CD4 Counts as Predictors of Opportunistic Pneumonias in Human Immunodeficiency Virus (HIV) Infection

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Study Objective: To determine if circulating CD4+ lymphocyte counts are predictive of specific infectious or neoplastic processes causing pulmonary dysfunction.

Design: Retrospective, consecutive sample study.

Setting: Referral-based clinic and wards.

Patients: We studied 100 patients infected with human immunodeficiency virus (HIV) who had had 119 episodes of pulmonary dysfunction within 60 days after CD4 lymphocyte determinations.

Measurements and Main Results: Circulating CD4 counts were less than 0.200×10^9 cells/L (200 cells/mm^3) before 46 of 49 episodes of pneumocystis pneumonia, 8 of 8 episodes of cytomegalovirus pneumonia, and 7 of 7 episodes and 19 of 21 episodes of infection with *Cryptococcus neoformans* and *Mycobacterium avium-intracellulare,* respectively. In contrast, circulating CD4 counts before episodes of nonspecific interstitial pneumonia were quite variable: Of 41 episodes, 11 occurred when CD4 counts were greater than 0.200×10^9 cells/L. The percent of circulating lymphocytes that were CD4+ had a predictive value equal to that of CD4 counts. Serum p24 antigen levels had no predictive value.

Conclusions: Pneumocystis pneumonia, cytomegalovirus pneumonia, and pulmonary infection caused by *C. neoformans* or *M. avium-intracellulare* are unlikely to occur in HIV-infected patients who have had a CD4 count above 0.200 to 0.250×10^9 cells/L (200 to 250 cells/mm^3) or a CD4 percent above 20% to 25% in the 60 days before pulmonary evaluation. Patients infected with HIV who have a CD4 count below 0.200×10^9 cells/L (or less than 20% CD4 cells) are especially likely to benefit from antipneumocystis prophylaxis.

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Clinical studies and autopsy series show that opportunistic infections are the major recognized cause of life-threatening illnesses and death in patients infected with human immunodeficiency virus (HIV) (1-5). These opportunistic infections are a direct consequence of the immunosuppression caused by HIV as a result of CD4-cell depletion. Clinicians could clearly benefit by knowing when in the natural history of HIV infection these serious opportunistic infections are most likely to occur. With such information, clinicians would know when to be most vigilant for opportunistic infections and when prophylactic therapies would be warranted and cost-effective.

The absolute number of circulating CD4+ lymphocytes (CD4 count) has been shown to be a clinically useful indicator of immune function in HIV-infected persons. Counts of CD4+ cells can be used to objectively stratify HIV-infected patients according to severity of clinical illness (6-10). The CD4 counts have also been shown to be useful for predicting which HIV-infected patients will develop the acquired immunodeficiency syndrome (AIDS): Patients with fewer than 0.150 to 0.300×10^9 cells/L (150 to 300 cells/mm^3) are more likely to develop AIDS during the initial 12 to 36 months of follow-up than are patients with higher CD4 counts (6-9, 11-14). Moreover, HIV-positive patients with Kaposi sarcoma are more likely to develop pneumocystis pneumonia within 24 months of follow-up if their CD4 counts before study were below 0.200×10^9 cells/L (200 cells/mm^3) than if they had higher counts (15). No analysis, however, has assessed the range of circulating CD4 counts at which different, specific, life-threatening opportunistic infections occur. The purpose of this study was to evaluate the usefulness of the peripheral blood CD4 count or CD4 percent for the differential diagnosis of pneumonia in patients with HIV infection.

Materials and Methods

Patient Population

All patients seen at the Clinical Center, National Institutes of Health (NIH), from January 1982 to April 1988 were included in this study if they had the following characteristics: infection with HIV as determined by a licensed HIV serologic test (both enzyme-linked immunosorbent assay [ELISA] and Western blot) or an HIV culture, or (before 1986) the presence of a risk factor for AIDS; a clinical pulmonary disorder recognized by history, physical examina-

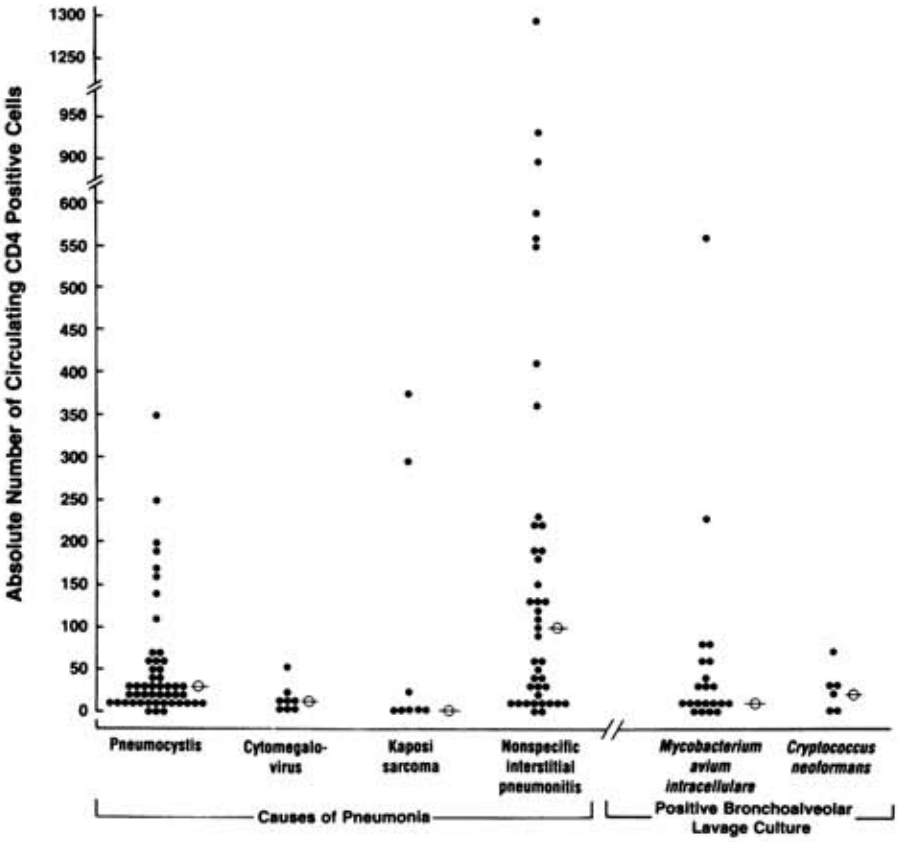

Figure 1. Circulating CD4 counts determined within 60 days of pulmonary diagnosis for 119 episodes of pulmonary dysfunction in 100 HIV-infected persons. Each solid circle represents one episode of pulmonary dysfunction. The open circle represents the median CD4 count.

tion, or chest roentgenogram; a specific pulmonary infection or disorder diagnosed by sputum, bronchoscopy or open-lung biopsy assessment; a CD4 count during the 60 days immediately before the diagnostic pulmonary procedure; and age greater than 18 years. If a patient had had more than one episode of a specific pulmonary process, only the first episode was included in the analysis to prevent one patient from unduly influencing the assessment: that is, if a patient had one episode of cytomegalovirus pneumonia and two episodes of pneumocystis pneumonia, the second episode of pneumocystis pneumonia would be deleted from analysis.

Pulmonary Disease

Patients were considered to have a pulmonary disorder if they presented with any constellation of symptoms, signs, or radiologic abnormalities that caused the health care providers to order bronchoscopy or open-lung biopsy. Patients were also included if an induced sputum examination established a diagnosis. At NIH, all HIV-infected patients are managed by at least one of the authors of this report, and almost all HIV-positive patients with serious pulmonary dysfunction have bronchoscopy with bronchoalveolar lavage and transbronchial biopsy if sputum examination is nondiagnostic. Empiric anti-infective or antineoplastic therapy is almost never permitted for more than 48 hours. Bronchoscopy included examination of the tracheobronchial tree, bronchoalveolar lavage, and three to five transbronchial biopsies (16, 17). Induced sputum examination was done as previously described by Kovacs and colleagues (18).

Pneumocystis pneumonia was defined by the presence of at least one cluster of typical organisms when samples from lung biopsy, bronchoalveolar lavage fluid, or sputum were assessed by toluidine blue O or immunofluorescent stains (17, 18). Cytomegalovirus pneumonia was defined, in the absence of other identifiable causative processes, by the histologic presence of interstitial pneumonitis with at least three typical inclusion bodies observed in the lung biopsy specimen. For the purpose of this study, a diagnosis of cytomegalovirus pneumonitis was not made if another pathogen or tumor could be histologically identified. Criteria for cytomegalovirus disease other than histologic presence were not used. Cryptococcal pneumonia was defined by histologic evidence of yeast that was morphologically consistent with cryptococcus. Cryptococcal infection was defined by positive culture of a lung biopsy specimen or bronchoalveolar lavage fluid for *Cryptococcus neoformans* regardless of what other processes were seen or agents cultured.

Pneumonia caused by *Mycobacterium avium-intracellulare* was defined by histologic evidence of mycobacteria in a lung biopsy specimen and a positive culture of a pulmonary secretion or tissue for *M. avium-intracellulare.* Pulmonary infection by *M. avium-intracellulare* was defined by a positive culture of bronchoalveolar lavage fluid or a lung biopsy specimen regardless of what other processes were seen or agents cultured. *Mycobacterium tuberculosis* was not seen in this population of patients.

Nonspecific pneumonitis was defined by a mononuclear cell inflammatory process observed in a lung biopsy specimen in addition to the histologic absence of an identifiable infectious agent or tumor in the biopsy sample (19). However, if an autopsy done within 21 days of the biopsy showed histologic evidence of a microbial or neoplastic process, then the episode was attributed to that specific autopsy finding. Pulmonary Kaposi sarcoma was defined by the presence of consistent histopathologic findings in a lung biopsy sample and the absence of any other infectious or neoplastic process on histologic evaluation of bronchoscopic or open-lung biopsy specimens (20).

Immunologic and Virologic Studies

Peripheral blood mononuclear cells used in immunologic studies were isolated from whole blood by Ficoll-hypaque density-gradient centrifugation within 60 days before the diagnostic pulmonary procedure as part of routine prospective monitoring associated with many HIV-related protocols

(10). Cells were washed twice in RPMI 1640 (MA Bioproducts, Walkersville, Maryland) and then suspended in RPMI 1640 supplemented with 10% fetal bovine serum (GIBCO, Grand Island, New York). Determination of the percentage of peripheral blood mononuclear cells bearing CD4+ or CD8+ markers was done by conventional fluorescent antibody cell-sorter analysis of the mononuclear cell population as previously reported (10). Absolute numbers of CD4+ and CD8+ lymphocytes were determined by multiplying the total lymphocyte count (computed from the manually assessed circulating leukocyte count and differential) by the percent of mononuclear cells, gated to remove monocytes and stained with the appropriate monoclonal antibody. Virologic study included serum p24 antigen assays, which were done during the 60 days immediately before pulmonary diagnosis using the Abbott kit (Abbott Laboratories, North Chicago, Illinois).

Statistics

To assess possible differences with respect to absolute CD4 counts, CD4 percents, or p24 antigen levels among the four primary diagnostic groups (pneumocystis pneumonia, nonspecific interstitial pneumonia, cytomegalovirus pneumonia, and pulmonary Kaposi sarcoma), standard one-way analysis of variance (ANOVA) was first done. If the ANOVA was statistically significant at the 0.05 level, pairwise *t*-tests with *P* values adjusted by Bonferroni's inequality were then done to assess which groups were different and which appeared to be roughly equivalent (this procedure protects against the problem of multiple comparisons [21]). The exact form of the two sample *t*-tests reported depends on whether there was significant evidence that the variances in the two groups were not equal. If there was not significant evidence, then the standard *t*-test with pooled variance was used; if the variances appeared different, then the test of Satterthwaite (22) was considered more appropriate.

Both Pearson correlations (the standard method that assumes the data pairs follow a normal distribution) and nonparametric Spearman correlations (a method that does not rely on the normality assumptions but uses the ranks of the data [23]) are reported. For the data in this study, which appear to have a small number of "outlier" data points, the nonparametric correlation is probably more reliable.

To compare the predictiveness of CD4 counts with that of CD4 percents for categorizing pulmonary episodes, McNemar's test for assessing correlated 2×2 tables was used in conjunction with associated point estimates and 95% confidence intervals (24). The 2×2 table that was constructed had cells for the following: both methods predicted correctly (+,+); count method predicted correctly but the percentage method predicted incorrectly (+,−); count method predicted incorrectly but the percentage method predicted correctly (−,+); and both methods predicted incorrectly (−,−). The test assesses whether the off-diagonal values (+,− and −,+) appear to be evenly distributed (which they would be if the two methods were equally predictive).

Medians and interquartile ranges are reported. For the data in this study, which are typically skewed and not normally distributed, these summary measures are more meaningful than the standard ones of the mean and standard error. The median is defined as the value that has half the data below it and half above it. The interquartile range goes from the first quartile (one quarter of the data is below this value, three quarters above it) to the third quartile (three quarters of the data are below this value, one quarter above it.) All *P* values are two-sided.

Results

Population of Patients

From 1982 to 1988, data were gathered on 127 episodes of pneumonitis involving 100 HIV-seropositive patients who had had CD4 counts done within 60 days before the pulmonary diagnosis was established. For this study, 119 of these episodes were considered usable. Eight episodes were eliminated from analysis because patients had already had an earlier episode with the same diagnosis; that is, no patient was allowed to influence the analysis disproportionately by being represented twice in the pneumocystis pneumonia category or twice in the cytomegalovirus pneumonia category. A patient could be represented once in several different categories if an episode of pneumocystis pneumonia was followed, for example, by another discrete episode of cytomegalovirus pneumonia.

For this statistical analysis an initial episode was considered the first episode for which data were avail-

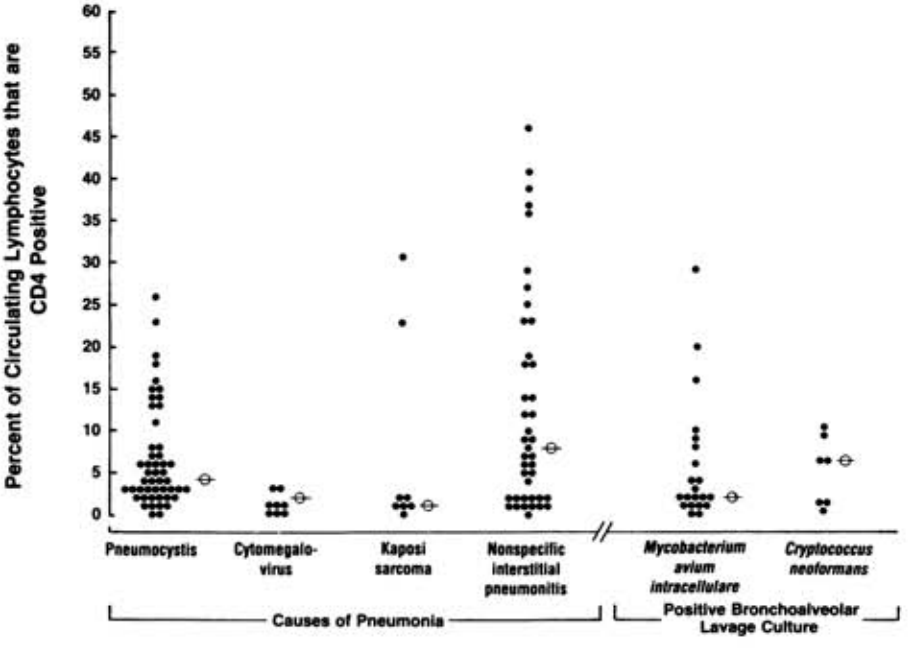

Figure 2. Percent of circulating lymphocytes that are CD4+ determined within 60 days of pulmonary diagnosis for 119 episodes of pulmonary dysfunction in 100 HIV-infected persons. Each solid circle represents one episode of pulmonary dysfunction. The open circle represents the median CD4 percent.

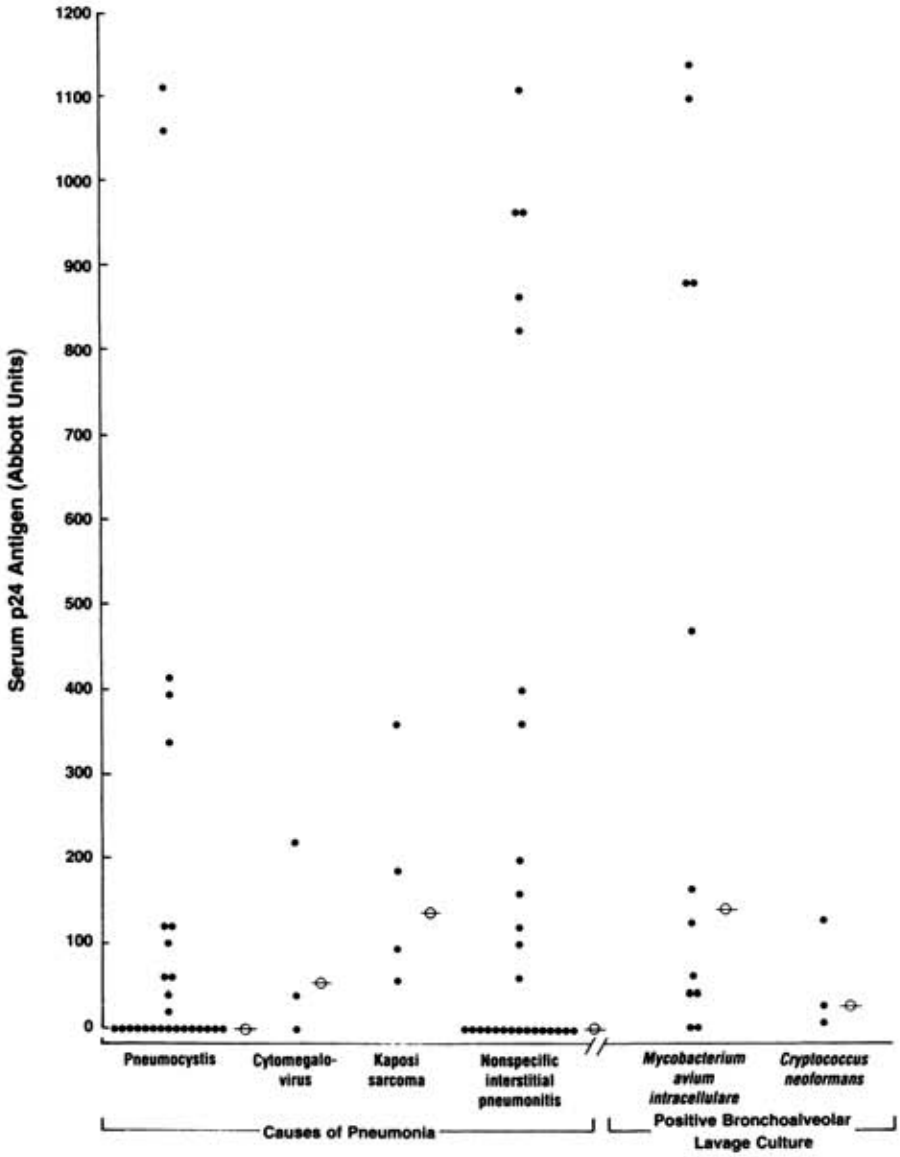

Figure 3. Serum p24 antigen determinations within 60 days of pulmonary diagnosis for 71 episodes of pulmonary dysfunction in 57 HIV-infected persons. Each solid circle represents an episode of pulmonary dysfunction. The open circle represents the median p24 level.

able in this series and was not necessarily the first episode the patient had ever had. Thus, by this definition, 100 of these 119 episodes in 100 patients represent the patient's initial episode. In all formal statistical estimates and tests, only these 100 initial (statistically independent) episodes are used. In the descriptive statistics and in Figures 1, 2, and 3, the additional 19 episodes are included to give the maximum information regarding our experience with this population of patients, especially because episodes in some diagnostic categories (such as cytomegalovirus pneumonia) were rarely the initial presentation.

Most of the patients had 300 to 500 CD4+ lymphocytes/mm^3 when first seen at NIH because of the entry criteria for most protocols. Subsequently, however, the CD4 counts gradually decreased in each patient as part of the natural history of HIV infection. The patients with pneumonitis included 96 men and 4 women. Risk factors for these 100 patients included homosexuality (94 patients), transfused blood products (3 patients), and heterosexual contact (3 patients). Before the 119 episodes of pulmonary dysfunction were diagnosed in this study, the HIV-infected patients had manifested the following clinical HIV-related disorders: no disorders (4 episodes), Kaposi sarcoma without opportunistic infections (68 episodes), life-threatening opportunistic infection (44 episodes), other AIDS-related conditions (11 episodes). During the 4 weeks before the diagnostic procedure for the 119 episodes, the patients had received zidovudine (36 episodes), interferon (23 episodes), recombinant interleukin-2 (3 episodes), cytotoxic chemotherapy (16 episodes), dideoxycytidine (6 episodes), muramyl tripeptide (1 episode), suramin (6 episodes), heteropolyanion 23 (5 episodes), zidovudine plus interferon (5 episodes), nonablative bone marrow transplantation (4 episodes). Twenty-two episodes occurred in patients who had been receiving neither experimental therapy nor zidovudine.

Correlation of CD4 Results with Pulmonary Findings

Figure 1 shows the circulating CD4 count for 119 episodes measured within 60 days before establishing a

diagnosis of pneumocystis pneumonia (49 episodes; median, 26 cells/mm^3; interquartile range, 12 to 62.5 cells/mm^3), cytomegalovirus pneumonia (8 episodes; median, 7.5 cells/mm^3; interquartile range, 5.2 to 15.8 cells/mm^3); pulmonary Kaposi sarcoma (8 episodes; median, 5.5 cells/mm^3; interquartile range, 5 to 228.7 cells/mm^3), or nonspecific pneumonitis (41 episodes; median, 100 cells/mm^3; interquartile range, 15.5 to 222.5 cells/mm^3). Figures 1, 2, and 3 do not show two episodes of cryptococcal pneumonia, one episode of *M. avium-intracellulare* pneumonia, and 10 episodes in which no diagnosis was established because lavage was nondiagnostic and biopsy was not feasible or adequate lung biopsy specimens were not obtained.

Patients who had a positive culture from either bronchoalveolar lavage fluid or a lung biopsy specimen for *C. neoformans or M. avium-intracellulare* are also represented in Figures 1, 2, and 3. Because the diagnostic implications of positive cultures are not clear, data related to positive pulmonary cultures for *C. neoformans* or *M. avium-intracellulare* are considered separately from data related to specific diagnoses. Figure 2 shows the percent of circulating lymphocytes that were CD4+ for these same episodes. The data in Figures 1 and 2 show that only 3 of 49 patients with pneumocystis pneu nia had a CD4 count greater than 0.200×10^9 cells/L (200 cells/mm^3) within the 60 days before pulmonary diagnosis, and only 2 patients had more than 20% of circulating lymphocytes that were CD4+. All 8 patients with cytomegalovirus pneumonia, all 7 patients with cryptococcal infection, and 19 of 21 patients infected with *M. avium-intracellulare* had CD4 counts less than 0.100×10^9 cells/L (100/mm^3). In contrast, 2 of 8 patients with pulmonary Kaposi sarcoma and 11 of 41 patients with nonspecific interstitial pneumonitis had CD4 counts greater than 0.200×10^9 cells/L (200 cells/mm^3). In 2 of 8 patients with pulmonary Kaposi sarcoma and 10 of 41 patients with nonspecific interstitial pneumonitis, at least 20 percent of circulating lymphocytes were CD4+.

The correlation of CD4 count values with CD4 percents for the 100 initial episodes was 0.737 by standard Pearson correlation and 0.895 by Spearman nonparametric correlation. Pairwise *t*-tests adjusted by Bonferroni's inequality for the multiple comparisons were used to assess which diagnostic groups were significantly different (using absolute CD4 numbers) and showed that patients with pneumocystis pneumonia were different from patients with nonspecific interstitial pneumonitis ($P < 0.016$), and from patients with cytomegalovirus pneumonia ($P < 0.0006$).

The predictiveness of various CD4 numbers and CD4 percents to correctly identify pneumocystis or cytomegalovirus pneumonia as opposed to interstitial pneumonitis or Kaposi sarcoma was assessed statistically: By McNemar's test, there was no difference in predictiveness when CD4 counts of 100, 200, 250, and 300 cells/mm^3 were compared with CD4 percents of 10%, 20%, 25%, and 30%, respectively (*P* values were 0.27, 1.0, 1.0, and 0.69, respectively). Point estimates and 95% CI for the improvement in predictiveness using CD4 counts rather than CD4 percents at these four cutoff sets were as follows: 0.054, −0.032 to 0.14; 0.011, −0.063 to 0.085; 0, −0.07 to 0.07; and 0.022, −0.04 to 0.084.

When the diagnostic predictability of CD4 counts was assessed at the various cutoff points, the following observations were made: If the CD4 count was above 300 cells/mm^3, 1 in 10 episodes was due to pneumocystis or cytomegalovirus pneumonia (10% predictability; CI, 0.3% to 44.5%); if the CD4 count was above 200 cells/mm^3, 2 in 15 episodes were due to pneumocystis or cytomegalovirus pneumonia (13.3% predictability; CI, 1.7% to 40.5%); if the CD4 count was below 100 cells/mm^3, 41 of 61 episodes were due to pneumocystis or cytomegalovirus pneumonia (67.2% predictability; CI, 54% to 78.7%).

Because the diagnostic usefulness of circulating CD4+ lymphocyte measurements may depend on how rapidly these measurements change during the days immediately before diagnosis of the pulmonary disease, we compared CD4 counts done 30 to 60 days before diagnosis with counts obtained immediately before diagnosis (0 to 7 days). The data indicate that absolute CD4 counts done 30 to 60 days before the pulmonary diagnosis were not significantly different from counts done within 7 days of diagnosis for these patient groups (Table 1).

Figure 4 shows sequential CD4 lymphocyte counts in a typical patient with Kaposi sarcoma who was followed for 14 months while receiving zidovudine. Pneumocystis pneumonia was diagnosed when the patient's most recent circulating CD4 lymphocyte count was 0.024×10^9 cells/L (24 cells/mm^3). In our experience, more precipitous falls in circulating CD4 lymphocyte counts have occurred in only a small number of patients. Since data acquisition for this study was

Table 1. *Median (Interquartile Range) CD4 Counts Measured at Two Time Intervals before Pulmonary Diagnosis for 100 Initial Episodes of Pulmonary Dysfunction and 21 Infections with Mycobacterium avium-intracellulare*

Diagnosis	CD4 Count at 0 to 7 days		CD4 Count at 30 to 60 Days		Two-Sided *P* Value
	Episodes, *n*	Median (Interquartile Range), *cells/mm^3*	Episodes, *n*	Median (Interquartile Range), *cells/mm^3*	
Pneumocystis pneumonia	21	22 (10 to 41)	10	42 (22.5 to 81.5)	0.95
Nonspecific interstitial pneumonia	22	184.5 (40.3 to 414.8)	7	61 (26 to 126)	0.26
Mycobacterium avium-intracellulare infection	10	10 (5.8 to 69.8)	6	32.5 (10.5 to 62.3)	0.47

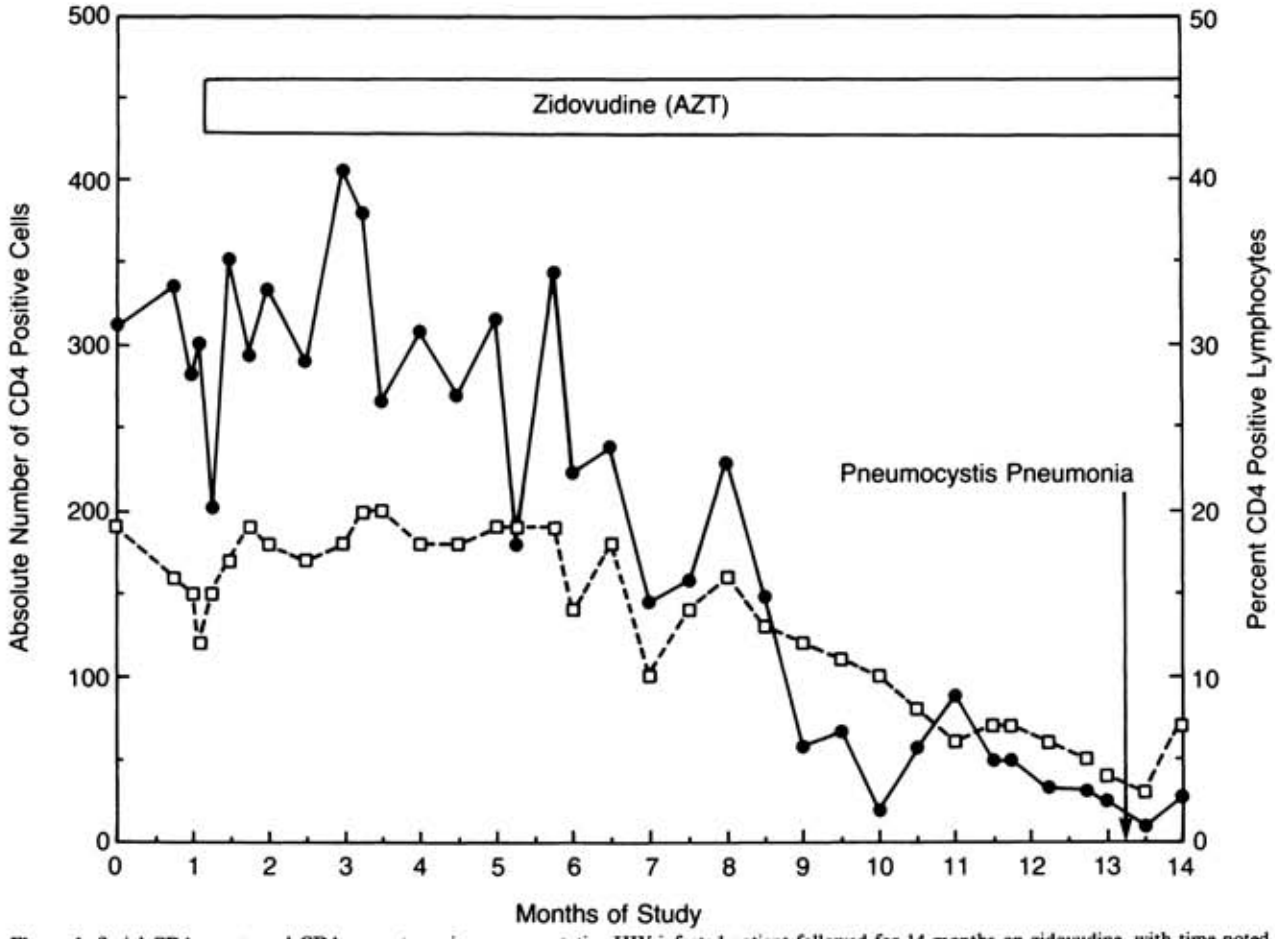

Figure 4. Serial CD4 counts and CD4 percentages in a representative HIV-infected patient followed for 14 months on zidovudine, with time noted when pneumocystis pneumonia was diagnosed. The open circles and dotted line represent the CD4 percentages; the closed circles and solid line represent the absolute CD4 counts.

closed, however, two unusual patients receiving chronic zidovudine therapy have been observed whose CD4 count fell precipitously during the 60 days before they developed pneumocystis pneumonia. No infectious, pharmacologic, or environmental causes for this fall were identified.

Correlation of p24 Antigen Levels with Pulmonary Findings

Because serum p24 antigen levels have been shown to have prognostic value in predicting the development of AIDS and response to therapy, we analyzed the predictive value of p24 antigen levels in our patients as well (25-29). Serum p24 antigen levels were ascertained within 60 days before pulmonary diagnosis for 71 of the 119 episodes in 57 patients. The relation of serum p24 antigen levels and pulmonary diagnosis is shown in Figure 3. No predictive association between p24 antigen level and pulmonary diagnosis is apparent (for the 53 initial episodes that led to one of the four primary pulmonary diagnoses, ANOVA P value was 0.78). In fact, most patients who developed pneumocystis pneumonia had negative p24 antigen levels at the time of diagnosis and were not statistically different from patients who developed nonspecific interstitial pneumonitis ($P = 0.50$ for initial episodes). In all 57 initial episodes, there was also no correlation between serum p24 antigen level and circulating CD4+ lymphocyte number (nonparametric Spearman correlation and standard Pearson correlation were −0.09 and −0.18, respectively) (data not shown).

Discussion

When an HIV-infected person presents with pulmonary complaints such as chest tightness, dyspnea, exercise intolerance, or cough, it is often difficult to be certain how aggressive the diagnostic and empiric therapeutic approach should be. Accumulating data indicate that early therapeutic intervention (when symptoms, signs, and laboratory findings are minimally abnormal or even normal) can dramatically improve prognosis for patients with an entity such as pneumocystis pneumonia (29). It seems logical to presume that early therapeutic intervention is a worthwhile strategy for other opportunistic pneumonias as well. Thus, the clinician needs some supporting data to indicate when an aggressive evaluation directed at opportunistic pathogens is likely to be productive.

This study shows that HIV-infected patients with CD4 counts greater than 0.200 to 0.250 $\times$ 10^9 cells/L (200 to 250 cells/mm^3) or a CD4 percent greater than 20% to 25% are at very low risk for developing pneu-

mocystis or cytomegalovirus pneumonia, or for having pulmonary infection caused by *M. avium-intracellulare* or *C. neoformans*. The data in Figures 1 and 2 suggest that when HIV-infected patients present with pulmonary dysfunction, measurements of circulating CD4+ lymphocytes within the previous 60 days are diagnostically useful. If patients have CD4 counts greater than 0.200×10^9 cells/L (200 cells/mm^3), or if more than 20 percent of circulating lymphocytes are CD4+ then the likelihood that pneumocystis or cytomegalovirus pneumonia is present is very low. Only 2 of 100 patients in this series had a serious pulmonary opportunistic pneumonia at a time when the CD4 count was greater than 0.200×10^9 cells/L (200 cells/mm^3), and only 2 patients had an opportunistic infection when the percentage of circulating lymphocytes that were CD4+ was greater than 20%.

The absolute number and the percent of circulating lymphocytes that are CD4+ could both be used to establish a cutoff point above which opportunistic infectious pneumonias were unlikely to occur. The Spearman correlation coefficient for these two variables was 0.895 when all 100 initial episodes were evaluated. Statistically these two CD4 indices appeared to be equally useful for predicting susceptibility to pneumocystis or cytomegalovirus pneumonia. When the CD4 count was above 300 cells/mm^3, the likelihood that the diagnosis was pneumocystis or cytomegalovirus pneumonia was 10% (CI, 0.3% to 44.5%). When the CD4 count was below 100 cells/mm^3, the likelihood that the diagnosis was pneumocystis or cytomegalovirus pneumonia was 67.2% (CI, 54% to 78.7%).

Patients with CD4 counts greater than 0.200 to 0.250×10^9 cells/L (200 to 250 cells/mm^3) can certainly develop viral processes in the upper respiratory tract or serious pulmonary disease caused by common, community-acquired pathogens (for example, influenza, Legionella) whose frequency or severity are not influenced by HIV infection; common, community-acquired bacteria (for example, pneumococcus, hemophilus) that may produce somewhat more frequent or serious disease in HIV-infected patients compared with non-HIV-infected patients; noninfectious HIV-related processes such as Kaposi sarcoma, nonspecific pneumonitis, or congestive heart failure caused by AIDS-related cardiomyopathy; HIV-related opportunistic infections caused by organisms such as *Mycobacterium tuberculosis, Histoplasma capsulatum*, or *Coccidioides immitis* that were not present in our population of patients but may be commoner in other geographic areas or risk groups.

It is clinically obvious that in any situation involving respiratory disease, the rapidity and invasiveness of diagnostic evaluation needs to be strongly influenced by the rate of progression and severity of pulmonary dysfunction. However, for HIV-infected patients with CD4 counts greater than 0.200 to 0.250×10^9 cells/L (200 to 250 cells/mm^3) and mild symptoms of brief duration, the urgency to do induced sputum examination and bronchoscopy is less compelling than in patients with lower CD4 counts. If, in fact, the patient has nonspecific interstitial pneumonitis, a common finding in our patients who had a respiratory syndrome and a CD4 count greater than 0.200 to 0.250×10^9 cells/L (200 to 250 cells/mm^3), the delay in diagnosis or omission of bronchoscopy will not be detrimental because this disease in adults is almost always self-limiting, and no therapy is available or necessary (19). If the patient has pulmonary Kaposi sarcoma, an open-lung biopsy would be warranted only if the pulmonary dysfunction was progressive and severe, which becomes obvious as the patient is observed (20).

In contrast to the above patient group, HIV-infected persons with CD4 counts below 0.200×10^9 cells/L (200 cells/mm^3) or a CD4 percent less than 20%, and especially those with CD4 counts below 0.100×10^9 cells/L (100 cells/mm^3) or a CD4 percent less than 10%, are clearly susceptible to pneumocystis pneumonia, cytomegalovirus pneumonia, and pulmonary infection caused by *M. avium-intracellulare* and *C. neoformans* (Figures 1 and 2). Because pneumocystis pneumonia ultimately occurs in at least 80% of HIV-infected persons, and because early institution of antipneumocystis therapy has been shown to improve prognosis, this population deserves especially prompt and aggressive diagnostic efforts directed at detecting *Pneumocystis carinii* (29, 30). The development of induced sputum examination as a highly sensitive and specific test for pneumocystis pneumonia has provided a rapid, economical, and noninvasive initial test (18).

Although cytomegalovirus pneumonia and fungal pneumonias have not been as carefully studied as pneumocystis pneumonia, the frequency of these processes in clinical and autopsy series and the availability of effective anticytomegalovirus and antifungal drugs suggest that a similarly aggressive diagnostic approach would be appropriate. A reasonable diagnostic approach for these HIV-infected patients with CD4 counts below 0.200×10^9 cells/L (200 cells/mm^3) or CD4 percent below 20% who present initially with pulmonary symptoms or signs, and whose chest roentgenogram and routine sputum examination fail to show an obvious cause, would be to do an induced sputum examination, followed, if necessary, by bronchoalveolar lavage and transbronchial biopsy in the next 48 to 72 hours. Microbiologic and histopathologic studies should be directed primarily at pneumocystis, cytomegalovirus, fungus, and *M. tuberculosis,* although common, community-acquired pathogens need to be considered as well.

The CD4 data shown in Figures 1 and 2 have implications for designing prophylaxis strategies in HIV-infected patients before they develop an initial episode of pneumocystis pneumonia. Trimethoprim-sulfamethoxazole and aerosol pentamidine have been shown to be effective antipneumocystis prophylaxis, and promising agents such as dapsone are being developed (15). These prophylactic agents would not have optimal efficiency if initiated when the CD4 count is above the 0.200 to 0.300×10^9 cells/L (200 to 300 cells/mm^3) range on two consecutive determinations: At higher CD4 counts the likelihood of pneumocystis

pneumonia developing is so low that the cost, inconvenience, and potential toxicity of prophylactic regimens are not likely to be warranted. This study did not assess the incidence of pneumocystis pneumonia in patients with fewer than 0.200 to 0.300 $\times$ 10^9 cells/L (200 to 300 cells/mm^3), but it is clearly this population, or a subset of this population, that is most likely to benefit from prophylaxis (31). Data from the prospective Multicenter AIDS Cohort Study (MACS) currently under analysis should provide specific incidence figures (Phair J. Personal communication).

Are CD4 counts done 60 days before pulmonary diagnosis satisfactory for predicting susceptibility to opportunistic pathogens? In this study, determinations made 30 to 60 days before pulmonary diagnosis were as predictive as those made 0 to 7 days before diagnosis (Table 1). Although it would be desirable to know the CD4 count when the pulmonary process is first evaluated by the health care provider, such an approach is not economical, results may not be expeditiously available, and the acute pulmonary process could distort the true CD4 count. Knowledge of a CD4 count within the past 60 days appears to be adequate: Whether CD4 counts done earlier than 60 days before evaluation are also useful still needs to be determined.

Limited, prospective serial data suggest that the slow fall in CD4 count as shown in Figure 4 appears to be typical of HIV-infected patients receiving chronic zidovudine therapy (6-14, 32-34). Rapid immunologic declines can occasionally occur (5% to 10% of all cases), however, so that pneumocystis or cytomegalovirus pneumonia must remain in the differential diagnosis for patients with CD4 counts above 0.300 $\times$ 10^9 cells/L (300 cells/mm^3), although their likelihood is low. Clinicians must also be aware that some therapies such as splenectomy, corticosteroids, or cytotoxic agents can seriously disrupt lymphocyte distribution, radically altering the meaning of CD4 counts. It should be noted that, in the case of splenectomy, total CD4 count may be elevated, but percent of CD4 cells is not altered. Moreover, certain ethnic groups, such as blacks, may occasionally have absence or partial deficiency of the OKT4 epitope so that use of the OKT4 monoclonal antibody would result in a substantially underestimated number of CD4+ cells (33, 35). In this study, many patients were receiving zidovudine or experimental drugs when they developed their pulmonary process. Zidovudine, dideoxycytidine, and certain other therapies sometimes affected the CD4 counts at least transiently; they did not, however, appear to alter the relationship between CD4 count and infection susceptibility (34, 36).

Is there a better predictor of pathogen susceptibility than CD4 count? The percentage of peripheral lymphocytes that are CD4+ is directly measured from a fluorescent antibody cell sorter, whereas the absolute CD4 count is derived from this percent and the leukocyte count and differential. Figure 2 shows that the percent of peripheral lymphocytes that are CD4+ is as useful a predictor of pathogen susceptibility as the absolute number of CD4 cells (37). We also assessed p24 antigen levels (Figure 3), but these levels (assessed at one time point) were not useful (21, 38-43). Other factors such as lymphocyte blastogenesis, gamma-interferon production, or cytomegalovirus-specific cellular cytotoxicity may also be useful, but they are not as easily available as CD4 cell determinations (43-46). Other clinical findings (such as fever or oral candidiasis) and laboratory values (such as serum lactic dehydrogenase levels) may also be useful for identifying subpopulations of patients with low CD4 counts who are at especially high risk for developing pneumocystis pneumonia.

This study indicates that CD4 counts are useful for predicting the likelihood that a person infected with HIV has or will soon develop certain opportunistic infectious processes. Patients infected with HIV with CD4 counts below 0.200 to 0.250 $\times$ 10^9 cells/L (200 to 250 cells/mm^3) or CD4 percents less than 20% to 25% (and especially those with fewer than 0.100 $\times$ 10^9 cells/L [100 cells/mm^3] or percent less than 10%) deserve particular attention for the possible presence of opportunistic infections when they present with pulmonary syndromes. Patients with these low CD4 counts also are most likely to benefit from antipneumocystis prophylaxis before an episode of pneumonia occurs (31).

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