

Editorials

Interactions between opportunistic micro-organisms and HIV in the lung

J R Clarke, D Israel-Biet

The lung is a major focus of disease in patients with acquired immunodeficiency syndrome (AIDS) and particular emphasis has always been placed upon the diagnosis and treatment of the opportunistic micro-organisms responsible for the severe and life threatening pneumonias.^{1,2} Numerous prophylactic approaches for preventing and controlling these opportunistic pathogens have been published. Despite the implementation of these procedures the prognosis for patients with AIDS is poor with an average survival time from diagnosis to death of 17 months.¹ As a result of the profound immunosuppression induced by HIV, pneumonias are common during the course of the disease, due to three major types of pathogens: *Pneumocystis carinii*, *Mycobacterium tuberculosis*, and pyogenic bacteria. Indeed, even with widespread prophylaxis *Pneumocystis carinii* remains the commonest opportunistic micro-organism of the lung among patients with AIDS in the industrialised world.³ In subSaharan Africa and Asia the most common pulmonary complication in HIV infected individuals is tuberculosis.⁴ Coupled with the spread of multiple drug-resistant strains of tuberculosis amongst subjects with AIDS in the USA, tuberculosis threatens to spread into the general community. Furthermore, pyogenic bacterial infections are common in patients with AIDS and are an important cause of death in Africa.^{5,6} The role of viral infections of the lung in HIV infected individuals, particularly those due to cytomegalovirus, remains controversial.

Various mechanisms exist in which immune responses mounted by the host during pneumonia may modify the growth of HIV. These interactions between HIV and infectious agents in the lung may be harmful for the lung itself, and quite probably enhance the progression of the HIV disease in general.⁷ As HIV replicates best in activated or differentiated cells of the immune system, co-infections of these cells with opportunistic micro-organisms and HIV could enhance viral replication. Alternatively, cells releasing cytokines in response to a pathogen could trigger HIV replication in adjacent cells through a paracrine process. The high frequency of detection of HIV proviral DNA in alveolar lymphocytes and alveolar macrophages from patients with AIDS⁸ indicates that there is ample opportunity for interaction between opportunistic micro-organisms and HIV in the lung.

Depletion of CD4 + T lymphocytes and subsequent abrogation of the immune system by HIV greatly facilitates

the development of *Pneumocystis carinii* pneumonia and onset of AIDS. However, *P carinii* pneumonia does not predispose alveolar lymphocytes or macrophages to infection in vivo and, conversely, although *P carinii* pneumonia is a marker for AIDS, HIV-1 infection of alveolar lymphocytes and macrophages is not a prerequisite for *P carinii* pneumonia.⁹ However, *P carinii* does significantly increase the recovery of HIV-1 from these cells,^{10,11} and there is a fourfold increase in the number of HIV virions detectable in the cell free fluid obtained by bronchoalveolar lavage from individuals with *P carinii* pneumonia.¹² The cellular mechanisms underlying this phenomenon remain unclear, although increased levels of tumour necrosis factor α (TNF α) are secreted by the immunocompetent host in response to *P carinii* pneumonia.¹³ Likewise, high levels of TNF α are released by alveolar macrophages in the lung of HIV-1 infected individuals,^{14,15} particularly during *P carinii* pneumonia.¹⁶ Interestingly, increased production of TNF α by alveolar macrophages does not correlate with an increase in the number of cells infected with HIV.¹⁷ Furthermore, TNF α has been shown to be a potent stimulator of HIV-1 replication¹⁸ and thus could offer a mechanism by which significant replication of HIV may occur in the lung. Conversely, in vitro experiments on HIV infected macrophages exposed to *P carinii* show that they release less TNF α than uninfected cells.¹⁹

An early effect of infection with HIV-1 is the reactivation of previously dormant tubercle bacilli. One consequence of interaction between *Mycobacterium tuberculosis* and HIV is a decreased control of both infections by host cells. An important action of HIV is inhibition of T lymphocyte mediated immune functions that maintain mycobacterial dormancy.²⁰ Both CD4 and CD8 T lymphocyte functions are essential for protection against *M tuberculosis*. Even a moderate reduction in the number of CD4 T lymphocytes is sufficient to enable reactivation of tuberculosis.²¹ Furthermore, peripheral blood mononuclear cells from HIV infected subjects with tuberculosis have decreased proliferative and type 1 responses on stimulation with *M tuberculosis*.²² Consequently, blood monocytes from patients with tuberculosis are more susceptible to the growth of HIV.²³ The phagocytosis of *M tuberculosis* by monocyte cell lines enhances the replication of HIV-1 and HIV-2 in these cell lines^{24,25} but, surprisingly, whilst virus transcription is increased, release of infectious virus from the cells is reduced. This scenario may facilitate the spread of HIV by

increasing cell to cell spread of the virus. This would in turn reduce extracellular levels of virus that would normally be recognised by the immune system, possibly leading to poor local antibody production and a reduction in the neutralisation of virus resulting in the immune escape of HIV. A further mechanism by which HIV and the tubercle bacilli may interact is by upregulation of TNF α . Indeed, peripheral blood mononuclear cells from HIV infected subjects have an enhanced release of TNF upon stimulation with purified protein derivative (PPD).²⁶ Increased transcription of HIV-1 in lymphocytes and monocytes that have phagocytosed *M tuberculosis* can be partially blocked by antibody to TNF.²⁷ However, PPD activation of HIV was abolished by mutations in the nuclear factor kappa B binding domains in the HIV genome,²⁷ which strongly suggests that interaction between tubercle and HIV may be occurring at multiple levels. Surprisingly, to date little information is available on how infection of monocytes/macrophages with HIV affects the replication and spread of *M tuberculosis*. Whilst it is known that the tubercle bacillus can infect and replicate in macrophages, infection with HIV may further compromise the ability of the host cells to limit bacterial growth. It is important to establish if release of *M tuberculosis* from macrophages is also inhibited when the cells are co-infected with HIV.

Several observations argue for in vivo interactions between tuberculosis and HIV. Firstly, HIV infection is associated with a risk of tuberculosis and these patients develop a more severe and life threatening form of the illness.²⁸ Secondly, there is an accelerated course of HIV disease in patients with tuberculosis.²⁹

Despite the high frequency of bacterial pneumonias in patients with AIDS, very few data are available on the interactions between bacteria and the growth of HIV. However, one group has shown that the HIV DNA copy number was higher in alveolar cells of individuals with AIDS when bacteria were recovered from their lung,³⁰ which suggests an enhancing effect of this type of pathogen on the number of HIV infected cells during active pyogenic infection. The mechanism underlying this observation is so far unknown.

Certain viruses may be involved in the infectious pulmonary complications of AIDS, although their direct role in pneumonia remains questionable. However, the ubiquitous nature of human herpes viruses (HHV) within groups at high risk for HIV infection, and their ability to set up latent or persistent life-long infection within the host, render them ideal candidates as co-factors for the spread of HIV disease. The major mechanism of interaction between HHV and HIV is the ability of the former to stimulate HIV replication in co-infected cells. This capability is reciprocal with HIV replication stimulating the growth of latent herpes viruses.³¹ Viral proteins required for the replication of HIV, such as the HIV transactivation of transcription (*Tat*) protein, can be released from infected cells in high concentrations; it is possible that this protein may activate HHV in an autocrine or paracrine fashion. HHV-6 can replicate in and destroy CD4 + T lymphocytes in the absence of co-infection with HIV, and in this way may hasten the onset of AIDS.³² There appears to be enhanced killing of CD4 + T lymphocytes doubly infected with HHV-6 and HIV. HHV-6 is also capable of upregulating CD4 expression on the surface of CD8 bearing T lymphocytes and natural killer cells making them susceptible to infection with HIV-1, and this could potentially facilitate the spread of HIV in vivo.³² Interestingly, there appears to be a high frequency of HHV-6 reactivation in HIV infected individuals which increases as disease spreads from asymptomatic to symptomatic disease.³²⁻³⁴

It has been reported that co-infection of cells in vitro with cytomegalovirus (CMV) stimulates HIV replication. Again the viral proteins produced by CMV and required for the initiation of replication by this virus can also directly stimulate HIV transcription,³⁵ and it is possible that co-infection with CMV could amplify the effects of HIV infection in the lung. Furthermore, CMV infection of human fibroblasts in vitro has been shown to upregulate cellular nuclear factors within these cells with resultant stimulation of HIV-1 replication.³⁶ However, the isolation of CMV from respiratory secretions of patients with AIDS and pneumonia did not appear to affect the prognosis adversely,³⁷⁻⁴⁰ although the isolation or cytological detection of CMV in bronchoalveolar fluid from HIV infected individuals was associated with a significant increase in mortality at three and six months after bronchoscopy in the absence of other complicating factors such as CD4 count.⁴¹ Our own studies indicated that, in patients with AIDS who had detectable HIV and CMV in their alveolar cells, there was no additional reduction in pulmonary function.⁴²

Recently, reciprocal enhancement of HIV-1 and HSV-1 replication associated with co-infection of keratinocytes and macrophages in vivo has been reported.⁴³ Interestingly, the virions were found to be morphologically atypical hybrids and, if verified, this observation could have profound implications for the pathogenesis of AIDS, as it would increase the spread of both viruses in cells and tissues that would not ordinarily be infected due to the lack of appropriate receptors for virus entry.

In summary, a number of pathogens can be found in the lung of HIV seropositive subjects. Whilst some such as *P carinii*, *M tuberculosis*, and pyogenic bacteria undoubtedly cause pneumonia, others such as CMV may be innocent passengers at the time of respiratory episodes. However, from in vitro studies it is clear that these micro-organisms can enhance HIV replication. Furthermore, some clinical observations now support the belief that interactions between micro-organisms and HIV occur in vivo and hasten the onset of AIDS. To date the exact mechanisms involved are poorly understood. A better understanding could be beneficial in designing future treatment strategies which limit the deleterious effects of opportunistic infections on disease progression in HIV infected subjects.

Virology Research,
St Mary's Hospital Medical School,
London W2 1PG, UK

JOHN R CLARKE

Service de Pneumologie,
Hôpital Laënnec,
75007 Paris, France

DOMINIQUE ISRAËL-BIET

- Mitchell DM, Miller RF. New developments in the pulmonary diseases affecting HIV-infected individuals. *Thorax* 1995;50:294-302.
- Miller RF, Mitchell DM. *Pneumocystis carinii* pneumonia. *Thorax* 1995; 50:191-200.
- Hawley PH, Ronco JJ, Guillemi SA, Quieffin J, Russell JA, Lawson LM, et al. Decreasing frequency but worsening mortality of acute respiratory failure secondary to AIDS-related *Pneumocystis carinii* pneumonia. *Chest* 1994; 106:1456-9.
- Daley CL. Pulmonary infections in the tropics: impact of HIV infection. *Thorax* 1994;49:370-8.
- Wallace J, Rao A, Glassroth J, Hansen N, Rosen M, Arakaki C, et al. Respiratory illness in persons with HIV infection. *Am Rev Respir Dis* 1993;148:1523-9.
- Lucas S, Hounnou A, Peacock C, Beaumel A, Djomand G, N'Gbhici J-M, et al. The mortality and pathology of HIV infection in a West African city. *AIDS* 1993;7:1569-79.
- Clarke JR, Robinson DS, Coker RJ, Miller RF, Mitchell DM. Role of the human immunodeficiency virus within the lung. *Thorax* 1995;50:567-76.
- Clarke JR, Taylor IK, Fleming J, Nukuna A, Williamson JD, Mitchell DM. The epidemiology of HIV-1 infection of the lung in AIDS patients. *AIDS* 1993;7:555-60.
- Clarke JR, Taylor IK, Fleming J, Williamson JD, Mitchell DM. Relation of HIV-1 in bronchoalveolar lavage cells to abnormalities of lung function and to the presence of pneumocystis pneumonia in HIV-1 seropositive patients. *Thorax* 1993;48:1222-6.

- 10 Clarke JR, Williamson JD, Mitchell DM. A comparative study of the isolation of human immunodeficiency virus from the lung and peripheral blood of AIDS patients. *J Med Virol* 1993;39:196-9.
- 11 Israel-Biet D, Cadranet J, Even P. Human immunodeficiency virus production by alveolar lymphocytes is increased during *Pneumocystis carinii* pneumonia. *Am Rev Respir Dis* 1993;148:1308-12.
- 12 Lu W, Israel-Biet D. Virion concentration in bronchoalveolar lavage fluids of HIV-infected patients. *Lancet* 1993;342:298.
- 13 Pesanti EL. Interaction of cytokines and alveolar cells with *Pneumocystis carinii* in vitro. *J Infect Dis* 1991;163:611-6.
- 14 Israel-Biet D, Cadranet J, Beldjord K, Andrieu M, Jeffrey A, Even P. Tumour-necrosis factor production in HIV-seropositive subjects: relationship with lung opportunistic infections and HIV expression in alveolar macrophages. *J Immunol* 1991;147:490-4.
- 15 Agostini C, Zambello R, Trentin L, Cerutti A, Enthammer C, Facco M, et al. Expression of TNF receptors by T cells and membrane TNF α in the regulation of the local immune responses in the lung of HIV-1 infected patients. *J Immunol* 1995;154:2928-38.
- 16 Krishnan V, Meager A, Mitchell DM, Pinching AJ. Alveolar macrophages in AIDS patients: increased spontaneous tumor necrosis factor- α production in *Pneumocystis carinii* pneumonia. *Clin Exp Immunol* 1990;80:156-60.
- 17 Sierra-Madero JG, Toossi Z, Hom DL, Finegan CK, Hoenig E, Rich EA. Relationship between load of virus in alveolar macrophages from human immunodeficiency virus type 1 infected persons, production of cytokines and clinical status. *J Infect Dis* 1994;169:18-27.
- 18 Navikas V, Link J, Persson C, Olsson T, Hojberg B, Ljungdahl A, et al. Increased mRNA expression of IL-6, IL-10, TNF α and perforin in blood mononuclear cells in human HIV infection. *J AIDS* 1995;9:484-9.
- 19 Kandil O. Human immunodeficiency virus type 1 infection of human macrophages modulates the cytokine response to *Pneumocystis carinii*. *Infect Immun* 1994;62:644-50.
- 20 Stanford JL, Onyebujah PC, Rook GA, Grange JM, Pozniak A. Old plague, new plague, and a treatment for both? *AIDS* 1993;7:1275-6.
- 21 Grange JM, Stanford JL, Rook GA, Onyebujah P, Bretscher PA. Tuberculosis and HIV: light after darkness. *Thorax* 1994;49:537-9.
- 22 Zhang M. T cell cytokine responses in persons with tuberculosis and human immunodeficiency virus infection. *J Clin Invest* 1994;94:2435-42.
- 23 Toossi Z. Enhanced susceptibility of blood monocytes from patients with pulmonary tuberculosis to productive infection with human immunodeficiency virus type 1. *J Exp Med* 1993;177:1511-6.
- 24 Shattock RJ, Friedland JS, Griffin GE. Phagocytosis of *Mycobacterium tuberculosis* modulates human immunodeficiency virus replication in human monocytic cells. *J Gen Virol* 1994;75:849-56.
- 25 Zhang Y, Nakata K, Weiden M, Rom WN. *Mycobacterium tuberculosis* enhances human immunodeficiency virus-1 replication by transcriptional activation at the long terminal repeat. *J Clin Invest* 1995;95:2324-31.
- 26 Wallis R. Influence of tuberculosis on HIV: enhanced cytokine expression and elevated β_2 microglobulin in HIV-1 associated tuberculosis. *J Infect Dis* 1992;167:43-8.
- 27 Lederman MM, Georges DL, Kusner DJ, Mudido P, Giam C-Z, Toossi Z. *Mycobacterium tuberculosis* and its purified protein derivative activate expression of the human immunodeficiency virus. *J AIDS* 1994;7:727-33.
- 28 Daley C. An outbreak of tuberculosis with accelerated progression among persons with the human immunodeficiency virus. *N Engl J Med* 1992;326:231-5.
- 29 Whalen C. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med* 1995;151:129-35.
- 30 Clarke J, Gates A, Coker R, Williamson J, Mitchell D. The relationship between HIV-1 proviral DNA copy number in alveolar macrophages and clinical disease in the lung of AIDS patients. *Am J Respir Crit Care Med* 1995;151:A795.
- 31 Sieczkowski L, Chandran B, Wood C. The human immunodeficiency virus *tat* gene enhances replication of human herpesvirus-6. *Virology* 1995;211:544-53.
- 32 Ablashi DV, Bernbaum J, Di Paolo JA. Human herpesvirus 6 as a potential co-pathogen. *Trends Microbiol* 1995;3:324-7.
- 33 Lusso P, Ensoli B, Markham PD, Ablashi DV, Salahuddin SZ, Tschachler E, et al. Productive dual infection of human CD4 + T lymphocytes by HIV-1 and HHV-6. *Nature* 1989;337:370-3.
- 34 Levy JA, Landay A, Lennette ET. Human herpesvirus 6 inhibits human immunodeficiency virus type 1 replication in cell culture. *J Clin Microbiol* 1990;28:2362-4.
- 35 Davis MG, Kenney SC, Kamine J, Pagano JS, Huang E. Immediate early gene region of human cytomegalovirus transactivates the promoter of human immunodeficiency virus. *Proc Natl Acad Sci USA* 1987;84:8642-6.
- 36 Rando RF, Srinivasan A, Feingold F, Gonczol E, Plotkin S. Characterisation of multiple molecular interactions between human cytomegalovirus (HCMV) and human immunodeficiency virus type 1 (HIV-1). *Virology* 1990;176:87-97.
- 37 Bower MB, Barton SB, Nelson MR. The significance of the detection of cytomegalovirus in the bronchoalveolar lavage fluid in AIDS patients with pneumonia. *AIDS* 1990;4:317-20.
- 38 Millar AB, Patou G, Miller RF, Grundy JE, Katz DR, Weller IV, et al. Cytomegalovirus in the lungs of patients with AIDS: respiratory pathogen or passenger. *Am Rev Respir Dis* 1990;141:1474-7.
- 39 Jacobsen MA, Mills J, Rush J, Peiperl L, Seru V, Mohanty PK, et al. Morbidity and mortality of patients with AIDS and first episode *Pneumocystis carinii* pneumonia is unaffected by concomitant pulmonary cytomegalovirus infection. *Am Rev Respir Dis* 1991;144:6-9.
- 40 Bozzette SA, Arcia J, Bartok AE, McGlynn LM, McCutchan A, Richman DD, et al. Impact of *Pneumocystis carinii* and cytomegalovirus on the course and outcome of atypical pneumonia in advanced human immunodeficiency virus disease. *J Infect Dis* 1992;165:93-8.
- 41 Hayner CE, Baughman RP, Linnermann CC, Dohn MN. The relationship between cytomegalovirus retrieved by bronchoalveolar lavage and mortality in patients with HIV. *Chest* 1995;107:735-40.
- 42 Clarke JR, Fleming J, Donegan K, Moss FM, Nieman R, Williamson JD, et al. Effect of HIV-1 and cytomegalovirus in bronchoalveolar lavage cells on the transfer factor for lung carbon monoxide in AIDS patients. *AIDS* 1991;5:1333-8.
- 43 Heng MC, Yang Meng S, Allen SG. Co-infection and synergy of human immunodeficiency virus-1 and herpes simplex virus-1. *Lancet* 1994;343:255-8.