

AIDS and the Lung

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3—Prevention of lung infections associated with human immunodeficiency virus infection

PHILIP C HOPEWELL

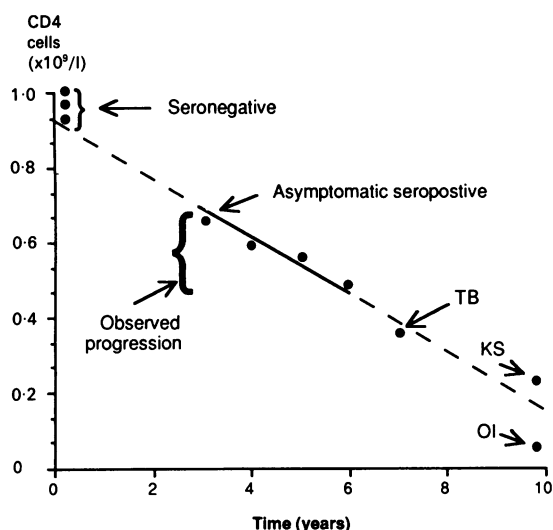
ABSTRACT Current evidence indicates that the length of survival for patients with the acquired immunodeficiency syndrome (AIDS) is increasing, thereby affording a greater opportunity for strategies designed to prevent the infectious diseases that mark the syndrome. Because these infections may occur at different stages of immunosuppression caused by the human immunodeficiency virus (HIV), effective application of preventive measures depends not only on detection of HIV infection but also on the use of staging indicators. The diseases that serve to define AIDS, such as *Pneumocystis carinii* pneumonia, tend to occur late in the course of HIV infection and often when the T helper lymphocyte (CD4⁺ cells) count is less than $0.2 \times 10^9/l$. Other infections, such as tuberculosis and pyogenic bacterial pneumonia, may develop at any point after HIV infection has occurred. Given this relation between the degree of immunosuppression and the occurrence of particular pulmonary infections, different preventive interventions should be applied at different times. It is now known that the incidence of several of the pulmonary infections that are common in patients with HIV infection can be reduced by prophylactic measures. *Pneumocystis pneumonia* is decreased in frequency by any one of several prophylactic agents, the best established being pentamidine administered as an inhaled aerosol. The role of isoniazid in the chemoprophylaxis of tuberculosis in patients not infected with HIV is well established. Although there is little evidence of benefit so far from isoniazid in HIV infected patients with a positive tuberculin skin test response, it is logical to assume that there could be some effect. The use of pneumococcal polysaccharide vaccine may also be of some benefit in reducing the frequency of pneumococcal pneumonia in patients with AIDS. In addition to these specific measures, the antiretroviral agent zidovudine decreases both the frequency and the severity of opportunist infections, at least during the first few months of treatment. A comprehensive strategy for prevention of HIV associated lung infection first requires detection of HIV seropositivity, staging the immunosuppression by the CD4⁺ cell count, and determining whether tuberculous infection is present by a tuberculin skin test. All seropositive individuals should be given pneumococcal vaccine and those with evidence of tuberculosis infection should be treated with isoniazid for one year. Zidovudine should probably be started when CD4⁺ cell counts are in the range $0.4-0.5 \times 10^9/l$ and prophylaxis against pneumocystis infection when CD4⁺ cell counts are in the range $0.2-0.3 \times 10^9/l$.

Introduction

Although the acquired immunodeficiency syndrome (AIDS) appears to be uniformly fatal, mounting evidence indicates that life expectancy for patients with the syndrome is increasing.^{1,2} The reasons for

this observation have not been determined but are probably multiple. Increasing familiarity with the diagnosis and management of the disorders that occur in patients with the syndrome, more effective use of antimicrobial treatments, and the use of zidovudine in patients with human immunodeficiency virus (HIV) infection all are likely to be playing a part. Possibly also in some areas, such as San Francisco, where the infected population probably acquired the virus a mean of five to seven years ago, the current survivors

Address for reprint requests: Dr Philip C Hopewell, Chest Service, University of California, San Francisco, PO Box 0841, San Francisco, CA 94143-0841, USA.



Postulated effects of HIV infection on CD4⁺ lymphocytes. The solid line represents the decline observed in a cohort of "healthy" HIV seropositive persons who were estimated to have been infected three years before the first determination of CD4⁺ cell counts (from ref 6). The points along the dashed line are the observed CD4⁺ cell counts in seronegative persons, HIV seropositive patients with tuberculosis (TB), and patients with AIDS who had Kaposi's sarcoma (KS) and opportunistic infections (OI).

represent a tougher, more resilient group with an immune system that has responded more effectively to HIV and other potential pathogens. Regardless of the causes, the observation of longer survival is a reason for optimism and underscores the potential usefulness of interventions to prevent HIV associated infections.

More to the point of this discussion, current data show that prevention of *Pneumocystis carinii* pneumonia, the most common of the AIDS defining diseases, increases longevity, indicating that the natural history of HIV infection is altered and that another pathogen does not promptly fill the void left by *P. carinii*.³⁴ Whether prevention of other HIV associated infections is possible and, if so, whether prevention would alter survival is not known, but the possibility is at least strongly suggested by the findings with *P. carinii*.

Relation of the natural history of HIV infection to pulmonary infections

Infection with HIV causes a progressive and ultimately profound reduction in the host immune response. This is perhaps best quantified by the

progressive loss of T helper lymphocytes (CD4⁺ cells), as shown in the figure.⁵⁶ The development of secondary infections in patients with HIV infection results from interactions between specific organisms and host defences. The infections that serve to define AIDS, such as *P. carinii* pneumonia, tend to occur late in the course of HIV infection, when there has been substantial depletion of CD4⁺ cells.⁷ Presumably, the late emergence of *P. carinii* relates to its relatively low pathogenicity. Organisms having greater pathogenicity, such as *Mycobacterium tuberculosis*, seem to cause disease earlier in the course of HIV infection, as evidenced by the higher CD4⁺ lymphocyte counts in these patients.⁸ Encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, are also much more virulent than *P. carinii*, for example, and may cause disease at any point in the course of HIV infection.

In view of the presumed relation between HIV induced immunosuppression and pulmonary infections, different preventive interventions need to be considered and applied at different points in the course of HIV infection. This implies that it is useful to determine the severity of HIV infection by a staging process, and to follow the staging indices over time to determine the optimum point at which an intervention should be applied. This approach is described in the summary section at the end of this paper.

Effects of antiviral treatment in preventing lung infections

Azidothymidine (zidovudine) is the only specific antiretroviral agent that has been found in clinical trials to have a beneficial effect on the course of HIV infection^{9,10} (see also the previous article in this series—Nov 1989;44:971). This agent inhibits the enzyme reverse transcriptase, thereby preventing viral replication within infected cells. As a consequence, immune responsiveness is improved and the onset of AIDS defining diseases is delayed. In addition, when opportunistic infections such as *P. carinii* pneumonia develop in patients treated with zidovudine they are less severe.⁹ It is logical to assume that the beneficial effects on immune function would reduce the frequency and severity of other pulmonary opportunistic infections.

Currently, zidovudine is recommended for symptomatic HIV infected patients who have fewer than 0.2×10^9 /l circulating CD4⁺ lymphocytes or who have had diseases usually associated with low CD4⁺ cell counts, such as pneumocystis pneumonia.¹⁰ Preliminary data suggest that zidovudine is beneficial for HIV infected patients with CD4⁺ cell counts of $0.4-0.5 \times 10^9$ /l or less. An important factor limiting broader application of zidovudine (in addition to its cost) is its toxicity, especially its effects on bone

marrow.¹¹ For this reason there is concern about the possibly additive side effects of zidovudine combined with other drugs.

Little is known about the interactions of zidovudine with systemically administered agents used for preventing HIV associated lung infections. Data from a very small retrospective examination (in only eight patients) of the rates of adverse reactions in those taking zidovudine and isoniazid plus other antituberculosis agents showed no increase in their frequency.¹² More data of this sort are urgently needed.

Although several other antiretroviral agents are being evaluated, their effects on opportunist pulmonary infection remain speculative.

Prevention of *P carinii* pneumonia

The use of zidovudine or other antiretroviral drugs will probably cause the frequency of *P carinii* pneumonia to decrease. Nevertheless, estimates suggest that in 1990 there will be 40 000–60 000 patients in the United States with their first episode of this disease.¹³ Without effective prophylaxis 30–35% of patients who have had one episode of *P carinii* pneumonia will have at least one subsequent episode.¹⁴ Paradoxically, by prolonging survival zidovudine may actually cause an increase in the total numbers of patients with *P carinii* pneumonia. Thus the development and implementation of effective means of prophylaxis are extremely important.

Trimethoprim-sulfamethoxazole Because of the effectiveness of trimethoprim and sulfamethoxazole (TMP-SMX) in preventing *P carinii* pneumonia in children with haematological malignancies the disease has largely disappeared from this population.¹⁵ Unfortunately, prevention of *P carinii* pneumonia in patients with AIDS presents more of a problem. The difficulties are mainly due to the high frequency of adverse reactions to TMP-SMX.¹³ In a study reported by Kaplan and coworkers¹⁶ the frequency of adverse reactions was such that it was impossible to reach a conclusion about the efficacy of TMP-SMX.

Fishl and associates³ reported a lower frequency of adverse reactions with TMP-SMX than had been found in previous studies and significant effectiveness in primary prophylaxis with a dose of 160 mg/800 mg plus 5 mg folic acid twice a day. In this study five of 30 patients given the drug had adverse effects that necessitated discontinuing the agent and 15 had minor adverse reactions. Four of the five patients in whom TMP-SMX was discontinued subsequently developed *P carinii* pneumonia, as did 16 of the 30 patients given placebo. Perhaps the most important observation from this study was that the median survival in the group given TMP-SMX was 20 months compared with 11 months in the control group. This study

therefore substantiated the beneficial effect of *P carinii* prophylaxis on the natural history of HIV infection.

Pentamidine As with TMP-SMX, the use of pentamidine to treat patients with *P carinii* pneumonia has been marked by a high frequency of adverse reactions.¹³ This, plus the need for parenteral administration, caused interest in the parenteral form of the drug as a preventive agent to wane. Because *P carinii* is located predominantly within alveoli, however, administration of pentamidine as an aerosol has been investigated and has proved both to be effective and to have a low frequency of adverse effects.⁴

Leoung and coworkers,⁴ in a prospective, randomised trial of aerosolised pentamidine, found an inverse relation between the dose of pentamidine and the frequency of *P carinii* pneumonia. The largest number of cases occurred in the patients receiving pentamidine 30 mg every two weeks; those receiving 150 mg every two weeks had an intermediate frequency of the disease, and those given 300 mg once a month had the lowest frequency. The difference in frequency of *P carinii* pneumonia between the 30 mg and the 300 mg doses was significant; the differences between 30 and 150 mg and between 150 and 300 mg were not. The aerosol was generated by a small particle producing jet nebuliser (mean aerodynamic diameter 1.6 μ m) delivered through a unidirectional breathing circuit that had a small particle filter on the expiration limb of the device (Respirgard II, Marquest Company, Englewood, Colorado).

Investigators noted that in patients receiving pentamidine aerosol prophylaxis who developed *P carinii* pneumonia the upper lobes of the lungs were the predominant sites of disease.¹⁷ This observation strongly suggests that the disease emerges where the concentrations of pentamidine are lowest. It would be predicted that with normal tidal breathing little of the aerosol would be deposited in the upper lung zones, whereas with deep breathing (exhalation to residual volume followed by inhalation to total lung capacity) more even deposition would be achieved.¹⁸ Extrapulmonary pneumocystosis has also been noted in patients receiving aerosol pentamidine prophylaxis.

Adverse reactions to inhaled pentamidine aerosol have been few and generally mild. Coughing is common, especially in cigarette smokers, and bronchoconstriction may occur. Each of these complications may be minimised by pretreatment with an inhaled bronchodilator such as salbutamol. A few patients have had hypersensitivity reactions, but in general even patients who have had adverse reactions to intravenous pentamidine have tolerated the aerosol well.¹⁹

In the report by Leoung and associates⁴ there was no detectable additive toxicity from aerosol pentamidine and zidovudine. Patients who received both agents

had greater levels of protection than those receiving either drug alone.

Diaminodiphenylsulfone (dapsone) Dapsone, an antileprosy agent, has been used successfully in combination with trimethoprim to treat *P carinii* pneumonia; dapsone alone appears to be effective as a preventive agent. Reports from two groups of investigators suggest that the drug is both safe and effective. Metroka and associates²⁰ reported substantial protection from dapsone given in a dose of 25 mg four times a day. Adverse reactions occurred in 10% of patients. Similarly, Lang and coworkers²¹ found that dapsone 50–100 mg/day was effective in preventing *P carinii* pneumonia and had a low rate of adverse effects.

Dapsone offers the advantage of being very cheap and easily administered. The cost savings, however, are offset to some extent by the need to monitor for adverse reactions, especially anaemia. Possible additive toxic effects from dapsone and zidovudine have not been determined.

Pyrimethamine-sulfadoxine (Fansidar) The combination of pyrimethamine and sulfadoxine, tried in small numbers of patients, seems to decrease the incidence of *P carinii* pneumonia.²² A major concern, however, has been the propensity of the drug to cause severe adverse reactions, including fatal Stevens-Johnson syndrome. For this reason its use has been limited. Given the better safety and probably at least equal efficacy of other regimens, pyrimethamine-sulfadoxine should not be used for preventive treatment.

Prevention of tuberculosis

Tuberculosis has been recognised with increasing frequency as an HIV associated infection both in the United States and in Africa.²³ Because tuberculosis, like *P carinii* pneumonia, is mainly due to endogenous reactivation of latent infection, it is amenable to preventive treatment. Current data suggest that a very large proportion of people with both HIV and tuberculous infection will develop tuberculosis. In a report by Selwin and coworkers²⁴ tuberculosis developed in eight (16%) of 49 intravenous drug users who were tuberculin skin test positive and infected with HIV, in a methadone treatment programme in New York City during a mean follow up period of 22 months. Only one case developed in a patient with a negative tuberculin skin test response during the initial evaluation period, and none of 62 tuberculin positive, HIV seronegative drug users developed tuberculosis. Moreover, none of those who had been given isoniazid prophylaxis developed tuberculosis.

There is a very large experience now of the use of isoniazid preventive treatment in patients not infected with HIV.²⁵ Many at risk groups have taken part in prospective, double blind, placebo controlled ran-

domised trials, all of which have had remarkably similar outcomes. During the year in which the medication was administered about 80% protection was conferred by the drug by comparison with placebo, and in ensuing years the protective effect remained at about 50%. None of these studies, however, addressed the issue of HIV infection directly and no such studies have been conducted subsequently. Thus the efficacy of isoniazid preventive treatment in persons with tuberculosis and HIV infection has not been determined. There is no reason, however, to think that isoniazid would be ineffective in this group. On the basis of this assumption, the American Thoracic Society and Centers for Disease Control (ATS, CDC) have recommended that HIV seropositive persons who have a positive tuberculin skin test response should be treated with isoniazid preventive treatment.^{26,27} Although studies from Europe have indicated that six months of preventive treatment with isoniazid is nearly as effective in some circumstances as 12 months, the ATS-CDC recommendations specify that a full year of preventive treatment should be given.

Although the data are not in complete agreement, some of the published evidence suggests that HIV infected patients treated for tuberculosis have a higher rate of adverse drug reactions than non-HIV infected patients given the same drugs.²⁸ Many of the reactions appear to have been caused by rifampicin; nevertheless some caution in the use of isoniazid as preventive treatment is warranted. Patients should be seen at least monthly and questioned about possible adverse drug reactions, as is recommended for all patients taking isoniazid. If patients are also receiving zidovudine, routine measurements of haemoglobin, white blood cell count, and liver function are particularly important.

The possibility that HIV induced immunosuppression will cause a false negative tuberculin reaction is a cause of some concern. If the tuberculin test is performed relatively early in the course of HIV infection, however, it tends to be positive in patients infected with *M tuberculosis*. It is recommended therefore that tuberculin testing should be carried out in all patients found to be HIV positive. Patients with a reaction of ≥ 5 mm to 5 tuberculin units of commercial purified protein derivative should be offered preventive treatment with isoniazid.

Immunisation against tuberculosis using BCG should not be performed in patients with AIDS because of the risk of disseminated BCG infection.²⁷ The use of BCG in HIV infected persons without AIDS, though not shown to be associated with a high risk of dissemination, is probably not advisable, at least in countries where the prevalence of tuberculosis is low.

Prevention of bacterial pneumonia

The frequency of pyogenic bacterial pneumonia is increased in patients with HIV infection. The most common organisms are *Streptococcus pneumoniae* and *Haemophilus influenzae*.²⁹ Group B streptococci and *Branhamella catarrhalis* also have been reported, as have various other organisms. The frequency with which bacterial pneumonia develops in patients with HIV infection is not known precisely. Selwin and coworkers,³⁰ however, found an annual incidence of 10% in 144 HIV seropositive intravenous drug users compared with 2% in a group of seronegative drug users. Not only is the frequency of pneumonia increased but the pneumonia tends to be associated more frequently with bacteraemia and with recurrence after successful treatment.

Given these features prevention of bacterial pneumonia in HIV infected patients is clearly a high priority. Unfortunately there are no good data on which to base preventive interventions. HIV infection appears to diminish the antibody response to capsular polysaccharide vaccines for pneumococcal pneumonia; the more severe the HIV induced immunosuppression the lower are the antibody titres.^{31,32} Moreover, HIV infected patients tend to have lower baseline antibody titres than non-infected control subjects, suggesting a loss of antibody production. Nevertheless, the Immunization Practices Advisory Committee of the Centers for Disease Control has recommended that pneumococcal polysaccharide vaccine should be given to all patients older than 2 years with HIV infection.³³

In some patients with recurrent pneumococcal infections oral penicillin prophylaxis may be useful, although there is no documentation of benefit.

Passive immunotherapy with immunoglobulin G is recommended for children with HIV infection. Children should also receive *H influenzae* type B capsular vaccine. The potential benefits of *H influenzae* vaccine in adults are not known.

Strategies for preventing pulmonary infections in HIV infected patients

Applying a comprehensive strategy for preventing HIV associated pulmonary infections depends on several critically important pieces of information: (1) Is the patient infected with HIV (HIV seropositive)? (2) What is the stage of the HIV infection? (3) Has the patient been infected with *Mycobacterium tuberculosis*? Answering the first of these questions obviously requires that anyone at risk of having acquired HIV infection should be tested for the presence of antibodies to the virus. Testing for HIV was of little value when there was little treatment to

offer infected persons. Now, given current methods of treatment and prevention, testing should be encouraged.

Probably the simplest and most clinically relevant means of staging HIV infection is measurement of circulating CD4⁺ lymphocytes. This measurement appears to be the best single indicator of the degree of immunosuppression. Unfortunately, there are wide variations in these measurements among laboratories and even within the same laboratory. Moreover, CD4⁺ cell counts may fluctuate over time in the same person. Given these limitations, CD4⁺ cell counts must be interpreted in a clinical context. Generally speaking, however, AIDS defining opportunist infections such as pneumocystis pneumonia do not occur with CD4⁺ cell counts greater than $0.2 \times 10^9/l$, whereas tuberculous and bacterial pneumonia may occur with normal CD4⁺ cell counts.

Detection of tuberculous infection relies on the tuberculin skin test, an imprecise tool at best. All patients who are HIV seropositive should have a tuberculin skin test (Mantoux method, not a multiple puncture test). If time and resources permit, "control" antigens may be applied to assist in separating true negative from false negative skin test results. Control antigens are those to which most (but not all) individuals with intact cell mediated immunity will respond; the most useful are those made from candida and mumps organisms. A negative reaction to both antigens suggests that the person is anergic and a negative (< 5 mm) tuberculin reaction may then be a false negative as a result of HIV induced immunosuppression. If a positive reaction is elicited with the control antigens, a negative tuberculin reaction may be assumed to be a true negative.

With this information a prevention programme can be developed. All seropositive persons should be given pneumococcal polysaccharide vaccine. Although the patients with very low CD4⁺ cell counts are unlikely to respond, there is little risk and perhaps some gain. If resources are limited, the vaccine should be given only to those with counts of more than $0.2 \times 10^9/l$.

Any seropositive person with a positive (≥ 5 mm) tuberculin reaction should be offered preventive treatment with isoniazid 300 mg/day for one year. Isoniazid may be considered for anergic persons who, because of epidemiological circumstances, are likely to be infected with *M tuberculosis*. This would include patients from countries with a high prevalence of tuberculosis and individuals who are contacts of patients known to have tuberculosis.

Seropositive patients who have CD4⁺ counts of $0.2 \times 10^9/l$ or less, or who have had clinical evidence of immunosuppression, should be offered prophylaxis for pneumocystis pneumonia.³⁴ The choice appears to be between aerosol pentamidine and dapsone. In

patients who are taking zidovudine aerosol pentamidine may be safer. The dose of aerosol pentamidine is 300 mg given once a month. Dapsone can be given in a single daily dose of 100 mg or divided doses. If dapsone is used, monitoring for haematological toxicity should be done at least monthly and weekly if the patient is taking zidovudine. Dapsone is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.

Currently zidovudine is recommended for persons who have clinical evidence of immunosuppression or who have CD4⁺ counts of $0.2 \times 10^9/l$ or less, and preliminary data indicate benefit for those with counts of $0.4-0.5 \times 10^9/l$. This is a rapidly evolving area, however, and recommendations are likely to be changing in the near future.

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