The provisions of this Article apply to reports of Writing Subcommittees as well as other reports based on study data.

Section 5. The decision of the Steering Committee may be appealed to the appropriate authority within the NHLBI and NIAID. The authors shall abide by the final decision of the NHLBI.

Article 15. Amendment

This Constitution shall be amended at any Committee meeting by two-thirds vote of all regular members whether present or not, provided

that the amendment has been submitted in writing to all representatives not less than two weeks prior to voting on such amendment.

Article 16. Veto

The Director, Division of Lung Diseases, NHLBI or AP, NIAID is empowered to exercise a veto on any decisions of the Committee including amendments to the Constitution which he/she considers not in the interest of the study. The veto, if exercised, should be communicated in writing to the Chairman within 30 days of the Committee decision.

Article 17. Human Use Review

Certifications of Human Use Review Committees of participating clinical centers are mandatory for the study. The participating clinical centers shall arrange for the certification before the study begins, and on a yearly basis thereafter. This will be the responsibility of principal investigators from clinical centers.

Article 18. Non-Directly Funded Centers

Non-directly funded collaborators, either domestic or foreign, may withdraw from the study after a written request for such action is submitted to the Chairperson of the Steering Committee. Pooled data will be jointly analyzed by the Coordinating Center. Raw data will remain the property of the non-directly funded collaborators.

16. Publications and Presentations

16.1 Guidelines

The principles under which the Publications and Presentations Subcommittee will operate are stated in the following goals:

1. dissemination by publication of the maximum amount of information pertinent to the outcome of the collaborative study;
2. maximal sharing of results pertaining to ancillary studies;
3. the first priority of publication shall be to those related to major results;
4. encouragement of the highest quality publication;
5. responsibility shall reside within each center to be cognizant of all other studies involving the collaborative

trial patients and potential publications on studies involving these patients;

6. studies shall be brought to publication in a timely fashion through participation and critique of all of the investigators; and
7. all efforts shall be made to facilitate the publication and presentation of ancillary studies in a fashion that will not intrude upon nor have a deleterious effect on the presentation or publication of data from the overall study.

The Subcommittee will use the following definitions and procedures in monitoring study publications and presentations.

16.2 Press Release

A press release is defined as a document given to radio, television, newspapers, scientific journals not indexed in the Index Medicus, and popular periodicals without national circulations.

Local press releases will not be reviewed by the Publications and Ancillary Studies Subcommittee. Nevertheless, all these press releases must limit their substantive content to information items that have been described in the most recent request for proposals. A copy of each prepared release must be sent to the NHLBI/NIAID Project Officers prior to release, for approval and for updating the Program Office files on current knowledge to be used for responses to national queries. Also, copies of all press releases should be retained and sent to the Project Officer with Quarterly Reports as required by the contracts. A central file of all press releases will be maintained by the Project Officer.

Project-wide press releases will be initiated by the Program Office (NHLBI and NIAID) and reviewed by the Publications and Ancillary Studies Subcommittee.

16.3 Interview

An interview is any discussion with a member of the press, a science writer, or a radio or television commentator, which provides information for public dissemination.

Interviews are subject to the same editorial rules as press releases. Local information concerning participation by local

organizations can be provided to encourage cooperation and acceptance of the program. The ethics and legalities of medical confidentiality apply to the names and risk statuses of individual participants.

16.4 Presentation

A presentation is the delivery of information that may be disseminated as a press release. This definition is independent of the forum. Under these guidelines a seminar within a closed academic setting would not be classified as a presentation.

Material for all presentations given outside closed academic communities must be reviewed by the Publications and Presentations Subcommittee. These include presentations given to scientific, professional, or public groups. Particular attention is drawn to presentation of material when proceedings of the meeting or workshop are likely to be published or publicized.

Presentations are subject to the same rules as press releases. If a presentation is limited to substantive information in the RFP and has no added interpretation or inferences, it can be given without prior review by the Publications and Presentations Subcommittee. Any discussion of the true or ancillary projects that goes beyond those items of information must be submitted for review at least two weeks prior to the date of presentation. The Publication and Presentations Subcommittee will identify scientific and professional forums where presentations about the Study should be made on behalf of the Steering Committee. It will bring these proposed forums for presentation to the Steering Committee for approval. From a list of volunteer investigators the Steering Committee will identify one or more persons to prepare and present the material. The written presentation must be reviewed by the Steering Committee before it is presented.

16.5 Publication

A publication is any document submitted to a professional journal or any popular periodical with national circulation.

All publications of primary and ancillary studies will be prepared under the direction of the Publications and Presentations Subcommittee. All official publications of the Study will be written by committee and credit for authorship will be to the "Pulmonary Complications of HIV Infection Study Group". Publication of results of

ancillary studies performed on participants admitted to the Study will be allowed by individual investigators. Approval by the Publications and Presentations Subcommittee is required if the ancillary study makes use of data collected according to the Study protocol. After the final results of the Study are compiled and submitted for publication, individual investigators involved in the Study may request access and publisher rights to data accumulated during the Study.

Two categories of publications are discussed.

(1) Publications prepared on behalf of a limited number of investigators or centers. All manuscripts which describe:
   (a) primary screening and recruitment procedures;
   (b) any process of the Study or information collected using defined procedures and protocols;
   (c) any approved or informal ancillary study carried out in Study population; or
   (d) any work supported partially or wholly by this Study must be submitted to the Publications and Presentations Subcommittee for review prior to submission to publication.

The Subcommittee will review draft publications with the following objectives in mind:

   (a) to make sure that no publication will have a deleterious effect on the Study process, acceptance, or on the interpretation of its results;
   (b) to correct factual and conceptual inaccuracies;
   (c) to safeguard the rights of volunteer participants;
   (d) to prepare comments to assist collaborating scientists to publish papers of the highest quality (the latter is accepted as a responsibility because all publications related to this Study will affect public perception of its scientific rigor and operational activities); and
   (e) to inform the Steering Committee and Policy and Data Safety Monitoring Board of all public dissemination of information.

(2) Publications prepared as study-wide documents. Basic papers of the Study which must draw on data collected by all Centers will be identified by the Publications and Presentation Subcommittee. The proposed series of publications will be submitted to the Subcommittee for approval. An ad hoc committee of volunteers from the professional staffs of all collaborating Centers may be appointed to draft each paper. Each ad hoc committee will be charged with responsibility for writing the paper in a prescribed format within a stated time limit. The senior author of the paper will be clearly denoted as "The Pulmonary Complications of HIV Infection Study Group" with an asterisk to refer to the name of the Centers and their principal investigators. Under this title and the appropriate reference to the Study's investigators as the main author of the paper, the names of the members of the ad hoc committee who prepared the paper will be printed in sequence. The senior author will be either the Chairman of the ad hoc committee or the person who undertook most of the work in preparation of the paper. Other members of the ad hoc committee will be co-authors. This policy permits:

(a) the investigators of all Centers to be recognized and list the paper in their bibliographies;

(b) the preparation of a paper by a small group of investigators; and

(c) all investigators in all Centers to have an opportunity to participate in the preparation of basic papers and gain academic recognition for their contribution to the program.

The objective of the proposed Editorial Policy is:

(a) to have the highest quality presentations and papers from the Study and its collaborating investigators;

(b) to make sure that all investigators have the opportunity to participate in study-wide presentations and the preparation of papers; and

(c) to make sure that no press release, interview, presentation or publication will have a deleterious effect on the collaborative trial and the acceptance of its results.

16.6 Review Process

Review of these documents will fulfill two additional objectives: (1) protect academic prerogatives, and (2) avoid time restrictions on authors.

All press releases, interviews, presentations, and publications that require review by the Publications and Presentations Subcommittee should be sent directly to the Project Officer who will immediately communicate with the Subcommittee. At least three reviewers will be identified from a pre-prepared study-wide list of volunteers. Reviewers will be chosen for their expertise in the subject matter of the particular document and for their understanding of the study as a whole. Each reviewer will be asked to judge whether or not the publication as written will affect the Study's process, its acceptance or the interpretation of its results. If the Committee agrees that the document can have a deleterious effect, the manuscript will be returned to the author with suggestions for appropriate changes. If the Committee agrees that the manuscript can have no deleterious effects, a letter so stating will be returned to the author with the manuscript. He/she will be free to follow through with presentation, press release, or submission of the manuscript for publication.

Each manuscript prepared for publication will be reviewed by a minimum of three reviewers. At least one will be a member of the Publications and Presentations Subcommittee. When there is a particular technical question that cannot be confidently answered by the reviewers, the Publications and Presentations Subcommittee will use outside consultants to obtain technical advice. Investigators who challenge a Publications and Presentation Subcommittee decision will be able to appeal to the Chairman of the Steering Committee. The Policy Advisory Board of the NHLBI will be the final arbiter.

17. Ancillary Studies

Studies that involve study subjects and study investigators but that are not directly related to study objectives (page 5) will be considered ancillary. Studies that are within the primary and secondary objectives of the study will be considered as part of the main study itself. Specifically, any study, procedure, or measurement required by the protocol, and any study bearing on a study end point. Studies that rely on data collected by less than the total group will be considered ancillary, as will studies utilizing non-study data.

Studies meeting this definition will be reviewed and approved by the Ancillary Studies Subcommittee. The goal of the review and approval process is to ensure that ancillary studies do not impinge on the primary study objectives or interfere with the ability to complete the primary study. Ancillary studies should be consistent with the primary mission of the study and will be governed by the same ethical and confidentiality considerations.

should be sent directly to the Project Officer who will immediately communicate with the Subcommittee. At least three reviewers will be identified from a pre-prepared study-wide list of volunteers. Reviewers will be chosen for their expertise in the subject matter of the particular document and for their understanding of the study as a whole. Each reviewer will be asked to judge whether or not the publication as written will affect the Study's process, its acceptance or the interpretation of its results. If the Committee agrees that the document can have a deleterious effect, the manuscript will be returned to the author with suggestions for appropriate changes. If the Committee agrees that the manuscript can have no deleterious effects, a letter so stating will be returned to the author with the manuscript. He/she will be free to follow through with presentation, press release, or submission of the manuscript for publication.

Each manuscript prepared for publication will be reviewed by a minimum of three reviewers. At least one will be a member of the Publications and Presentations Subcommittee. When there is a particular technical question that cannot be confidently answered by the reviewers, the Publications and Presentations Subcommittee will use outside consultants to obtain technical advice. Investigators who challenge a Publications and Presentation Subcommittee decision will be able to appeal to the Chairman of the Steering Committee. The Policy Advisory Board of the NHLBI will be the final arbiter.

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the primary study objectives or interfere with the ability to complete the primary study. Ancillary studies should be consistent with the primary mission of the study and will be governed by the same ethical and confidentiality considerations.

Appendix 1

Questions to be Addressed: Study Groups, Variables Examined, and Analysis

Introduction

The information provided in relation to each of the questions includes: population groups studied, predictive variables, confounding variables, outcome variables, analytical strategies and the expected precision of the calculated rates based on the planned sample size.

The purpose of this section is to describe the general approach to utilizing the study data for addressing the substantive questions of interest; this is not meant to be an exhaustive list of analytical approaches, variables and outcomes which will be used to make inferences from these data. For example, because only the HIV seropositive groups are relevant to the estimation of the rates of HIV-related conditions, only these groups will be listed under "groups studied." A diagnosis is associated with HIV if: (1) it occurs only in the HIV seropositive group or (2) it occurs at a significantly higher rate in the HIV seropositive group than in the HIV seronegative group. Therefore, some comparisons with the HIV seronegative group are implicit in addressing some of the questions. Unless such comparisons are the major focus of the question, the HIV seronegative group is not explicitly listed under the groups studied. Another variable that is not explicitly mentioned is the Clinical Center. Because this is a multicenter study, the center is a major variable (predictive or confounding variable) that must be included in most of the analyses. Many of the analyses revolve around appropriate regression models. Where appropriate, nonparametric methods will also be used.

Question 1. What are the specific lung diseases associated with HIV infection and what is their prevalence and incidence?

Groups studied:

All HIV seropositive subjects

Predictive variables

HIV antibody status

Stage of HIV infection (clinical and immunologic)

HIV transmission category

Confounding variables

Preventive treatment for infections

AntiHIV therapy

Immunosuppressive drugs

Outcome variables

Presence of specific diseases as defined in Appendix 2 or other diseases

Analysis

Calculation of prevalence and incidence type measures (crude rates) for specific diseases for various subgroups of the population (determined by predictive variables), and estimation of adjusted rates (adjusted for confounding variables) using regression type models. These rates will be combined using appropriate weighting schemes to estimate "standardized" rates.

Comparisons with corresponding rates in the HIV negative group will be made where appropriate to assess whether these conditions are HIV-related (occur only in the HIV seropositive group or occur in the seropositive group with a significantly higher rate than in the seronegative group).

Precision

Half-width 95% confidence interval for incidence of *P. carinii* pneumonia is 2% in Group A and 3% in Group B.

Question 2. What is the association of the following pulmonary diseases with subsequent morbidity and mortality: *P. carinii* pneumonia, tuberculosis, *Mycobacterium avium* complex infection, cytomegalovirus infection? Associations with subsequent morbidity and mortality will also be sought for less frequent processes including NIP, LIP, pyogenic bacterial infections, fungal infections and Kaposi's sarcoma involving the lungs. However, because of the infrequency of these processes, associations may be difficult to establish.

Groups studied

All HIV seropositive subjects

Predictive variables

Specific diseases as defined in Appendix 2

Confounding variables

HIV transmission category

Clinical and immunologic stage of HIV infection

Coexisting diseases

Diseases developing subsequently

Multiple pathogens present in the same patient

Outcome variables

Survival

Rate of change in pulmonary function

Days in hospital

Rate of weight loss

Rate of change in performance status

Evolution of chest film

Analysis

The analyses will be based on regression type models (linear, logistic, Cox regression) or multiple contingency tableanalysis models. Statistical measures studied will include differences in the rates (e.g., differences in the rates of specific abnormalities on chest films between those who had and those who did not have a specific pulmonary process) or means (e.g., days in hospital, rate of weight loss)

Question 3. What is the frequency with which multiple pulmonary diseases are present simultaneously and what are the common associations?

Groups studied

All HIV seropositive subjects

Predictive variables

Specific diseases (Appendix 2)

Confounding variables

HIV transmission category

Clinical and immunologic stage of HIV infection

Preventive therapy for infections

Outcome variables

Coexisting diseases

Analysis

The joint distributions of pulmonary diseases present at the same time in a patient will be analyzed using methods for categorical data. Significant associations among diseases will be described.

Question 4. What are the prevalence and incidence of specified symptoms, signs, radiographic findings, pulmonary function test abnormalities, laboratory findings, immunologic abnormalities and presence of indicators of HIV activity in patients with specific pulmonary diseases?

Groups studied

All HIV seropositive subjects

Predictive variables

Symptoms - cough, shortness of breath, fever, weight loss, fatigue, diarrhea

Signs - cutaneous Kaposi's sarcoma, oral thrush, hairy leukoplakia, adenopathy, wheezes, rales

Radiographic findings (defined in Section 7.2.4)

Pulmonary function tests - vital capacity, total lung capacity, forced expiratory volume in one second, diffusing capacity

Laboratory findings - hemoglobin, hematocrit, white blood cell count, absolute number of neutrophils, lymphocytes and monocytes, liver function tests (bilirubin, SGOT, SGPT, alkaline phosphatase, total serum proteins, albumin) erythrocyte sedimentation rate, lactate dehydrogenase

Tests of immune status - intradermal tests (tuberculin, trichophyton, candida), lymphocyte subsets (CD3, CD4, CD8)

Tests of HIV activity - P-24 antigen, beta-2 microglobulin

Confounding variables

Coexisting nonHIV-related diseases

Immunosuppressive therapy or conditions

Multiple coexisting HIV-related diseases

Outcome variables

Specific HIV-related diseases (Appendix 2)

Analysis

The broad objective of the sequence of analyses in this context is to assess the strength of association between the predictive variables (in a univariate and in a multivariate sense) and specific diseases. Analytic techniques used will include both simple contingency table analyses.

The statistical treatment of the data will also include the calculation of prevalence and incidence type measures (crude rates) for specific diseases for various subgroups of the population (determined by predictive variables), and estimation of adjusted rates (adjusted for confounding variables) using regression type models. These rates will be combined using appropriate weighting schemes to estimate "standardized" rates.

Question 5. What are the symptoms, signs, radiographic findings, pulmonary function abnormalities, laboratory findings, tests of immune status and tests of HIV activity that are associated with recurrent episodes of P. carinii pneumonia?

Groups studied

All HIV seropositive subjects who have had P. carinii pneumonia

Predictive variables

Symptoms - cough, shortness of breath, fever, weight loss, fatigue, diarrhea

Signs - cutaneous Kaposi's sarcoma, oral thrush, hairy leukoplakia, adenopathy, wheezes, rales

Radiographic findings (defined in Section 7.2.4)

Pulmonary function tests - vital capacity, total lung capacity, forced expiratory volume in one second, diffusing capacity

Laboratory findings - hemoglobin, hematocrit, white blood cell count, absolute number of neutrophils, lymphocytes and monocytes, liver function tests (bilirubin, SGOT, SGPT, alkaline phosphatase, total serum proteins, albumin) erythrocyte sedimentation rate, lactate dehydrogenase

Tests of immune status - intradermal tests (tuberculin, trichophyton, candida), lymphocyte subsets (CD3, CD4, CD8)

Tests of HIV activity - P-24 antigen, beta-2 microglobulin.

Confounding variables

Coexisting nonHIV-related diseases

Immunosuppressive therapy or conditions

Multiple coexisting HIV-related diseases

Antiviral therapy

Antipneumocystis preventive therapy

Outcome variables

Presence of recurrent P. carinii pneumonia

Analysis

Analysis strategies will be similar to those used in answering Question 4.

Question 6. Are the relative frequencies of pulmonary diseases different in homosexual/bisexual men compared with intravenous drug abusers?

Groups studied

All HIV seropositive subjects

Predictive variables

HIV transmission category

Confounding variables

Place of residence (Clinical Center)

Age

Sex

Clinical and immunologic stage of HIV infection

Coexisting nonHIV-related diseases

Antiviral therapy

Preventive therapy for HIV-related processes

Outcome variables

Specific HIV-related diseases

Analysis

Categorical data analysis techniques based on minimum Chi-square methods (e.g., the CATMOD procedure in SAS) will be used to address this question. Some comparisons with the HIV negative group may also be used in this context

Precision

Half-width 95% confidence interval for the differences in prevalence of defined diseases between homosexual/bisexual and IV drug user is 4%.

Question 7. Do the relative frequencies of pulmonary diseases differ among the different Clinical Centers participating in the study?

Groups studied

All HIV seropositive subjects

Predictive variables

Clinical Center in which the subject is enrolled

Confounding variables

HIV transmission category

Age

Sex

Clinical and immunologic stage of HIV infection

Coexisting nonHIV-related diseases

Antiviral therapy

Preventive therapy for HIV-related diseases

Outcome variables

Specific HIV-related diseases

Analysis

This question will be addressed with the mathematical model used to answer Question 6.

Question 8. Are different stages of HIV infection as defined by absolute and relative numbers of CD4 cells associated with different HIV-related pulmonary diseases?

Groups studied

All HIV seropositive subjects

Predictive variables

Absolute and relative numbers of CD4 cells. The CD4 cells will be grouped into 3 categories (>399, 200-399, <200) in some analyses.

Confounding variables

Antiviral therapy

Preventive therapy for HIV-related lung diseases

Outcome variables

Specific HIV-related lung diseases

Analysis

Regression models, appropriate when time dependant covariates are present, will be used to study this question.

Question 9. Do HIV infected persons who have not had lung diseases diagnosed have a greater incidence/prevalence of respiratory symptoms, pulmonary function abnormalities and unexplained radiographic findings than HIV seronegative subjects in the same transmission category?

Groups studied

All HIV seropositive and seronegative subjects

Predictive variables

HIV status

Transmission category

Confounding variables

Previous or current lung disease (recognized HIV-related or nonHIV- related)

Smoking

Outcome variables

Symptoms

Vital capacity, total lung capacity, forced expiratory volume in one second, diffusing capacity

Radiographic findings

Analysis

Analytic strategies involving regression models (linear and logistic) will be used

Question 10. Does pulmonary function deteriorate more rapidly in HIV infected persons who have not had lung diseases diagnosed compared with HIV seronegative subjects in the same transmission category?

Groups studied

All HIV seropositive and seronegative subjects

Predictive variables

HIV status

Transmission category

Confounding variables

Previous or current lung disease (recognized HIV-related or nonHIV- related)

Smoking

Outcome variables

Changes in vital capacity, total lung capacity, forced expiratory volume in one second, diffusing capacity over time

Analysis

Regression models will be used to address these questions. Appropriate measures of decline (change) in lung function measurements will be used as outcome variables

Precision

Half-width 95% confidence intervals of DLCO for A versus C and B versus C are 2.0 for IV drug users and 1.3 for gays.

Question 11. How sensitive are symptoms for specific HIV-related lung diseases?

Groups studied

All HIV seropositive and seronegative subjects

Predictive variables

Fever (> 38R oral for > 5 days)

Cough (with or without sputum for > 5 days)

Shortness of breath (mild to moderate > 5 days, severe > 1 day)

Confounding variables

Preexisting lung disease

NonHIV-related lung diseases

Outcome variables

Presence of specific HIV-related lung diseases (Appendix 2)

Absence of specific HIV-related lung diseases. Determined by lack of findings on evaluations as specified in Section 7.2.4 or by clinical course during one month following the evaluation

Analysis

Calculation of sensitivity. Regression models will be used to adjust for confounding variables.

Question 12. Does diagnosis of P. carinii pneumonia by intensive screening decrease both short- and long-term mortality?

Groups studied

All HIV seropositive subjects

Predictive variables

Diagnosis by intensive or routine screening or by symptom evaluation

Confounding variables

Treatment regimens for P. carinii pneumonia

Coexisting diseases

Antiviral therapy

Preventive therapy for HIV-related lung diseases

Outcome variables

Mortality rate at one month after diagnosis of P. carinii pneumonia

Median survival from time of study entry

Median survival from estimated time of HIV infection using slope of decline in CD4 cells

Analysis

Appropriate regression models and nonparametric techniques will be used to address this question

Precision

Half-width 95% confidence interval on long-term mortality rate differences between "routine" and "intensively" screened groups is 6%.

Question 13. Does diagnosis of P. carinii pneumonia by intensive screening decrease number of days of hospitalization?

Groups studied

All HIV seropositive subjects

Predictive variables

Diagnosis by intensive or routine screening or by symptom evaluation

Confounding variables

Treatment regimens for P. carinii pneumonia

Coexisting diseases

Antiviral therapy

Preventive therapy for HIV-related lung diseases

Outcome variables

Days in hospital after PCP diagnosis

Analysis

These data will be analyzed using linear models.

Question 14. Does diagnoses of P. carinii pneumonia by intensive screening decrease the rate of deterioration in performance status?

Groups studied

All HIV seropositive subjects

Predictive variables

Diagnosis by intensive or routine screening or by symptom evaluation

Confounding variables

Treatment regimens for P. carinii pneumonia

Coexisting diseases

Antiviral therapy

Preventive therapy for HIV-related lung diseases

Outcome variables

Rate of decline in performance score

Analysis

These data will be analyzed using linear models.

Appendix 11

Protocol Changes

1. New Date of Protocol
2. Page 40, #10: "... or other qualified professional staff".
3. Page 41, Paragraph 7.2.3, line 3; ..(except for induced sputum exams) added.
4. Page 41, Paragraph 7.2.4, line 6; "...or pulmonary function abnormalities" deleted.
5. Page 42. Induced Sputum only prescheduled for Entry exam.
6. Page 43. #3: Second paragraph is new.
7. Pages 44-91 are renumbered.
8. Page 44. #4 rewritten.
9. Page 44. #4, Paragraph 3: First sentence rewritten.
10. Page 44. #8 "...reduced DLCO" deleted.
11. Page 45. Pulmonary Function Abnormalities-last three lines of paragraph, #1 deleted.
12. Page 45, #2: New paragraph.
13. Page 45. Paragraph 2 "...reduced DLCO value" deleted.
14. Page 46. First paragraph line 1 "...with normal or stable DLCO values" deleted.
15. Page 46. First paragraph, line 3 "...or restricted without reduced DLCO" deleted.
16. Page 46. Last paragraph, line 3 "...and DLCO" deleted.
17. Page 46. Last paragraph, line 4 "...or the DLCO is reduced by at least ≥ 20% and 3 ml/min/mmHg from the previous value" deleted.
18. Page 47. Paragraph 7.2.6, line 4 "...a normal DLCO" deleted.
19. Page 47. Paragraph 7.2.6, line 5 "...normal DLCO" deleted.
20. Page 47, #6. New paragraph.
21. Page 50. Expanded definition of pleural effusion.
22. Page 70. Paragraph 10.2.7 line 6 and line 11: "...two maneuvers".
23. Page 71. Paragraph 10.2.8 "... follow-up and symptom evaluations".
24. Appendix 2: Changes in the definitions of PCP, Toxoplasmosis, Candidiasis, Bacterial Pneumonia.
25. Appendix 5: Page 13 Chest Radiography Procedures - New

26. Appendix 6: Previously Appendix 7.
27. Appendix 7: Previously Appendix 8.
28. Appendix 8: Serum Tracking and Shipping - New
29. Appendix 9: Skin Testing - New
30. Appendix 10: Previously Appendix 12.

Appendix 2

Definitions of Diagnoses

For purposes of the study, specific lung diseases are defined as follows (when processes are diagnosed from samples from extrapulmonary sites, in order to be considered as a pulmonary complication there must be a measurable pulmonary abnormality not associated with a compatible alternative pulmonary diagnosis):

Pneumocystis carinii pneumonia - Definite: Recovery of organisms on smear of lung derived specimens. Presumptive: The physician investigator must first review all available medical information and make a decision that a diagnosis of presumptive Pneumocystis carinii pneumonia is justified. First episode: The diagnosis of Pneumocystis carinii pneumonia (either definite or presumptive, as defined above) on the first such occasion. Episodes subject to first: the finding of P. carinii in any lung derived specimen, or the diagnosis of presumptive P. carinii pneumonia (as defined above) more than 2 months after completion of treatment for a previous episode and compatible clinical findings.

Tuberculosis - Pulmonary: Positive culture of lung derived specimen and an abnormality on chest x-ray or a compatible clinical picture. Extra pulmonary: Isolation of M. tuberculosis from any extra pulmonary source.

M. avium complex and other nontuberculous mycobacteria - Pulmonary: Isolation of M. avium or other nontuberculous mycobacteria from a lung-derived specimen in a patient with clinical illness who has no other pulmonary diseases identified. Extrapulmonary: Isolation of M. avium or other nontuberculous mycobacteria from an extrapulmonary source.

Cytomegalovirus Infection - Pulmonary: Demonstration of lung cell (including alveolar macrophage) infection by characteristic intranuclear and/or cytoplasmic inclusion bodies or by labelled specific DNA probes or monoclonal antibodies. Isolation of CMV from a respiratory specimen is desirable but optional for confirmation. Extrapulmonary: Demonstration of cell infection by characteristic intranuclear and/or cytoplasmic inclusion bodies. Isolation of CMV from blood.

Toxoplasmosis - Pulmonary: Histopathologic identification of T. gondii in lung tissue. Extrapulmonary: Histopathologic identification of T. gondii in extrapulmonary tissue. Diagnostic changes (2 fold in 3 weeks) in IgG titer or single IgM titer of 1:160 or higher. Of the brain: radiographic improvement after specific treatment for toxoplasmosis or recovery of organisms from brain tissue.

Pulmonary strongyloidiasis - Demonstration of larvae in any lung-derived specimen or demonstration of larvae in stool or duodenal aspirate and a clinical picture compatible with disseminated infection involving the lungs.

Candidiasis - Pulmonary: Histologic demonstration of invasive pulmonary involvement. Extrapulmonary: Demonstration of characteristic lesions by visual or radiographic examination or demonstration of invasive Candida infection by biopsy. Confirmation by microscopy or culture is desirable.

Cryptococcosis - Pulmonary: Positive culture or microscopic demonstration of C. neoformans in any lung-derived specimen in a compatible clinical setting. Demonstration of tissue invasion is desirable, but not required in immunocompromised hosts. Extrapulmonary: Positive culture or microscopic demonstration of C. neoformans in CSF or any extrapulmonary tissue. CSF cryptococcal antigen $\geq$ 1:8 is diagnostic of meningitis.

Histoplasmosis or Coccidioidomycosis - Pulmonary: Positive culture or microscopic demonstration of H. capsulatum or C. immitis in any lung-derived specimen. Extrapulmonary: Positive culture or microscopic demonstration of H. capsulatum or C. immitis from any extrapulmonary source. CSF C. immitis complement fixation titer $\geq$ 1:8 is diagnostic of meningitis. Pulmonary and/or Extrapulmonary: C. immitis complement fixation titer > 1:16.

Herpes Simplex Virus (HSV) - Pulmonary: Culture or demonstration of typical multinucleate giant cells and/or intranuclear inclusions or isolation of HSV from lung-derived specimens. Extrapulmonary: Demonstration of typical multinucleate giant cells, inclusion bodies or positive culture for HSV from any extrapulmonary source.

Nocardiasis - Pulmonary: Isolation of Nocardia species from any lung- derived specimen. Extrapulmonary: Isolation of Nocardia species from any extrapulmonary source.

Bacterial Pneumonia

Aerobic Bacterial Pneumonia - Definite: Presence of a compatible clinical setting and isolation of a likely pathogen from: 1) blood; 2) adequate sputum specimen in relatively pure culture or as a predominant microorganism; 3) protected brush specimen in a concentration of $>10^3$ cfu/ml; or 4) recovery of a specific pathogenic microorganism from BAL in a concentration of $>10^5$ cfu/ml. Confirmation by gram stain of an adequate sputum specimen (defined as ≥25 PMN/100x field and ≤ 10 epthelial cells/100x field) is desirable.

Anaerobic Bacterial Pneumonia (Probable) - Presence of a compatible clinical setting and resolution of symptoms and roentgenographic abnormality with empiric antimicrobial theraphy (not TMP/SMX).

Legionella Pneumonia - Isolation of Legionella species from an appropriate respiratory sample. Demonstration by DFA stain or DNA probe should be confirmed by positive culture. Four-fold increase in IFA titers over ≤ 6 weeks.

Mycoplasma Pneumonia - Isolation of M. Pneumoniae from appropriate respiratory specimen. Complement fixation titer of 1:64 or greater or a four-fold rise over ≤ 3 weeks.

Lymphoid interstitial pneumonitis and nonspecific interstitial pneumonitis - Demonstration of the described histopathologic characteristics in lung tissue.

Kaposi's sarcoma - Demonstration of characteristic histopathologic findings in lung tissue or visualization of typical endobronchial lesions during bronchoscopy.

Lymphoma - Demonstration of the characteristic histopathologic findings in lung tissue.

Appendix 3

Precision Estimates

In terms of the principal objectives stated elsewhere in this protocol, four key questions have been isolated for precision calculations. From Appendix 1, these are: (1) What are the specific lung diseases associated with a HIV infection and what are their incidences? (6) Are the relative frequencies of pulmonary diseases different in homosexual/bisexual men compared with intravenous drug abusers? (10) Does pulmonary function deteriorate more rapidly in HIV infected persons who have not had lung disease diagnosed compared with HIV seronegative subjects in the same transmission category? and (13) Does intensive screening for the diagnosis of P. carinii pneumonia before symptoms develop decrease long term mortality?

In all of these calculations, the one-half 95% confidence interval is used as a measure of the precision of the comparison of interest and/or the estimate of prevalence or incidence. Tables 3.1 through 3.3 give the one-half 95% confidence intervals for estimates of the incidence rates of PCP for the different cells of the design as well as the confidence interval for various comparisons of interest. Entries in Tables 3.2 and 3.3 may be interpreted as differences which would be judged significant at the end of the trial. It is seen from Table 3.1 that the halfwidth of the 95% confidence interval for the estimate of incidence in Groups A and B are 2% and 3%, respectively.

The same tables may be used to judge the precision of the comparison between homosexual/bisexuals and IV drug users relative to the PCP as set forth in Question 6. Table 3.3 indicates that a difference of .04 at the end of one year of follow-up would be judged significant for the comparison of homosexual/bisexuals versus IV drug users.

Tables 3.4 through 3.6 are relevant in answering questions about the precision of comparisons in Question 10. Tables 3.4-3.6 deal with the precision of comparisons in DLCO. Groups A, B and C are of interest in these tables. A standard deviation of 2.5 is used for the DLCO calculations. According to Question 10, the primary comparisons of interest are Group A versus Group C and Group B versus Group C; these

comparisons being made within risk categories. This being the case, it is seen that the respective comparisons for DLCO in IV drug users would be declared significant if the difference were greater than 0.8 and would be declared significant for the homosexual/bisexual comparisons if differences greater than 0.5 were observed.

Finally, Tables 3.7 through 3.10 show precision estimates for long-term mortality estimates and comparisons. In terms of Question 13, the comparison of interest is between the "intensively" screened and the "routinely" screened groups. For the overall long term mortality comparisons between the two groups, a mortality difference of 6% would be judged significant at the end of the study with this design.

Precision Estimates for
PCP Incidence Estimates and Comparisons*

Table 3.1

1/2 Confidence Intervals for Incidence

	A	B	C	Total
H/BS	0.02	0.04	0	0.02
IV	0.04	0.07	0	0.03
OTH	0.07	0.13	0	0.08
TOT	0.02	0.03	0	

Table 3.2

1/2 Confidence Intervals (Comparisons)

	AvsB	AvsC	BvsC
H/BS	0.05	0.02	0.04
IV	0.08	0.04	0.07
OTH	0.15	...	...
TOT	0.04	0.02	0.03

Table 3.3

1/2 Confidence Intervals (Comparisons)

	A	B	C	Total
H/BSvsIV	0.04	0.08	0	0.04
H/BSvsOTH	0.08	0.14	.	0.08
IVvsOTH	0.08	0.15	.	0.08

* Assumption for calculations were: After one year of follow-up,
Prevalence in A = 5%
Prevalence in B = 20%
Prevalence in C = 0%. (Source: Moss et al., Brit. Med. J., 1987; 1)

Precision Estimates for Comparison of DLCO Among Disease and Transmission Groups****

Table 3.4

1/2 Confidence Intervals

	A	B	C	Total
H/BS	0.8	0.8	1.0	0.5
IV	1.0	1.0	1.8	0.8
OTH	2.0	2.0	...	1.5
TOT	0.5	0.5	1.0	

Table 3.5

1/2 Confidence Intervals (Comparisons)

	AvsB	AvsC	BvsC
H/BS	1.0	1.3	1.3
IV	1.5	2.0	2.0
OTH	3.0	...	...
TOT	0.8	1.0	1.0

Table 3.6

1/2 Confidence Intervals (Comparisons)

	A	B	C	Total
H/BSvsIV	1.3	1.3	2.0	0.8
H/BSvsOTH	1.3	2.3	...	1.5
IVvsOTH	2.3	2.3	...	1.5

**** Assumption in calculations was that the standard deviation of DLCO is 2.5. (Source: Data from 878 patients in PACS.)

Precision Estimates for
Mortality Estimates and Comparisons*****

Table 3.7

1/2 Confidence Intervals

	Intensive	Routine	Total
H/BS	0.05	0.05	0.03
IV	0.08	0.08	0.06
OTH	0.16	0.16	0.11
TOT	0.04	0.04	

Table 3.8

1/2 Confidence Intervals (Comparisons)

	Intensive vs Routine
H/BS	0.07
IV	0.11
OTH	0.22
TOT	0.06

Table 3.9

1/2 Confidence Intervals (Comparisons)

	Intensive	Routine	Total
H/BSvsIV	0.09	0.09	0.07
H/BSvsOTH	0.16	0.16	0.11
IVvsOTH	0.17	0.17	0.12

***** Assumption made in the calculations was that the three year mortality rates in A and B are 15% and 50%, respectively. (Source: Dr. William Fulkerson et al., private communication.)

Appendix 4

Recruitment Strategies

1. Mount Sinai Medical Center
2. New Jersey College of Medicine and Dentistry
3. Henry Ford Hospital
4. Northwestern University
5. UCLA
6. UCSF/SFGH
7. Frankfurt University

Mount Sinai Medical Center

Subjects will be recruited from the following sources:

1) Mount Sinai Clinics
   - AIDS Clinic
   - Chest Clinic
   - Hemophilia Clinic
   - Methadone Maintenance Treatment Center
2) Private physicians on staff who treat large numbers of HIV-infected individuals;
3) Community groups (such as GMHC, People with AIDS Coalition, etc.);
4) Self-referrals from advertising in local newspapers and publicity in electronic media.

New Jersey College of Medicine and Dentistry

Subjects will be recruited from the following sources:

1) Pulmonary Consultation Service - contact made by attending physician, Co-PI of contract;
2) Infectious Disease Clinic and Infectious Disease Consultation Service - contact made by attending physician, Co-PI of contract;

3) Clients of Spectrum II, a licensed Methadone Maintenance Treatment Center with 3-400 current active participants seen daily for methadone. Several of these clients have been with Spectrum for 5-7 years. Seroprevalence at Spectrum is estimated at 50%. Contact has already been made through Spectrum administration (letter of agreement in original proposal) who have agreed to support and promote our studies. Contact being made at daily visits of clients to Spectrum by Margaret O'Toole, Project Director, in interviews with clients at Spectrum, reinforced by Spectrum physician;
4) Mothers of AIDS children, born and cared for in Children's Hospital of Newark (Service of Dr. Jim Olesky, letter of commitment in original proposal), interviewed by Co-PI;
5) HIV positive patients who responded to publicity surrounding receipt of original grant, and ongoing publicity provided by the University public relations department.

In all instances, presence of an easily accessible, compassionate program providing clinical evaluation and counseling help with social work situations are stressed. A field worker is on staff to retrieve patients who miss follow-up visits. Honoraria are budgeted to use if necessary.

Henry Ford Hospital

Laboratory diagnosed HIV seropositive patients, ages 18 and older, attending the Henry Ford Hospital clinics and identified between September 1987 and March 1988 will be recruited for the study. The sources of patients are described in the section entitled AIDS Clinical Activities. A subject will be classified as positive by HIV laboratory tests (ELISA with Western Blot confirmation).

The criteria used to classify patients will utilize the CDC Classification system published in the MMWR on May 23, 1986. This system is the most recent classification used by the CDC as well as other surveillance programs conducted by public health departments. Thus, using the CDC classification will be consistent with the terminology that future investigators will probably use. This classification is not intended for prognostic significance, but it is intended to be hierarchical. Those patients who are identified within a

particular CDC group cannot be reclassified into a preceding group if clinical findings resolve.

Admission lists for inpatients and appointment lists for outpatients in the clinic of the Infectious Disease Division will be reviewed daily to ascertain potential research subjects. Because appointment lists do not have diagnoses associated with names in order to protect patient confidentiality, the clerical support staff member will meet with the clinic physicians at the beginning of the clinic session to identify all known HIV seropositive cases. The clinic physicians are willing to recruit any HIV seropositive patient who is willing to participate. Patients under the age of 18 will be excluded in order to avoid the informed consent issues involved with minors.

In view of the anticipated recruitment for the study involving AIDS and alcohol, the investigators have available several lines of recruitment for this study. The American Red Cross, Wellness Networks, HFH staff physicians (480 group practice), substance abuse clinics, and gay organizations have been sources for the referrals to the AIDS clinic activities. These organizations have been faithful in their referral pattern and are committed to maintaining this relationship for the purpose of AIDS clinical research activities.

Northwestern University

Subjects will be recruited from the following sources:

1) After securing approval from the appropriate investigators, existing study cohorts will be reviewed to identify persons who are potentially eligible for the Pulmonary Complications of AIDS study;
2) Physicians at Northwestern known to be caring for significant numbers of HIV-infected persons will be contacted and asked to solicit interest in the study from the potentially eligible patients. Those patients who agree will have their names submitted to the PACS;
3) New patients presenting at the Northwestern HIV Care Center will be solicited for potential participation in PACS. Upon commencement of the study, the individuals identified from these groups will be contacted and asked to come to the study center where they will be assessed for participation in PACS;

4) Advertisements in a variety of local publications will be used to solicit participation in the study.

UCLA

Although it would be desirable to obtain a population based representative sample of HIV-infected adults in Los Angeles County, it will be difficult to ascertain if the sample is truly representative.Since a positive HIV test is not reportable, the available data on the number and demographic characteristics of HIV-infected individuals is based on the results of voluntary testing, and not necessarily representative of the entire population. In addition, the composition of the study population will be influenced by the feasibility of recruitment and follow-up of individuals in the different risk groups.For instance, although the prevalence of HIV infection among IV drug abusers and prostitutes may be increasing, many of these individuals will be difficult to recruit and maintain contact with over 4 years. We intend to aim our recruitment efforts primarily to homosexual and bisexual men, and to a lesser extent, intravenous drug abusers in methadone maintenance programs to attain the previously outlined target quota.

The degree to which the UCLA cohort is representative will depend on the ability of the investigators to contact individuals eligible for the study from as many sources as possible and to make participation as attractive as possible. Therefore we intend to: 1) maintain 3 clinics,each located and organized to provide maximum convenience and accessibility for the study participants; 2) name the study and clinics in such as way as to not disclose that they involve the study of HIV-infected persons; 3) establish a supportive relationship with each participant so that he feels he is benefiting from his role in the study; and 4) recruit from several sources.

Participants will bed recruited from the following sources:

A. Asymptomatic HIV-infected individuals and HIV seronegative controls.

1) The current cohort of 1700 homosexual male subjects participating in the "Natural History of Acquired Immune Deficiency Syndrome in Homosexual Men Study;"

2) The "Alternative Testing Centers" which provide voluntary HIV testing located in West Hollywood, Long Beach, East Los Angeles, South Central Los Angeles, the San Fernando Valley, and the San Gabriel Valley;
3) Gay events (e.g., the October Gay Health Fair) held by various gay men's associations;
4) Methadone Maintenance Clinics participating in the Los Angeles County Drug Abuse Program for Methadone Treatment;
5) Public service announcements and advertisements placed in local newspapers and magazines;
6) Friends and acquaintances of participants enrolled in the study;

B. Symptomatic HIV-infected Individuals
1) Symptomatic HIV-infected individuals seen in the outpatient facilities at UCLA Medical Center, LAC Olive View Medical Center and Wadsworth VA Hospital;
2) The NIH funded UCLA AIDS Treatment Evaluation Unit (ATEU).

II. Recruitment of Study Participants

Brochures explaining the rationale and procedures of the study will be given to each participant of the "Natural History of Acquired Immune Deficiency Syndrome in Homosexual Men" study during routine visits. Posters will be displayed and brochures distributed at both Alternative Testing Centers and in the Methadone Maintenance Clinics. The posters, brochures, and public service announcements will briefly announce the study and give the study telephone numbers for more information and to set up an appointment at one of the two clinics. A booth is planned for Gay associations and participate as appropriate in other Gay events. Symptomatic HIV-infected individuals considered to be candidates for the study will be approached by the primary physician or ATEU physician during a clinic visit and given the study telephone number.

III. Retention of Study Participants

The incentive to volunteer for the study will be the examinations for the early detection of AIDS, or detection and diagnosis of associated lung disease. The results of the examination and tests will be provided to the physician designated by the participant (with his/her consent), as well as to the participant. The incentive for staying in the study will be the opportunity to receive periodic monitoring for early detection of AIDS or lung disease, up to date information on new treatment, etc. for HIV infection and complications, counseling for participants, family and friends and referral to various community resources.

A substantial effort will be made to maintain a good working relationship with the participant's primary physician. As mentioned above, letters will be sent to the primary physician after each routine visit, and he will be contacted promptly if the participant is found to have symptoms indicative of respiratory illness or abnormal screening tests.

Every effort will be made to provide maximum telephone accessibility for the participants. During office hours at least one member of the Staff will be available to answer the telephone. During off hours, a telephone answering machine will be used, and messages will be answered daily.

Finally, in order to enhance continuing participation, a newsletter will be published at 6 month intervals for participants and their primary physicians.

University of California, San Francisco/
San Francisco General Hospital

Subjects for the PAC study will be recruited nearly exclusively from the San Francisco General Hospital cohort. This is a group of approximately 500 homosexual men, approximately 50% of whom are known to be HIV seropositive. This cohort was recruited by Dr. Andrew Moss and has been followed for a median of approximately three years. Dr. Moss has informed the cohort by letter of the value of the study and has strongly encouraged their participation. The same team that currently manages the cohort will be retained by the PACS study for this purpose.

If additional study subjects are needed they will be recruited from the San Francisco Men's Health Study cohort. This cohort is comprised of seropositive and seronegative homosexual men and was recruited by Dr. Warren Winklestein. Dr. Winklestein has indicated his willingness to participate in the study. A letter to this effect is contained in the original proposal.

Frankfurt University

Subjects will be recruited from the following sources:

1) From a pre-existing cohort of HIV-infected patients currently participating in a clinical trial using AZT. This cohort is attended by physicians from the Department of Internal Medicine;
2) HIV-infected patients treated at Frankfurt University Hospital Out Patient Department (currently approximately 1,000-1,300 patients eligible for PACS);
3) HIV-infected patients treated at Frankfurt University Hospital as in-patients during the recruitment period of PACS;
4) HIV-infected patients referred to Frankfurt University Hospital for evaluation or treatment from primary care physicians;
5) Selected physicians providing primary care to a large number of HIV-infected patients in Frankfurt will be approached and invited to refer their patients for regular pulmonary work-ups in our department.

In case the number of participants recruited from PACS from these sources during the first 3 months of the study is less than required, we intend to publish the aims of this study in regional newspapers and on radio and TV inviting potential participants to join the study.

Individuals for Group C (control) will be recruited from a cohort of non-infected sexual partners of HIV patients currently studied at Frankfurt University Hospital. A special effort is made to recruit HIV seronegative IV drug abusers who are treated in the emergency room of Frankfurt University Hospital.

Appendix 5

Procedures

Pulmonary Complications of HIV Infection

Manual for Diagnostic Procedures, Specimen Collection and Processing

PULMONARY COMPLICATIONS OF HIV INFECTION
DIAGNOSTIC SPECIMEN PROCESSING

I. Routine Studies

A. Sputum Collection -- induced with ultrasonic nebulizer (USN)
   1) Stains: P. carinii, (Giemsa, silver, toluidine blue, DFA), acid fast, papanicolaou, CMV DNA probe - optional)
   2) Cultures: mycobacterial (viral, fungal - optional)

B. Bronchoscopy -- Bronchoalveolar lavage -- optional
   1) Stains: P. carinii (Giemsa, silver, toluidine blue) acid fast, papanicolaou (CMV DNA probe - optional)
   2) Cultures: mycobacterial, fungal, viral

II. Diagnostic Evaluations

A. Sputum Collection
   1) Spontaneous:
      a) Stains: Gram's, acid fast
      b) Cultures: bacterial, mycobacterial, fungal
   2) Induced with USN
      a) Stains: P. carinii (Giemsa, silver, toluidine blue), acid fast, papanicolaou, CMV DNA probe, Legionella DFA or Probe, Mycoplasma Probe (e.g., all but Giemsa, Acid Fast - optional)
      B) Cultures: mycobacterial, fungal (viral, Legionella, Mycoplasma - optional)

B. Bronchoscopy
   1) Bronchoalveolar Lavage
      a) Stains: P. carinii (Giemsa, silver, toluidine blue), acid fast, (Papanicolaou, Legionella, DFA, CMV DNA Probe, Legionella Probe, Mycoplasma Probe - optional)
      b) Cultures: mycobacterial, fungal (viral, Legionella, Mycoplasma - optional)
   2) Transbronchial Biopsy
      a) Stains: Silver, Acid Fast, Hematoxylin and Eosin
      b) Touchprep: (Giemsa, silver, toluidine blue - optional)
      c) Cultures: (mycobacterial, fungal - optional)
   3) Transbronchial Needle Aspiration
      a) Stains: Papanicolaou, Silver, Acid Fast
      b) Cultures: mycobacterial, fungal

C. Pleural Fluid:
   1) Chemistry[1] : protein, glucose, LDH (amylase, pH - optional)
   2) Hematology: White cell count and differential

1/ Simultaneous serum specimen for protein and LDH determinations will be obtained.

3) Stains: Papanicolaou, Gram's, acid fast
4) Cultures: bacterial, mycobacterial, fungal

D. Pleural Biopsy:
1) Stains: acid fast, hematoxylin and eosin, silver
2) Cultures: mycobacterial, fungal

E. Percutaneous Needle Lung Aspiration
1) Stains: Papanicolaou, Giemsa, Gram's, acid fast
2) Cultures: If clinically appropriate, mycobacterial, fungal, bacterial

F. Diagnostic Thoracotomy:
1) Stains: Gram's, Giemsa, silver, acid fast, Legionella DFA, and/or probe, hematoxylin and eosin, (Periodic acid-Schiff, CMV probe, electron microscopic studies -- optional)
2) Cultures: bacterial, mycobacterial, fungal, Legionella, viral

Each center should submit to the Clinical Coordinating Center a list of media used for the various types of cultures and a description of any technique that is not standard.

PULMONARY COMPLICATIONS OF HIV INFECTION
PROCEDURE FOR SPUTUM INDUCTION, PROCESSING AND EXAMINATION

Sputum Induction

Patients should not take solid food for approximately 8 hours prior to induction. At the facility, the patient first gently brushes his/her tongue, buccal surfaces, teeth, and gingival margins with a new soft bristle toothbrush and water or normal saline. Toothpaste is not used because particulate material in toothpaste can obscure the microscopic field. The patient gargles once with tape water and thoroughly rinses the mouth three times with tap water. This procedure removes clumps of bacteria as well as free superficial squamous epithelial cells with their adherent bacteria, and is essential in obtaining an interpretable specimen. (Bacteria and bacteria coated squamous epithelial cells with stain and can interfere with examination and interpretation.)

A 3% saline solution (sterile solution for injection) mist is generated by an ultrasonic nebulizer and inhaled by the patient through disposable tubing and mouth piece. The nebulizer is set at approximately 3-6 ml/minute output and inhalation is continued for 15 to 20 minutes. Chest percussion is occasionally necessary to induce deep coughing.

The sputum produced is collected in sterile plastic screw-cap containers. Specimens should be collected in two parts, the first containing sputum produced immediately after cessation of inhalation of saline, and the second containing the sputum produced thereafter. The second usually contains the larger number of organisms, and is likely to represent sputum produced from deep in the bronchial tree. Sputum specimens likely to contain Pneumocystis carinii are clear in appearance and contain small white flecks of material floating in clumps. Specimens should be taken directly to the laboratory for immediate processing.

Sputum Processing

A 2 cc sample of the sputum specimen is overlaid with an equal volume of diluted Sputolysin (Stat-Pak Sputolysin, Behring Diagnostics, catalog no. 869224; diluted according to the manufacturer's instructions) in a 15 cc conical screw-cap tube. The mixture is vortexed vigorously but briefly three times, and incubated at 37°C for four minutes on a rotary platform shaker. The mixture is then vortexed briefly again. If large clumps of mucus are still present, further four minute incubations are repeated until the specimen is mostly liquified and contains only small clumps of mucus and cells. The mycolytic digestion should not require more than 12 minutes. Care should be taken so that the specimen is not completely liquified; if this occurs, the Pneumocystis will be completely dispersed and difficult to identify. An equal volume of 0.067 M phosphate buffer (pH 6.8) is added to the digested sample, and the mixture is centrifuged at 1300xg (2500 rpm, Sorvall GLC-1 centrifuge, Sorvall type HL-4 rotor) for 5 minutes at 24°C. The supernatant is discarded into a disinfectant solution (i.e.,

1/10 dilution of hypochlorite bleach, i.e., Clorox). The sediment is gently vortexed to disrupt clumps of cells, and centrifuged at 1300xg for 1 minute. Excess supernatant is removed with a Pasteur pipette, leaving approximately 1/2 volume of supernatant to 1 volume of pelleted cellular material. The supernatant and cellular material is gently mixed with a Pasteur pipette. Two drops of this resuspended sediment is delivered with a Pasteur pipette to an acetone cleaned glass microscope slide, and a thin smear made using the side of the Pasteur pipette. The smear is air dried, and then flamed for 8-10 seconds with a Bunsen burner. This extended heating is necessary to affix cellular material to the slide because natural adhesions normally present were removed during the mucolytic digestion. Two slides each are made from the sediment of the first and second parts of the induced sputum, resulting in a total number of 4 slides made per induced sputum sample.

Staining

Specimens should be stained for P. carinii using a standard method.

Examination

Two slides made from the second part of the induced sputum specimen are examined first. The two slides made from the first part of the induced sputum specimen are examined only if no P. carinii are found in the second part of the induced sputum. Identification of Pneumocystis carinii is made by finding clumps of trophozoites, precysts or fully mature cysts. A single clump of trophozoites with or without precysts with clear-cut morphology is sufficient for the diagnosis of PCP.

The length of time spent on each slide should not exceed 30 minutes. When questionable material is observed, additional slides should be made, stained and examined. If a specimen contains large numbers of squamous epithelial cells and no alveolar macrophages, a second sputum induction may be performed to obtain a satisfactory specimen.

PULMONARY COMPLICATIONS OF HIV INFECTION
METHODS FOR PULMONARY FUNCTION TESTING

I. Diffusing Capacity and Total Lung Capacity

A. Methods and Equipment

1. Single breath diffusing capacity (DLCO) will be measured, but equipment is not specified. The carbon monoxide analyzer may be an infrared, fuel cell, or chromatograph device. The helium analyzer must be linear.

2. Test Gas: 0.3% CO, 10% He, 21% O_2 (or sea level equivalent for the same P_IO_2, and the balance N_2). If a chromatograph is employed, neon may be used instead of helium for measurement of alveolar volume.

3. Special Considerations:

a. Leaks: The system must be checked daily. No change in volume of the pressurized system is required.

b. Absorbers: Prior to every test, the CO_2 and H_2O absorbers must be checked and both changed if either more than 1/2 exhausted.

c. CO Analyzers:

(1) Must be warmed up to maximum stability prior to use.

(2) Calibration (±5%):

(a) Linear Devices: Must be calibrated with test gases of at least two different known CO concentrations with fresh air as the zero. One of the calibrating gases should contain 0.3% CO and the other a lesser concentration. The system should be flushed completely and checked for zero after each test gas calibration.

(b) Alinear Devices: A calibration curve must be constructed for the meter. This may be accomplished by filling a calibrated one liter syringe filled variously with 100% of 0.3% CO, 90% of 0.3% CO, 80% of 0.3% CO, etc., and a gas mixture with a known He concentration. Each sample is delivered through the reservoir bag. The actual CO concentration at each dilution is calculated and plotted against the meter reading (usually as % full scale). For all testing,

the CO meter gain should be adjusted so the reference gas gives the same value as on the initial calibration. The analyzer should be completely recalibrated monthly.

d. Helium Analyzer:

(1) The device should be left on continuously if used frequently.

(2) Calibration: Should be calibrated in conjunction with the CO analyzer. Linearity should be tested using 100% of either 10 or 14% helium in the CO mixture used for CO analyzer calibration. Complete calibration should be done monthly.

e. Washout Volume: The volume exhaled before collecting the alveolar sample should be as close to 750 ml as possible. If the patient's vital capacity is less than 1.2 liters, then 600 ml is used.

f. Alveolar Sample: The standard goal will be 650 ml. If the vital capacity is low, the volume collected may be reduced to 400 ml. If the vital capacity is too low to achieve 400 ml, the test will not be done with the notation "patient too ill".

g. Breathholding Time: The duration of breathhold is from the onset of inhalation to start of alveolar sample collection. (Olgivie, et al. Journal of Clinical Investigation 36:1-7, 1967). The breathholding time should approximate 10 seconds. The expiration command should usually be given about 9 seconds from onset of inspiration. During breathholding the patient should breathhold, not rest against the shutter.

h. Reproducibility: One of the major variables in DLCO is the lung volume at which diffusion occurs. Consequently, attention must be directed at reaching TLC. The DLCO should be calculated as the average of three maneuvers that are within ±5% of one another. DLCO values will be used only from tests in which the patient achieves at least 90% of the slow vital capacity (corrected to STPD) measured on spirometry. If none of three procedures achieve the required volume, the result is the one from the biggest vital capacity.

B. Procedures

1. Exact details vary with manufacturer of equipment. General principles may be reviewed in Clinical Pulmonary Function Testing published by the Intermountain Thoracic Society, 1975. Investigators using the Collins system and Gaenslen-Smith automated valve should review the report of Gaenslen and Smith. (Chest 63:136, 1973).

2. General Guidelines:

   a. With nose clipped, have the subject breath normally through the mouthpiece until relaxed.

   b. Instruct the patient to exhale slowly to residual volume, then the patient is switched into the test gas circuit. Inhalation then proceeds rapidly to TLC.

   c. After 9 seconds of breathholding, instruct the patient to exhale rapidly to residual volume.

   d. After 750 ml are exhaled, the next 650 ml is collected for gas analysis (the Alveolar Sample).

   e. The subject is detached from the apparatus.

   f. The test is repeated twice, waiting for 5 minutes between each procedure.

C. Measurements:

1. Barometric pressure (Pb) and spirometer or room temperature in °C.

2. From the spirogram:

   a. Vital capacity (VC) corrected to STPD.

   b. Breathholding time (t in sec).

3. From the 0.3% calibration curve:

   a. expired CO (CO_E) as concentration in percent.

   b. inspired CO (CO_I) should be 0.3%.

4. From the He meter readings:

   a. inspired concentration of helium in percent (HE_I).

   b. expired concentration of helium in percent (HE_E).

D. Calculations:

VC _____ mls STPD

t _____ secs

CO_I _____ .3 % mmHg

CO_E _____ %

HE_I _____ %

HE_E _____ %

Pb

PiO_2 _____

$$VAml = VC \times \frac{He_I}{He_E}$$

$$COAo = CO_I \times \frac{He_E}{He_I}$$

$$DLCO = \frac{VAml \times 60 \text{ sec/min}}{t \text{ sec } (pb - 47 \text{ mmHg})} \times LN \frac{CO_{Ao}}{CO_E}$$

DLCO = _____ ml/min/mm Hg

Where: PiO_2 = partial pressure inspired O_2 (should approximate 150 mmHg)

CO_{Ao} = initial alveolar CO concentration

VA = alveolar volume (TLC at STPD)

II. Spirometry

A. Methods and Equipment

A volume displacement spirometer is preferred and a hard copy of the volume-time trace is essential.

B. Procedures

Nose clips are recommended.

1. Slow Vital Capacity (VC) (performed with subject seated): After several breaths to establish FRC, the subject inspires maximally to TLC then exhales maximally to RV. Repeat once. Inspiratory capacity (IC) and slow vital capacity are calculated.

2. Forced Vital Capacity (FVC): The forced vital capacity will be performed at least three times but not more than six (6) times. Acceptable curves will be those with smooth continuous exhalation with apparent maximal effort and without the following discredits defined by the American Thoracic Society (Snowbird Workshop on the Standardization of Spirometry held January 18, 1977 at Snowbird, Utah).

   a. Coughing

   b. Valsalva

   c. Early termination of expiration. Forced expiration must continue for at least six seconds.

   d. A leak

   e. Obstructed mouthpiece (including dentures and subject's tongue)

   f. Unsatisfactory start. Back extrapolation on time 0 on the volume time tracing must be less than 10% of FVC.

   g. Excessive variability between the three acceptable curves. The two best FVCs on the three acceptable curves must not vary more than ±10% or 200 ml, which ever is greater.

3. The spirometer should be flushed with fresh air between each maneuver.

C. Measurements:

Recorded in BTPS

1. Slow Vital Capacity

   The VC is the larger of the two values

2. Forced Vital Capacity: FVC and FEV_1. The single "best curve" is defined as the curve with the largest algebraic sum of FVC and FEV_1. These measurements may be determined by computer or by hand calculations.

3. Spirometry may be repeated after bronchodilator challenge.

D. Calibration:

1. Volume is calibrated by giant syringes. Must be independent of flow rate. Accuracy must be within ±50 ml.

2. Time (strip chart recorded) is checked by 60 cycle electrical oscillations. For kymographs, time calibration is performed by running the drum on rapid setting for a minimum of 10 seconds checked by stop watch. For x-y recorders, time is also checked by stop watch for 10 seconds.

PULMONARY COMPLICATIONS OF HIV INFECTION
FIBEROPTIC BRONCHOSCOPY PROCEDURES

A. Anesthesia

Premedication will be optional and the specific agents used will vary according to the preference of the bronchoscopist. Topical anesthesia will be accomplished using the usual procedure of the institution. The type of topical anesthesia and method of administration will be standardized within each institution, and reported to the clinical coordinating center. If at all possible, the amount of local anesthetic solution will be minimized.

B. Procedure

The bronchoscope will be passed transnasally or transorally and the tracheobronchial tree will be examined. The bronchoscope will be wedged in a subsegmental bronchus in the area of the greatest radiographic abnormality. BAL, with 100 to 300 ml normal saline 20 to 50 ml aliquots will be performed. The amount introduced and recovered will be recorded. If an endobronchial lesion is noted, except for KS lesions in patients with skin manifestations, endobronchial biopsies will be performed. If transbronchial biopsy is performed, at least 3 adequately sized pieces will be taken from the area of radiographic abnormality. Fluoroscopic guidance will be optional for transbronchial biopsy of diffuse abnormalities and mandatory for transbronchial biopsy of focal lesions. Biopsy specimens will be processed as fixed tissue sections and for microbiologic evaluation.

PULMONARY COMPLICATIONS OF HIV INFECTION
^{67}GALLIUM SCANNING TECHNIQUE AND EVALUATION

A) Isotope and Scanning Technique

1) 90 μ Ci of ^{67}Ga citrate/kg is injected via an upper extremity vein.

2) At 48-72 hours after the injection anterior and posterior scanning is performed with a scintillation camera.

3) For each projection, images of the thoracic and upper abdominal area preferably measuring 64 by 64 pixels will be made.

B) Scan Evaluation

1) Qualitative Interpretations

a) All qualitative interpretations will be made independently by one of three designated readers who has not performed the clinical assessment.

b) The qualitative interpretation will be based on visual evidence of ^{67}Ga uptake in the anterior and posterior projections. Uptake will be graded for the entire right and left lung and for the following regions within the right and left lung:
Upper 1/3
Middle 1/3
Lower 1/3

c) The grading criteria will be as follows:
0 = equivalent to or less than the thoracic soft tissues;
1 = lung can be visualized with intensity slightly greater than the thoracic soft tissue;
2-3 = intensity spaced equally between 1 and 4;
4 = intensity equal to or greater than uptake in the liver. If uptake in the liver is inhomogeneous, the are of greatest density should be used.

d) Further work-up will be indicated in all symptomatic individuals with whole lung uptake grade as 1 or greater or regional uptake graded as 2 or greater.

2) Quantitative Interpretations

All centers that have the capacity for drawing regions of interest (ROI) and measuring count density within the ROI (counts/pixel) will obtain quantitative pulmonary ^{67}Ga update data by the following method:

a) ROI will be outlined in the anterior and posterior projections as follows:

   i) Right and left lung. The cardiac area in the left projection will be excluded. The medial border of each lung ROI will be adjacent to the spine to exclude ^{67}Ga by bone in this area.

   ii) Right and left axilla (background). A ROI measuring 5 by 5 pixels will be drawn in an area inferior to the head of the humerus. This area will correspond in the anterior and posterior projections. If there is a visually apparent area of ^{67}Ga uptake (e.g., due to axillary lymph nodes), the axillary ROI should be drawn slightly above to exclude this area.

   iii) Liver (high count density). A ROI measuring 10 by 10 pixels will be drawn in the area of liver that visually appears most intense. This area will correspond in the anterior and posterior projections.

b) Count density in each ROI will be measured as counts/pixel.

   i) Geometric means (square root of the product) of the anterior and posterior projections of each ROI will be calculated and recorded.

   ii) the counts/pixel thus calculated for the right and left axillary ROI will be averaged and recorded.

c) The following ratios will be calculated and recorded:

   i) Right lung: axilla (background) ratio

   ii) Left lung: axilla (background) ratio

   iii) Right lung: liver (high count density) ratio

   iv) Left lung: liver (high count density) ratio.

The exact method for outlying ROI and calculating count densities and ratios should be agreed upon by representatives of the Nuclear Medicine Department at each center at the onset of the study and used consistently during the duration of the study. Examples illustrating the method will be distributed to each center.

PULMONARY COMPLICATIONS OF HIV/INFECTION
CHEST RADIOGRAPHY PROCEDURES

Standard posterior-anterior and lateral view chest radiographs will be taken on PACS subjects at each protocol-designated interval or event. If a subject is unable to stand or co-operate for a posterior-anterior and lateral film, an anterior-posterior supine film will be done. Designated PACS radiologists in each center will interpret each radiograph based on study-wide criteria and practice. PACS radiologists will complete Form R and return it to the study coordinator for form keying.

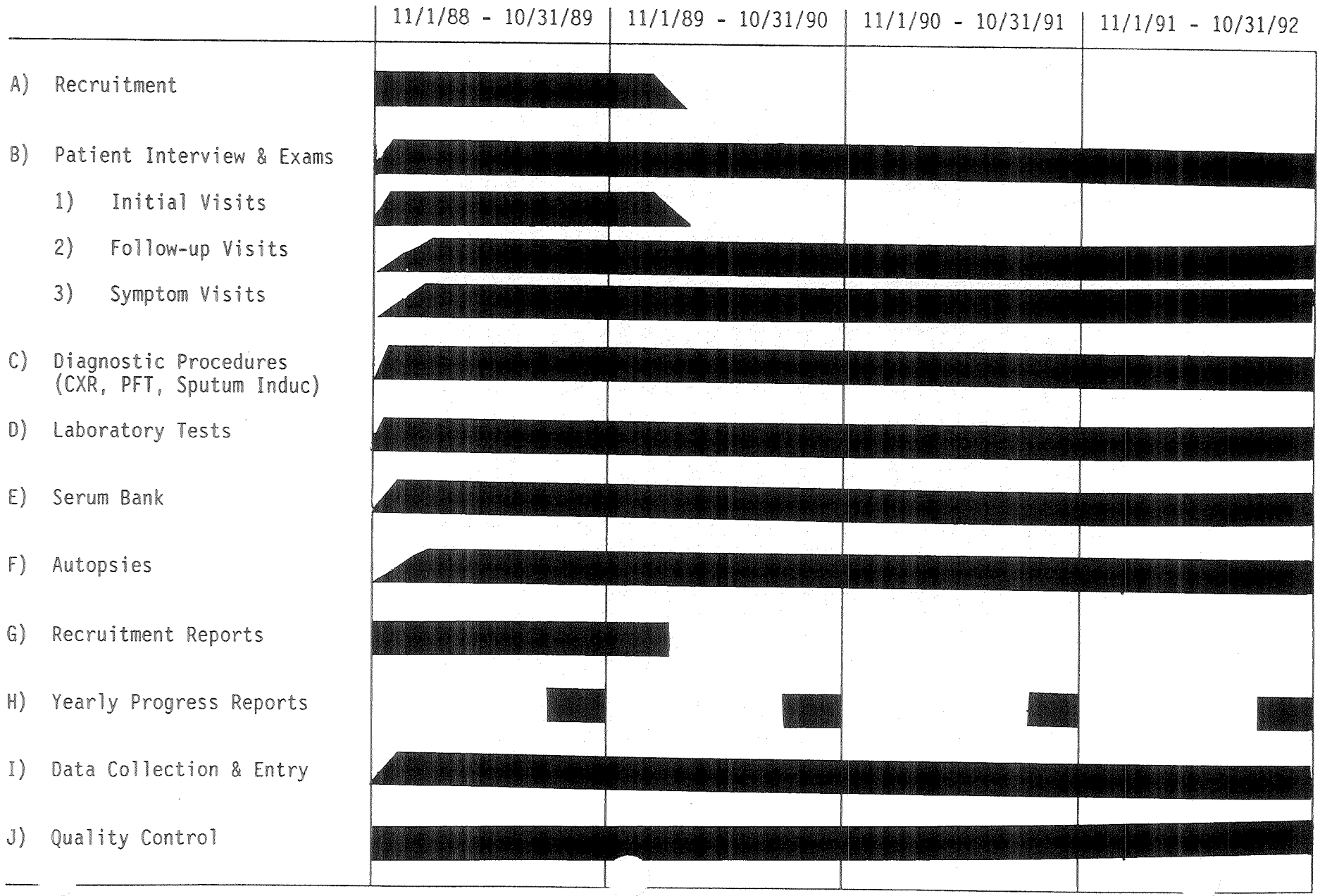
PULMONARY COMPLICATIONS OF HIV INFECTION
AUTOPSY PROCEDURES

An effort will be made to inform all participants about the importance of autopsy for advancing the state of medical knowledge about AIDS. The appropriate time to initiate such a discussion will vary according to the individual, but the following is offered as a guidelines: (1) during the first six months for study groups C and D; (2) during the first year for study groups A and B; and (3) at any time it seems likely that the participant will die soon (in most cases, due to an AIDS-related complication). The participant will be educated regarding the individuals who have the legal authority for autopsy consent during this discussion. If the setting appears inappropriate, the discussion of autopsy will be delayed accordingly.

If the participant dies while under the care of an attending physician from a hospital participating in the study, the autopsy will be performed at the hospital the next working day. Consent for autopsy will be obtained in the manner customary at the individual hospital and the standard hospital autopsy consent form will be used. Provided that there are no restrictions on the autopsy request form, a complete routine autopsy will be performed including gross examination and representative histologic sections of major organs including the heart, liver, spleen, bowel, kidney, enlarged lymph nodes, brain and eyes. Examination of the respiratory system will include at least five microscopic sections from trachea, lung, mediastinal and/or hilar lymph nodes, and any other area found to be of interest during the grass examination. Microscopic sections will be routinely stained with hematoxylin and eosin, gram, acid-fast and silver stains. Periodic and Schiff stains, Legionella DFA strains or probes, CMV probes or monoclonal antibody stains, and electron microscopy will be optional. If the autopsy is performed within 72 hours of death, mycobacterial, routine bacterial, fungal and viral cultures of pulmonary tissue will be submitted. The autopsy findings, microscopic and culture results, will be recorded on a standard Autopsy Form.

Appendix 6

TIME LINE - PHASE II



Appendix 7

PULMONARY COMPLICATIONS OF HIV INFECTION
CONSENT FORM

DESCRIPTION: The number of people who have been diagnosed as having the acquired immune deficiency syndrome (AIDS) has dramatically increased during the last few years. I am invited to participate in an international study of 1,000-2,000 individuals which will detect evidence of the pulmonary complications associated with AIDS or AIDS-related disease. This study will also help to define the risk factors involved in acquiring these complications. This study is being conducted by investigators at _____.

AIDS is the result of a suppressed immunity caused by infection with Human Immunodeficiency Virus (HIV). This lowered immunity can lead to infection with other viruses, bacteria or fungi. The most common site of these infections is the lungs. There is a great deal that is not known about AIDS. For example,what are the reason that some people get pulmonary complications and others do not? Are there early symptoms of the pulmonary complications which can be detected before the full-blown disease develops. Are there screening or diagnostic procedures which would be beneficial in detecting these pulmonary complications enabling earlier treatment?

I have been asked to take part in a detailed study, which is designed to follow my health status more closely to determine if screening methods can detect pulmonary complications of HIV infection.

I agree to participate in this detailed study.

(1) At periodic intervals, I will be given a careful medical history. I will be asked about my past or present medical problems.

(2) I will be given a physical examination by a physician, physician's assistant or a nurse-practitioner.

(3) I will be asked to give a sample of blood (about four tablespoons) obtained by venipuncture of my arm. My blood will be used to test for antibodies to HIV and other viruses, as well as for the numbers of different cells in my blood.

(4) I will have skin tests, sputum tests, pulmonary function tests and/or chest x-rays to determine if I have any of the pulmonary infections. I understand I will be notified if the results of these tests are positive and will be referred for treatment to a physician of my choosing.

(5) I will be notified of any abnormal results and will be referred for follow-up to a physician.

(6) I will be asked to return for follow-up every three to twelve months for the next four years to have the same investigation repeated.

RISK AND BENEFITS: The benefit of participating in this study is that any signs or symptoms of the early stages of pulmonary complications of HIV infection will be discovered. I will be given the results of these and referred for proper medical care. The free services provided are the routine checks and results of blood tests and cultures. The risks of participating are minimal. They include the discomfort of drawing a sample of blood, rare bruising at the site of needle stick, and very rarely, fainting. Pulmonary functions tests may make me feel short of breath or cough. Skin tests may temporarily cause a small swelling on my arm. There may be some inconvenience associated with attending the clinic. My privacy may be invaded to some extent as I will be asked personal questions. But this information will be strictly confidential. If an HIV serology is conducted, the results, with appropriate counseling, will be provided by a study physician or study nurse.

COSTS AND PAYMENTS: There will be no costs for participating in this study. Studies specifically for the project will be free of charge. Also,I understand that I will receive no payment for participating in this study.

CONFIDENTIALITY: I understand that any information about me obtained from this research, including answers to questionnaires, history,

laboratory data or findings on physical examination, will be kept strictly confidential. Such information which will carry personal identifying material will be kept in locked files accessible only to my physician and his associates. It has been explained to me that my identity will not be revealed in any description or publication of this research. Therefore, I consent to such publication for scientific purposes.

OTHER RECORDS: Because my medical and health history is extremely important to the study investigators and may impact upon my condition and the findings in this study, I hereby give my permission for my physicians to obtain any applicable medical or hospital records from other hospitals or providers of care. In doing so, naturally my diagnosis or condition will not be revealed to them.

RIGHT TO WITHDRAW: I understand that I am free to refuse to participate in this study or to withdraw at any time and that my decision will not adversely affect my care at this institution or cause a loss of benefits to which I might be otherwise entitled.

COMPENSATION FOR ILLNESS OR INJURY: I understand that in the event of a physical injury or illness resulting from this research procedure, no monetary compensation will be made, but any immediate emergency medical treatment which may be necessary will be available to me.

NEW IN FORMATION: New information about AIDS or HIV infection which comes to the attention of the investigators during the course of this research and which may relate to my willingness to continue participation will be provided to me or to my legal representative.

RANDOMIZATION: I understand that I may be part of a substudy which randomizes subjects to routine or intensive follow-up.

VOLUNTARY CONSENT: I certify that I have read the preceding or it has been read to me and that I understand its contents. Any questions I have pertaining to the preceding have been and will be answered by the physician, nurse-practitioner or the physician's assistant on call at this clinic. Any questions I have concerning my rights as a research subject will be answered by _____. I may contact clinic personnel at any time at the Phoneline ( ) for additional

information or in event of any problems related to this study. A copy of this consent form will be given to me. My signature below means that I freely agreed to participate in this experimental study.

Subject Signature _____ Date _____

I certify that I have explained to the above individual the nature and purpose, the potential benefits, and possible risks associated with parti-cipating in this research study, have answered any questions that have been raised, and have witnessed the above signature.

Investigator Signature _____ Date _____

Appendix 8

Serum Tracking and Shipment Proposal

For the Pulmonary Aids Clinical Study, serum should be collected at the initial visit, all follow-up visits, and during certain symptom generated visits. Symptom generated visits that require serum to be collected are those in which additional evaluation is required because of chest radiographic abnormalities, reduced DLCO values or abnormal GA scans.

Enough blood should be drawn so that four 1 ml cryotubes of serum can be obtained and saved by the center for shipment to the repository. Four cryotubes of serum should be sent to the repository for each patient, each time the patient receives one of the visits mentioned above in which serum should be collected. These cryotubes should be labeled using a study ID label.

The mechanics of how serum is processed at the centers is up to the particular center. Procedures for collecting and storing serum at the centers should be documented in a memo and sent to RTI. This memo should include information on who collects the serum, where it is collected, where it is temporarily stored before shipping, who is responsible for filling out data forms and who should be contacted for questions or problems.

The serum repository for the Pulmonary Aids Clinical Study is located at Program Resources, Inc. The address to be used in sending serum samples to the repository is:

Ronald S. Lees
Repository
Program Resources, Inc.
7655 Old Springhouse Road
McLean, Virginia 22102

Mr. Lees phone number should be put on the lower left corner of the address label as a backup in case some problem arises with the package. His number is: (703) 506-0191.

The repository will be responsible for sending you the necessary equipment for serum shipping. A shipping container containing serum storage boxes filled with empty cryotubes will be sent to each center as needed. Each box will contain 81 empty cryotubes laid out in 9x9 grid. Each cryotube is designed to hold 1.0 ml of serum.

II. Data Shipping Forms

Two data shipping forms, a serum storage log and a serum shipping form, have been devised to keep track of serum storage and shipment. The serum storage log is designed to keep track of the location of individual serum cryotubes within a serum storage box. The serum shipping form is designed to identify the serum storage boxes that are shipped from the center to the repository, to identify the condition of the serum shipped and to identify the storage location of the serum storage boxes at the repository. Examples of these two forms are attached and instructions on completing the forms will follow.

III. Box Labelling

It is very important that the serum storage box be labeled in the same manner as the serum storage log. This will help ensure that mistakes are not made when serum addresses in the particular cells of the serum storage box are recorded on the serum storage log. Any writing done on the serum storage box or on the cryotube labels should be done using a specialized freezer pen.

To label the serum storage box, remove the top from the serum storage box and set it aside. All labeling of the serum storage box will be done on the sides of the box and not the lid of the box. To begin, label one of the sides as FRONT (Figure 1). This will act as a reference point to keep the orientation of the box the same during form

completion. On the side that you labeled FRONT, number the columns of the grid from 1 to 9 starting in the left corner of the box and proceeding to the right (Figure 2). With the FRONT side of the box still facing you, locate the left side of the box. This side will be used to label the rows of the box. Label the rows A thru J on the side of the box (the letter 1 is omitted). Begin with A in the upper left corner of the box and proceed to J in the lower left corner of the box (Figure 3). This labeling should now match that of the serum storage log. The cell in the upper left corner of the box should be cell A1. The lower right cell should be J9. This labeling should be done immediately upon receipt of the serum storage boxes from the repository.

IV. Data Form Completion

For each serum storage box to be shipped, a separate serum storage log must be completed that identifies the ID number of the serum shipped and locates it within the serum storage box. Please note that no more than 6 serum storage boxes may be sent at one time.

The serum storage log contains 81 cells laid out in 9 rows and 9 columns that matches the 9x9 grid of the serum storage box you will be using. The FRONT label on the serum storage box should be oriented to correspond to the FRONT label on the serum storage log. This is done to ensure that the serum location in the box matches its address on the serum log. Check the box to ensure that the grid labeling is on the box and if not, write the grid labeling on the box as specified in the Box Labeling section of this document.

To complete the serum storage log, enter the ID number of the serum specimen and below it the date the serum was collected in the boxes provided (use the labels provided by RTI as much as possible). Be sure that the IDs entered in the cells of the serum storage log match the IDs of the cryotubes in the corresponding cells of the serum storage box.

Once all serum storage logs are completed, the serum shipping form can be completed and the serum storage box numbers can be assigned. To complete the serum shipping form, enter the appropriate center name and

shipping label number in the space provided on the form. The serum shipping label number is a number used to link the individual serum storage boxes with the shipping container they are shipped in. The shipping label number should be placed on the front and top of the shipping container as well as on the serum shipping form. The number is a 4 digit number that is assigned at the clinic. The first digit should be the center number and the last three digits should be a sequential box number (i.e., 1001 is the first shipping container should be labelled number and the last digit is a sequence number from 1 to 6 depending on how many serum storage boxes are sent in the shipment (i.e., 1001-1, 2, 1001-3, ...). One of these labels should go on the top of the serum storage box and the other should go on the front bottom right side of the box itself. A third label should go on the serum samples log to denote the box number. Figure 4 and 5 provide illustrations of the placement of these labels. Once the box numbers are assigned and labels are affixed, enter the date the serum was shipped to the repository and the number of serum storage boxes that were shipped to complete the serum shipping form.

V. Shipping Procedures

A. Shipping Forms

When serum is shipped to the repository, a serum shipping form should be sent along with serum storage logs for each serum storage box shipped. One copy of the serum storage log should be enclosed in its corresponding serum storage box. The original copy of the serum storage logs that are being shipped should be placed in an envelope and taped to the outside of the shipping container along with a copy of the serum shipping form. Keep an additional copy of these forms for your records and send another copy of each of these forms to RTI.

B. Shipping Storage Boxes

It is recommended that you accumulate five or six storage boxes filled with serum before sending a shipment to the repository. Specimen boxes should be wrapped in an absorbent and cushioned material such as a Pampers diaper. This help in conforming to the requirement that there be enough absorbent in the package to handle the entire fluid volume. Then place the wrapped box in a heavy plastic bag that can be heat sealed or made water-tight in some manner.

C. Shipping Container

Dry ice should be placed in the bottom of the shipping container. The wrapped and sealed specimen boxes should then be placed on the dry ice, and more dry ice should be added around the sides of the sealed specimen boxes. Enough cushioning or padding material should be added to prevent drastic shifting as the ice evaporates. On the outside of the shipping container, securely place the following labels:

1. A return address label containing your name, address and phone number.
2. An address label for the repository:

   Ronald S. Lees
   Repository
   Program Resources, Inc.
   7655 Old Springhouse Road
   McLean, Virginia 22102
   (703) 506-0191

Shipments are to be made only on Monday or Tuesday and are to be shipped via Federal Express to ensure quick delivery. Once the serum has been shipped, Ron Lees at the repository should be notified that the shipped is in route. Once the shipment arrives at the repository, he will alert the center that it has arrived.

D. A label stating the following:

MEDICAL MATERIALS
CONFORMS WITH FEDERAL STANDARD
49 CFR 173, 387; 42 CFR 72.25 (C);
AND NIH GUIDE, ...DATE.....

E. A label stating that BIOMEDICAL MATERIAL is being shipped and who to contact in case of leakage or damage.

Appendix 9

Diagnostic Skin Testing

Tuberculin

Introduction

The major tool in the diagnosis of tuberculosis is the tuberculin skin test. Tuberculin is a biologic product derived from cultures of tubercle bacilli composed largely of tuberculoprotein, the protein of Mycobacterium tuberculosis, human or bovine. Tuberculin is not a chemical or synthetic product.

Infection with M tuberculosis results in development of skin sensitivity to tuberculin. This occurs when an exposed individual (generally over a long period of time) inhales a droplet aerosol containing the infectious particle, M tuberculosis. This individual then may develop a delayed form of hypersensitivity to the tubercle bacillus resulting in a positive Mantoux test which is diagnostic of the infected state.

Infection with M tuberculosis results in skin sensitivity to tuberculin. There is an incubation period of six to eight weeks between infection and appearance of this sensitivity. In almost all infected individuals the tuberculin test elicits a measurable reaction. The average size reaction to the Mantoux test is 16 mm. The range forms a normal distribution from 8 mm to 24 mm. Three to 5 percent of the infected population fall outside this distribution.

Technique

The antigen is given in a single dose plastic syringe with a No. 26 or small gauge needle. Even though the material is Tween stabilized to keep it from being adsorbed through the glass, it should not remain in the syringe longer than one hour prior to testing. Intracutaneous injection of 0.1 milliliters PPD is given into the skin of the volar or dorsal aspect of the forearm. After cleaning with alcohol the injection is made with a short, bevelled needle just beneath the surface of the skin. A wheal of from 6 to 10 mm in diameter should be produced. Reading is done in 48 to 72 hours although readings beyond 96 hours are significant if present. A good light and flexible millimeter ruler

should be used. The margins of induration should be found by touch, not sight. The induration is measured in the skin at the point where the needle enters and is usually measured transversely. Recording should be made solely on the basis of size of induration. Erythema should be disregarded and not recorded.

Mumps

Mumps skin test antigen is used to determine the presence of a delayed hypersensitivity reaction. Since most of the population are considered to have had contact or infection with the mumps virus, they usually demonstrate such a reaction if an adequate cellular immune system exists. Therefore, absence of such a reaction suggests presence or anergy.

The Mantoux technique (see above under tuberculin test) is used. An injection of 0.1 ml antigen is given intradermally. Prior to injection the skin is cleansed with an alcohol sponge. The reaction should be examined in 48 to 72 hours (92 hours is permissable). A mean diameter of induration of 5 mm or more is considered positive.

Appendix 10

1987 Revision of Case Definition for AIDS for Surveillance Purposes

For national reporting, a case of AIDS is defined as an illness characterized by one or more of the following "indicator" diseases, depending on the status of laboratory evidence of HIV infection, as shown below.

I. Without Laboratory Evidence of HIV Infection

If laboratory tests for HIV were not performed or gave inconclusive results (see Appendix I) and the patient had no other cause of immunodeficiency listed in Section I.A below, then any disease listed in Section I.B indicates AIDS if it was diagnosed by a definitive method (see Appendix II).

A. Causes of immunodeficiency that disqualify diseases as indicators of AIDS in the absence of laboratory evidence for HIV infection

1. high-dose or long-term systemic corticosteroid therapy or other immunosuppressive/cytotoxic therapy ≤3 months before the onset of the indicator disease
2. any of the following diseases diagnosed ≤3 months after diagnosis of the indicator disease: Hodgkin's disease, non-Hodgkin's lymphoma (other than primary brain lymphoma), lymphocytic leukemia, multiple myeloma, any other cancer of lymphoreticular or histiocytic tissue, or angioimmunoblastic lymphadenopathy
3. a genetic (congenital) immunodeficiency syndrome or an acquired immunodeficiency syndrome atypical of HIV infection, such as one involving hypogammaglobulinemia

B. Indicator diseases diagnosed definitively

1. candidiasis of the esophagus, trachea, bronchi, or lungs
2. cryptococcosis, extrapulmonary
3. cryptosporidiosis with diarrhea persisting >1 month

4. cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes in a patient >1 month of age
5. herpes simplex virus infection causing a mucocutaneous ulcer that persists longer than 1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a patient >1 month of age
6. Kaposi's sarcoma affecting a patient <60 years of age
7. lymphoma of the brain (primary) affecting a patient <60 years of age
8. lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia (LIP/PLH complex) affecting a child <13 years of age
9. Mycobacterium avium complex or M. kansasii disease, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
10. Pneumocystis carinii pneumonia
11. progressive multifocal leukoencephalopathy
12. toxoplasmosis of the brain affecting a patient >1 month of age

II. With Laboratory Evidence for HIV Infection

Regardless of the presence of other causes of immunodeficiency (I.A), in the presence of laboratory evidence of HIV infection (see Appendix I), any disease listed above (I.B) or below (II.A or II.B) indicates a diagnosis of AIDS.

A. Indicator diseases diagnosed definitively

1. bacterial infections, multiple or recurrent (any combination of at least two within a 2-year period), of the following types affecting a child <13 years of age: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media or superficial skin or mucosal abscesses), caused by Haemophilus, Streptococcus (including pneumococcus), or other pyogenic bacteria

2. coccidioidomycosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
3. HIV encephalopathy (also called "HIV dementia," "AIDS dementia," or "subacute encephalitis due to HIV") (see Appendix II for description)
4. histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
5. isosporiasis with diarrhea persisting >1 month
6. Kaposi's sarcoma at any age
7. lymphoma of the brain (primary) at any age
8. other non-Hodgkin's lymphoma of B-cell or unknown immunologic phenotype and the following histologic types:
   a. small noncleaved lymphoma (either Burkitt or non-Burkitt type) (see Appendix IV for equivalent terms and numeric codes used in the International Classification of Diseases, Ninth Revision, Clinical Modification)
   b. immunoblastic sarcoma (equivalent to any of the following, although not necessarily all in combination: immunoblastic lymphoma, large-cell lymphoma, diffuse histiocytic lymphoma, diffuse undifferentiated lymphoma, or high-grade lymphoma) (see Appendix IV for equivalent terms and numeric codes used in the International Classification of Diseases, Ninth Revision, Clinical Modification)

   Note: Lymphomas are not included here if they are of T-cell immunologic phenotype or their histologic type is not described or is described as "lymphocytic," "lymphoblastic," "small cleaved," or "plasmacytoid lymphocytic"
9. any mycobacterial disease caused by mycobacteria other than M. tuberculosis, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)

10. disease caused by M. tuberculosis, extrapulmonary (involving at least one site outside the lungs, regardless of whether there is concurrent pulmonary involvement)
11. Salmonella (nontyphoid) septicemia, recurrent
12. HIV wasting syndrome (emaciation, "slim disease") (see Appendix II for description)

B. Indicator diseases diagnosed presumptively

Note: Given the seriousness of diseases indicative of AIDS, it is generally important to diagnose them definitively, especially when therapy that would be used may have serious side effects or when definitive diagnosis is needed for eligibility for antiretroviral therapy. Nonetheless, in some situations, a patient's condition will not permit the performance of definitive tests. In other situations, accepted clinical practice may be to diagnose presumptively based on the presence of characteristic clinical and laboratory abnormalities. Guidelines for presumptive diagnoses are suggested in Appendix III.

1. candidiasis of the esophagus
2. cytomegalovirus retinitis with loss of vision
3. Kaposi's sarcoma
4. lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia (LIP/PLH complex) affecting a child <13 years of age
5. mycobacterial disease (acid-fast bacilli with species not identified by culture), disseminated (involving at least one site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
6. Pneumocystis carinii pneumonia
7. toxoplasmosis of the brain affecting a patient >1 month of age

III. With Laboratory Evidence Against HIV Infection

With laboratory test results negative for HIV infection (see Appendix I), a diagnosis of AIDS for surveillance purposes is ruled out unless:

A. all the other causes of immunodeficiency listed above in Section I.A are excluded; **AND**

B. the patient has had either:

1. Pneumocystis carinii pneumonia diagnosed by a definitive method (see Appendix II); **OR**

2. a. any of the other diseases indicative of AIDS listed above in Section I.B diagnosed by a definitive method (see Appendix II); **AND**

   b. a T-helper/inducer (CD4) lymphocyte count <400/mm^3.

COMMENTARY

The surveillance of severe disease associated with HIV infection remains an essential, though not the only, indicator of the course of the HIV epidemic. The number of AIDS cases and the relative distribution of cases by demographic, geographic, and behavioral risk variables are the oldest indices of the epidemic, which began in 1981 and for which data are available retrospectively back to 1978. The original surveillance case definition, based on then-available knowledge, provided useful epidemiologic data on severe HIV disease (1). To ensure a reasonable predictive value for underlying immunodeficiency caused by what was then an unknown agent, the indicators of AIDS in the old case definition were restricted to particular opportunistic diseases diagnosed by reliable methods in patients without specific known causes of immunodeficiency. After HIV was discovered to be the cause of AIDS, however, and highly sensitive and specific HIV-antibody tests became available, the spectrum of manifestations of HIV infection became better defined, land classification systems for HIV infection were developed (2-5). It became apparent that some progressive, seriously disabling, and even fatal conditions (e.g., encephalopathy, wasting syndrome) affecting a substantial number of HIV-infected patients were not subject to epidemiologic surveillance, as they were not included in the AIDS case definition. For reporting purposes, the revision adds to the definition most of those severe non-infectious, non-cancerous HIV-associated conditions that are categorized in the CDC clinical classification systems for HIV infection among adults and children (4,5).

Another limitation of the old definition was that AIDS-indicative diseases are diagnosed presumptively (i.e., without confirmation by methods required by the old definition) in 10%-15% of patients diagnosed with such diseases; thus, an appreciable proportion of AIDS cases were missed for reporting purposes (6,7). This proportion may be increasing, which would compromise the old case definition's usefulness as a tool for monitoring trends. The revised case definition permits the reporting of these clinically diagnosed cases as long as there is laboratory evidence of HIV infection.

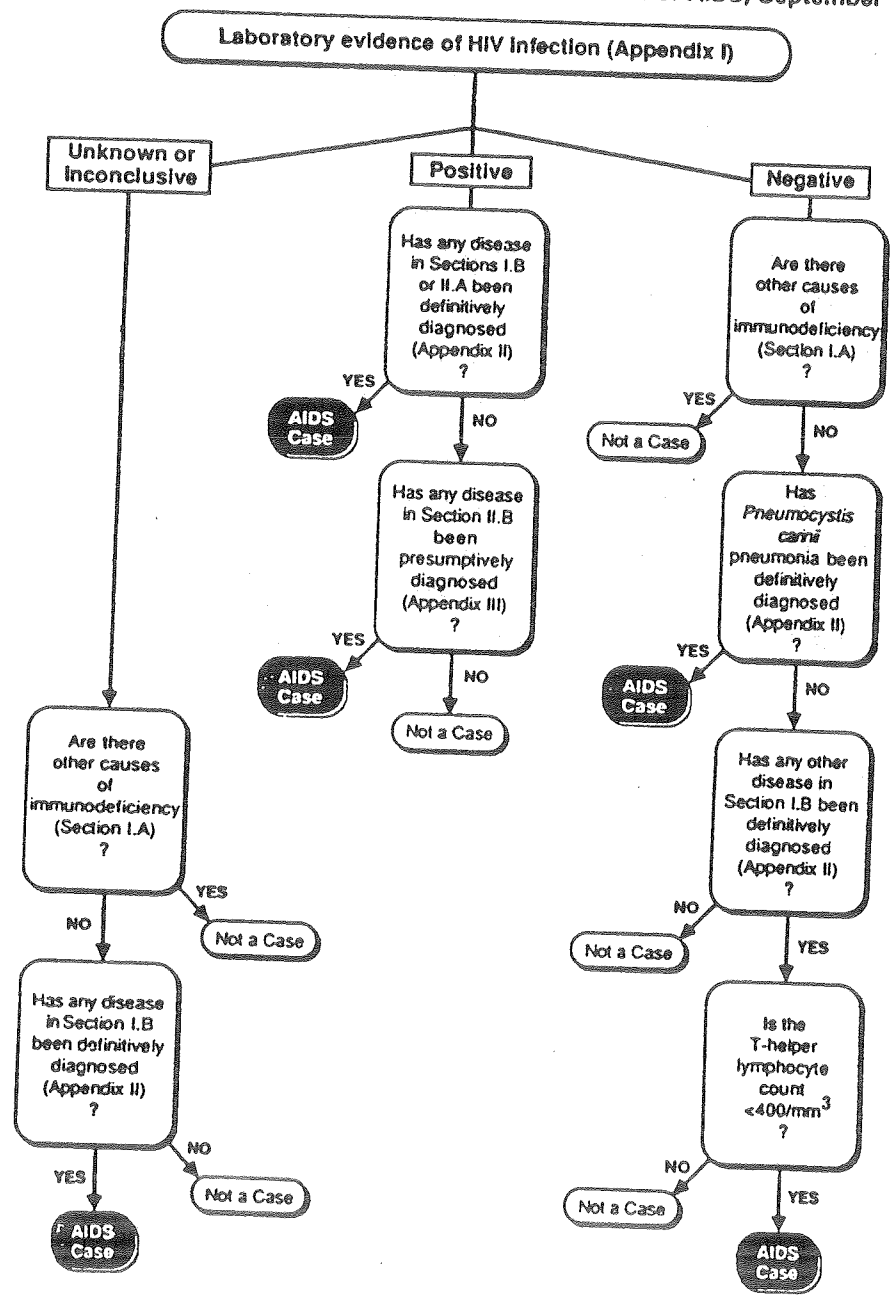
The effectiveness of the revision will depend on how extensively HIV-antibody tests are used. Approximately one third of AIDS patients in the United States have been from New York City and San Francisco, where, since 1985, <7% have been reported with HIV-antibody test results, compared with >60% in other areas. The impact of the revision on the reported numbers of AIDS cases will also depend on the proportion of AIDS patients in whom indicator diseases are diagnosed presumptively rather than definitively. The use of presumptive diagnostic criteria varies geographically, being more common in certain rural areas and in urban areas with many indigent AIDS patients.

To avoid confusion about what should be reported to health departments, the term "AIDS" should refer only to conditions meeting the surveillance definition. This definition is intended only to provide consistent statistical data for public health purposes. Clinicians will not rely on this definition alone to diagnose serious disease caused by HIV infection in individual patients because there may be additional information that would lead to a more accurate diagnosis. For example, patients who are not reportable under the definition because they have either a negative HIV-antibody test or, in the presence of HIV antibody, an opportunistic disease not listed in the definition as an indicator of AIDS nonetheless may be diagnosed as having serious HIV disease on consideration of other clinical or laboratory characteristics of HIV infection or a history of exposure to HIV.

Conversely, the AIDS surveillance definition may rarely misclassify other patients as having serious HIV disease if they have no HIV-antibody test but have an AIDS-indicative disease with a background incidence unrelated to HIV infection, such as cryptococcal meningitis.

The diagnostic criteria accepted by the AIDS surveillance case definition should not be interpreted as the standard of good medical practice. Presumptive diagnoses are accepted in the definition because not to count them would be to ignore substantial morbidity resulting from HIV infection. Likewise, the definition accepts a reactive screening test for HIV antibody without confirmation by a supplemental test because a repeatedly reactive screening test result, in combination with an indicator disease, is highly indicative of true HIV disease. For national surveillance purposes, the tiny proportion of possibly false-positive screening tests in persons with AIDS-indicative diseases is of little consequence. For the individual patient, however, a correct diagnosis is critically important. The use of supplemental tests is, therefore, strongly endorsed. An increase in the diagnostic use of HIV-antibody tests could improve both the quality of medical care and the function of the new case definition, as well as assist in providing counselling to prevent transmission of HIV.

FIGURE I. Flow diagram for revised CDC case definition of AIDS, September 1, 1987



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Appendix 11

Protocol Changes

1. Page 40, #10: "... or other qualified professional staff".
2. Page 41, Paragraph 7.2.3, line 3; ..(except for induced sputum exams).
3. Page 42. Induced Sputum only prescheduled for Entry exam.
4. Page 43. #3: Second paragraph is new.
5. Page 44. #4. ... and 3 ml/min/mm Hg.
6. Page 44. Paragraph 2: First sentence rewritten.
7. Page 46, #3: New paragraph.
8. Page 48, #6. New paragraph.
9. Page 51. Expanded definition of pleural effusion.
10. Page 72. Paragraph 10.2.7 line 6 and line 11: ...two maneuvers".
11. Page 72. Paragraph 10.2.8 "... follow-up and symptom evaluations".
12. Appendix 2: Changes in the definitions of PCP, Toxoplasmosis, Candidiasis, Bacterial Pneumonia.
13. Appendix 5: Page 13 Chest Radiography Procedures - New
14. Appendix 6: Previously Appendix 7.
15. Appendix 7: Previously Appendix 8.
16. Appendix 8: Serum Tracking and Shipping - New
17. Appendix 9: Skin Testing - New
18. Appendix 10: Previously was Appendix 12.