Published in final edited form as:
Clin Chest Med. 2013 June ; 34(2): 143–153. doi:10.1016/j.ccm.2013.01.003.

Abnormalities in Host Defense Associated with HIV Infection

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SUMMARY

Although depletion of CD4+ T cells is a major immunologic manifestation of HIV infection, multiple components of the host defense network are impaired. CD4+ T cells demonstrate impaired proliferative and cytokine responses, despite expression of activation signals. Lung CD8+ T cells are increased in number and cause lymphocytic alveolitis, but do not lyse target cells appropriately. Specific antibody responses and opsonization of microorganisms are impaired. Alveolar macrophages demonstrate intact phagocytosis and killing, enhanced antigen presentation, and increased tumor necrosis factor elaboration. Despite these findings, pulmonary infections in vivo may result from impaired activation signaling from T cells. Further investigation is needed to clarify discrepant results regarding pulmonary neutrophils' capacities for chemotaxis and phagocytosis. In the future, improved understanding of these impairments in the lung could lead to specific interventions aimed at prevention of lung infection.

Keywords

HIV infections; Lung diseases; Macrophages; alveolar; T-Lymphocytes; B-Lymphocytes; Bronchoalveolar lavage

INTRODUCTION

Since the early era of widespread HIV infection, the variety of pulmonary infections encountered in this population demonstrated that HIV severely impairs lung host defenses [1]. While most investigations focus on HIV's effects on systemic immunity, an increasing body of literature examines pulmonary immune and inflammatory mechanisms during HIV infection [2]. As impairments in pulmonary host defense are better understood, strategies to correct these defects may be developed for treatment and prophylaxis of pulmonary infections [3].

The advent of highly active antiretroviral therapy (ART) has decreased the incidence of pulmonary infections in HIV-infected individuals dramatically, but this population remains at risk for infection. This review will focus on immune and inflammatory deficits in HIV-infected individuals who are naïve to HIV treatment; the effects of anti-retroviral therapy on pulmonary host defense are summarized comprehensively in the subsequent review.

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Conflict of interest: The author has nothing to disclose.

Several mechanisms have been postulated to explain susceptibility to pulmonary infections [4]. First, HIV can directly infect and kill cells directed against specific pathogens, leaving decreased numbers of cells available to participate in host defense. Second, HIV can impair the metabolic or secretory functions of effector cells. Third, HIV-infected cells may shift their repertoires from elaboration of immunostimulating to immunosuppressive products, such as a shift from Th1 to Th2 cytokine production. Fourth, HIV infection may interfere with the ability of circulating immune cells to migrate into the lungs and to clear pathogens from the alveolar spaces. Finally, co-infection by a second pathogen may contribute to impaired host defense. In all likelihood, all of the mechanisms contribute to some extent to deficits in defense.

Although much useful knowledge has been generated by examination of systemic immunity, caution must be exercised in interpreting studies of systemic host defense and applying them to the pulmonary compartment. Many investigations have extrapolated data obtained from peripheral blood cells to reach conclusions about lung immunity. For example, monocyte-derived macrophages (peripheral blood mononuclear cells that are cultured and develop phenotypic characteristics of macrophages) yield important results, but these data may not be directly applicable to alveolar or other tissue macrophages. It is worth noting that the alveolar milieu has significant influence on cellular function in the lung. Therefore, interpretation of in vitro studies may be somewhat limited. The accessibility of lung cells for study by bronchoalveolar lavage (BAL) provides an opportunity to study the direct effects of HIV on lung host defenses.

Considering the function of lung cells, and not just their numbers, is also of importance. Because of the difficulty in studying functional capabilities of lung cells, current clinical practice often depends upon measuring numbers of cells rather than their function. For example, the most recent US Public Health Service recommendations suggest that providers should discontinue primary and secondary *Pneumocystis jirovecii* prophylaxis for sustained increases in CD4+ T cell counts of greater than 200 cells/μl for at least 3 months [5]. No other tests are available clinically to predict risk of *Pneumocystis* pneumonia, but it is reasonable to assume that the functional abilities of these CD4+ T cells are at least as important as their numbers. In fact, HIV-infected individuals with weak peripheral blood lymphocyte proliferation to *Pneumocystis* antigens are at significantly higher risk of infection than individuals whose lymphocytes proliferate vigorously [6]. As another example, antibody responses to *Pneumocystis* major surface glycoprotein recombinant fragment C1 distinguish HIV-infected individuals with and without clinical pneumonia [7]. When followed prospectively, lack of immunoglobulin G (IgG) response to the *Pneumocystis* antigen KEX1 predicts individuals who develop *Pneumocystis* pneumonia versus other AIDS-defining illnesses [8]. Although these tests are not available for clinical use, they emphasize the need for further functional investigation.

HIV INFECTION OF LUNG CELLS

HIV Tropism

HIV strains differ in their tropism for lymphocytes or monocytes/macrophages (Figure 1) [9]. The CD4 molecule, present on lymphocytes and monocytes/macrophages, serves as the primary cellular receptor for HIV-1. In the lung, CD4 serves as the primary receptor for HIV on alveolar macrophages [10]. Coreceptors are also needed for HIV entry into cells, and these cellular coreceptors define the tropism of HIV strains. Lymphocyte-tropic (T-tropic, X4) strains interact with the chemokine receptor CXCR4 (fusin) to control entry into target cells. Infection can be blocked by the CXC chemokine SDF-1, which is a CXCR4 ligand. Conversely, monocyte-tropic (M-tropic) strains interact with the chemokine receptor CCR5 to control entry into target cells. HIV infection of human alveolar macrophages is

preferentially mediated by the CCR5 receptor, although alveolar macrophages also express CXCR4 [11]. Infection of macrophages can be blocked with the CC chemokines RANTES, MIP-1α and MIP-1β, which are CCR5 ligands.

As HIV infection progresses, T-tropic virus strains replace M-tropic virus strains, and this change is accompanied by more rapid immunologic decline. Minor chemokine receptors have now been shown to influence progression to AIDS, as well as susceptibility to specific pathogens. For example, variation in CCRL2, which is closely related to CCR5, has been shown to increase progression to AIDS and risk of *Pneumocystis* pneumonia [12].

HIV Replication

Cytokines and chemokines modulate HIV expression and replication, but conflicts in reported literature probably reflect differences in experimental design. In general, proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), inteleukin-6 (IL-6), and granulocyte monocyte-colony stimulating factor (GM-CSF) induce HIV transcription. Immunosuppressive cytokines (IL-4, IL-10) have dichotomous effects, and chemokines (MIP-1α, RANTES, SDF-1) generally decrease transcription [9].

In the lung, HIV replication occurs in pulmonary lymphocytes and in alveolar macrophages, and infection can be identified in cells sampled by BAL. Alveolar macrophages are likely to be the primary reservoir of HIV in the lung. HIV reverse transcriptase can be detected in alveolar macrophages obtained by lavage from AIDS patients, and alveolar macrophages can be infected with HIV *in vitro* [13]. Interestingly, alveolar macrophages from smokers are more susceptible to HIV infection in vitro than alveolar macrophages from nonsmokers [14]. CD8+ T cells in blood [15] and lung [16] can be infected with HIV, and are likely to serve as additional reservoirs.

Reports comparing the HIV burden of alveolar macrophages and peripheral blood monocytes are discrepant. The relative importance of in situ HIV replication in the lung, compared with influx of previously infected cells from bone marrow and blood, is unclear. The percentages of alveolar macrophages expressing HIV antigens have varied considerably among different laboratories [17]. Detection of HIV by polymerase chain reaction suggests that HIV infection of alveolar macrophages is common [18], and alveolar macrophages become infected with increasing frequency as HIV infection progresses [19]. Direct comparison of alveolar macrophages and peripheral blood monocytes suggests that viral burden is equivalent [20]. The frequency of HIV-specific CD4+ and CD8+ T cells has been compared in blood, gut (terminal ileum biopsies), and lung (BAL) in treatment naïve, HIV-infected individuals. Compared with the gut, the lung contained much higher frequencies of HIV-specific CD4+ and CD8+ T cells [21].

Pulmonary infections increase the rate of HIV replication in the lung [22]. For example, BAL from lung segments involved by *Mycobacterium tuberculosis* contains higher viral loads than uninvolved lung segments in the same individual, suggesting increased local replication of HIV [23]. One mechanism leading to increased HIV replication is the ability of *Mycobacterium tuberculosis* infection to increase surface expression of CCR5 by alveolar macrophages [24] (Figure 1). Similarly, *Mycobacterium avium* infection activates NF-κB in macrophages, leading to increased CCR5 and TNF expression and increased susceptibility to HIV infection [25]. Patients with *Pneumocystis* pneumonia have increased viral loads in BAL compared with asymptomatic, HIV-infected individuals [26]. One mechanism of increased HIV replication may be increased production of TNF and IL-6, accompanied by decreased production of IL-10 [27].

The effects of anti-retroviral therapy on HIV infection of lung cells, and on replication, are discussed in the following review.

ALTERATIONS IN LUNG LYMPHOCYTES

Cell numbers

Data from the early period of the HIV epidemic indicated that lymphocyte percentages or concentrations [28] are increased in BALs from HIV-infected individuals, compared with uninfected individuals. However, most of these data were obtained during bronchoscopies performed during episodes of clinical pulmonary infections. Examination of BAL lymphocyte subsets from AIDS patients shows decreases in CD4+ T cells and increases in CD8+ T cells. Therefore, CD4 to CD8 ratios in BAL specimens may be even lower than the ratios in peripheral blood [29]. During HIV infection, BALs from smokers demonstrate decreased CD4 to CD8 ratios compared with nonsmokers, suggesting that cigarette smoke further suppresses lung defense [30]. As in peripheral blood, most T cells in the lung bear αβ T cell receptors on their surfaces, but a minority expresses γδ T cell receptors. Numbers of γδ T cells are reported to be decreased [31] or increased in HIV-infected patients with opportunistic infections [32]. Recent work demonstrates that most pulmonary CD4+ T cells are effector memory cells with increased expression of activation markers, at least during episodes of respiratory infection [33].

CD4+ T cells

Decreased numbers of CD4+ T cells in BALs from HIV-infected individuals, undergoing bronchoscopy to diagnose pulmonary infections, predict mortality [34]. Low numbers of CD4+ T cells in BAL from asymptomatic, HIV-infected individuals are an independent predictor of mortality [35]. In addition to accelerated destruction of CD4+ T cells by HIV infection, underproduction of T cells also occurs. Underproduction can occur from infection-mediated death of progenitor cells and destruction of the hematopoietic stroma [36]. Furthermore, proliferative responses are impaired. Peripheral blood T cells from AIDS patients do not proliferate normally in response to mitogens [37]. Even in AIDS patients showing serologic evidence of prior infection with cytomegalovirus or herpes simplex virus, lymphocytes fail to proliferate normally in response to these viral antigens [38].

Failure to proliferate may be caused in part by impaired elaboration of IL-2. Peripheral blood T cells from AIDS patients have impaired IL-2 secretion in response to a variety of stimuli [39]. *In vitro,* recombinant IL-2 can restore some mitogenic responses of AIDS patients' blood lymphocytes[40]. Clinical trials of IL-2 for HIV infection demonstrate that IL-2 increases CD4+ T cell counts in recipients, without increasing HIV replication, particularly when given intermittently [41]. While this therapy initially appeared to be promising, IL-2 may increase risk of bacterial pneumonia when administered frequently [42].

A major defect in T cell host defense during HIV infection is impaired production interferon–γ (IFN–γ) in response to mitogens [37] or antigens [43]. The relative ability of peripheral lymphocytes to elaborate IFN–γ correlates with clinical status and CD4+ T cell count [44], and predicts progression to AIDS [45]. A clinical example of this impairment occurs in interpretation of IFN–γ release assays for tuberculosis. For example, the performance of commercial assays is negatively influenced in *Mycobacterium tuberculosis* culture-positive patients with HIV infection and low CD4 counts [46].

Experimental work suggests that progression from asymptomatic HIV infection to AIDS is accompanied by a switch from Th1-like lymphocyte responses to Th2-like lymphocyte responses [47]. Prevention of this switch in lymphocyte responses could prevent progression to AIDS. IL-12, a cytokine that favors Th1 development and inhibits Th2 development, has

been shown to restore cell-mediated immunity in lymphocytes obtained from HIV-infected individuals [48]. Few data exist on the function of lung CD4+ cells, but activation status differs in BAL and blood from HIV-infected and uninfected subjects, and responses to infectious antigens are impaired in BAL CD4+ T cells [49].

CD8+ T cells

CD8+ T cell alveolitis occurs during HIV infection. Some HIV-infected individuals may manifest pulmonary symptoms as a result of CD8+ T cell influx into the lung, clinically diagnosed as lymphoid interstitial pneumonitis [50]. The functional capabilities of these cells (and their intended targets) require further investigation.

The alveolitis is a result, in part, of CD8+ T cells directed against HIV antigens, as subpopulations of CD8+ T cells are cytotoxic for macrophages or B cell lines expressing HIV antigens [51]. The intensity of CD8+ alveolitis correlates with HIV viral load, and the poor prognosis associated with alveolitis may be a result of the elevated viral burden [52]. One mechanism of alveolitis is overproduction of IL-15, a cytokine with IL-2-like effects, by alveolar macrophages. Alveolar macrophages from HIV-infected individuals produce large quantities of IL-15, which enhances antigen presentation by alveolar macrophages and causes proliferation of lung CD8+ T cells [53].

CD8+ T cells obtained from the lungs of HIV-infected individuals do not lyse appropriate targets *in vitro* [54]. For example, CD8+ T cell-mediated cytotoxicity for influenza virus is decreased in HIV-infected individuals [55]. Late in the course of HIV infection, numbers of CD8+ T cells decline. Depletion of CD8+ T cells may be associated with the development of disseminated cytomegalovirus and *Mycobacterium avium* infections [56].

Phenotypically, CD8+ T cells from AIDS patients express activation markers [57], and increased percentages of activated cells predict progression of HIV-related disease [58]. Peripheral CD8+ T cells in HIV-infected individuals may be poor effectors because they lack required maturation signals [59]. Unlike the periphery, local concentrations of IL-2 and IFN–γ may be increased in the lung during HIV infection, due to activation of CD8+ T cells [60]. Functionally, however, CD8+ responses may be deficient because of lack of local CD4+ T cell help. CD4+ T cells are needed for priming, maintenance of memory, and functional activation in CD8+ T cells [61].

In theory, modulation of CD8+ T cell populations directed against HIV-infected cells could provide a novel method to augment host defense. Studies have attempted to exploit this finding by infusion of CD8+ T cells into HIV-infected individuals [62]. CD8+ T cells, expanded in vitro and infused into the donor, result in increased killing of HIV-infected target cells [63]. These infused CD8+ T cells accumulate in the lung, but their eventual benefit as a therapeutic modality is uncertain.

Natural killer (NK) cells

Increased numbers of NK cells in BAL have been observed in HIV-infected individuals, but with progressive HIV disease, they lose functional capabilities. As with CD8+ T cells, NK cells may be impaired during HIV infection because they are dependent on signals from CD4+ T cells for optimal function [64]. Biological response modifiers such as recombinant IL-2 restore lytic ability *in vitro* [65], and IFN–γ may augment NK cell activity in early stages of HIV infection [66]. The combination of IL-12 and IL-15 is effective in restoring expression of cytolytic molecules in NK cells from HIV-infected individuals [67].

B cells and immunoglobulins

The polyclonal activation of B cells that occurs systemically during HIV infection has been appreciated since the early era of the epidemic. Compared with uninfected individuals, measurement of immunoglobulins in BAL from AIDS patients with pulmonary symptoms shows increases in total amounts of IgG, IgM, and IgA [29]. Local immunoglobulin synthesis may occur in the lung, shown by increased numbers of IgG, IgM, and IgA secreting cells [68]. In contrast to results obtained during episodes of clinical infection, BAL from asymptomatic HIV-infected individuals contains decreased concentrations of IgG compared with uninfected controls [69].

While generalized gammopathy occurs, antibody responses to specific antigens are impaired in HIV-infected individuals. B cell abnormalities begin early in HIV infection, with failure to produce antibody in response to mitogen at the time of HIV seroconversion, before T cell function is affected [70]. B cells from AIDS patients show impaired proliferation in response to mitogens, and do not initiate normal antibody synthesis in response to newly encountered antigens [71]. Altered IgG concentrations in the lung may be a result of impaired ability of alveolar macrophages to induce IgG secretion from B cells, likely as a result of TGF–β secretion [69]. Functionally, BAL and serum IgG from HIV-infected individuals demonstrate decreased opsonic activity against *Streptococcus pneumoniae* than IgG from uninfected controls [72].

Recent studies examining the utility of antibodies in detection of *Pneumocystis* are presented in the Introduction.

ALTERATIONS IN ALVEOLAR MACROPHAGES

Cell numbers

Macrophage numbers in BALs from AIDS patients are probably normal [28], but percentages are decreased by influx of other cells. As discussed above, HIV infection of alveolar macrophages establishes these cells as reservoirs of infection without depletion of their numbers.

Chemotaxis, phagocytosis, and killing

Elimination of pathogens by alveolar macrophages depends upon an orderly sequence of chemotaxis, phagocytosis, and killing. Peripheral blood monocytes from AIDS patients are reported to be defective in chemotaxis to several chemoattractants [73], but other investigators find unimpaired chemotaxis [74]. Alveolar macrophages from asymptomatic, HIV-infected subjects demonstrate enhanced phagocytosis for *Staphylococcus aureus* [75]. In contrast, binding of *Pneumocystis* to macrophages depends upon a variety of mediators, including mannose receptors [76]. Alveolar macrophages from HIV-infected individuals demonstrate decreased binding and phagocytosis of *Pneumocystis in vitro*, and this defect correlates with mannose receptor downregulation [77]. Importantly, phagocytic activity is decreased in alveolar macrophages from HIV-infected individuals who smoke [78].

The magnitude of the respiratory burst of alveolar macrophages from AIDS patients *in vitro* is not different from uninfected controls, and IFN–γ enhances the response in cells from both groups equivalently [43]. Alveolar macrophages and monocyte-derived macrophages do not kill *Toxoplasma gondii* or *Chlamydia psittaci*, whether obtained from AIDS patients or from uninfected individuals [43]. When exposed *in vitro* to IFN–γ, however, alveolar macrophages obtained from AIDS patients increase their killing of these organisms in a manner equivalent to uninfected individuals' cells [43, 79]. These data support the theory that

suboptimal activation of alveolar macrophages *in vivo* is a result of impaired signaling from T cells.

Antigen presentation

During HIV infection, blood monocytes do not present antigens to T cells normally [80]. Alveolar macrophages are relatively poor antigen-presenting cells, in comparison to blood monocytes, but alveolar macrophages from HIV-infected patients demonstrate enhanced ability to present antigen [81]. To explain the pulmonary infectious complications that occur in HIV-infected individuals despite enhanced antigen presentation, the role of dendritic cells must be considered. Dendritic cells may perform the majority of antigen presentation in the lung. HIV infection of dendritic cells is cytopathic for these cells, and the numbers of dendritic cells are decreased in asymptomatic HIV-infected individuals and in AIDS patients [82]. Dendritic cells from HIV-infected individuals exhibit defective antigen presentation, and may facilitate HIV infection of T cells [83].

TNF elaboration

The data regarding TNF production during HIV infection are discrepant. Some AIDS patients are reported to have elevated serum levels of TNF [84]. When peripheral blood monocytes are examined, they are reported to have either high spontaneous release of TNF [85] or to have suboptimal release after appropriate stimulation [86]. Paradoxically, some investigators have found that HIV infection of monocytes or monocyte-derived macrophages *in vitro* does not induce TNF release [87].

Alveolar macrophages from asymptomatic, HIV-seropositive individuals demonstrate increased spontaneous TNF release, which correlates with extent of HIV expression [88]. BAL cells from smokers release less TNF than BAL cells from nonsmokers, suggesting that smoking and HIV interact to suppress macrophage function [30]. Recent work examining responses of alveolar macrophages to *Salmonella typhimurium* demonstrates no differences in phagocytosis or killing between cells from HIV-infected individuals and controls, but TNF elaboration is increased significantly in cells from HIV-infected individuals [89]. The literature does not reach consensus, however, and there are experimental examples of impaired TNF release as well. Some of this discrepancy may be explained by the stimuli used to provoke TNF elaboration. For example, when stimulated with lipopolysaccharide (LPS), alveolar macrophages show decreased TNF release via a toll-like receptor 4- (TLR4-) dependent mechanism [90]. Conversely, it has been demonstrated that TNF release from alveolar macrophages in response to HIV-1 single-stranded RNA is dependent upon TLR8 signaling [91].

TNF may have beneficial and detrimental effects during *Pneumocystis* pneumonia. *Pneumocystis* infection stimulates production of TNF by macrophages [92], and alveolar macrophages from HIV-infected individuals with *Pneumocystis* pneumonia elaborate increased amounts of TNF [93]. Expression of TNF by human alveolar macrophages during *Pneumocystis* pneumonia correlated with decreased arterial oxygenation, suggesting that TNF-induced inflammation is detrimental [94]. Part of the beneficial effect of corticosteroid therapy during *Pneumocystis* pneumonia may be to inhibit TNF elaboration [95].

ALTERATIONS IN LUNG NEUTROPHILS

Cell numbers

Several BAL series have reported increases in the concentrations [96] or in the percentages of neutrophils [28] obtained from AIDS patients, compared with uninfected controls. Although

AIDS patients may have increased numbers of neutrophils at the time of BAL, little is known about the host defense capabilities of these cells.

Chemotaxis and phagocytosis

Peripheral neutrophils from some AIDS patients with frequent localized infections, show decreased chemotaxis *in vitro* [74]. Neutrophils from HIV-infected individuals have decreased expression of CD88, the ligand for complement factor 5a, which could contribute to increased susceptibility to bacterial infections [97]. The phagocytic capacity of neutrophils during HIV infection is controversial. Individuals with early HIV infection demonstrate enhanced phagocytosis [98]. Phagocytosis of opsonized *Staphylococcus aureus* is decreased in some, but not all, AIDS patients' peripheral blood neutrophils [99]. The defect in phagocytosis can be corrected by *in vivo* administration of granulocyte colony stimulating factor [100]. Neutrophils from individuals with HIV infection express decreased IgG Fc-γ receptor 1 expression compared with uninfected volunteers [101].

Considering *Pneumocystis* pneumonia, increased numbers of neutrophils in BAL fluid from patients with HIV infection and *Pneumocystis* pneumonia correlates with impaired oxygenation [102], poor outcome [103], and increases in mechanical ventilation and mortality [104]. Neutrophils obtained from non-HIV infected donors are able to ingest and kill *Pneumocystis* organisms and generate superoxide when challenged by organisms [105]. Anti-*Pneumocystis* IgG and complement are required to opsonize the organism and increase the respiratory burst of neutrophils [106]. *In vivo*, BAL IL-8 concentrations during *Pneumocystis* pneumonia correlate with clinical severity and mortality [107].

Acknowledgments

Supported by: NHLBI U01 HL98961

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SYNOPSIS

The broad variety of pulmonary infections encountered in HIV-infected individuals demonstrates that the host defense network is impaired. An improved understanding of these events in the lung can lead to specific interventions aimed at restoration of deficient function. This review summarizes the pulmonary host defense deficits in HIV-infected individuals, focusing on lymphocytes, alveolar macrophages, and neutrophils.

KEY POINTS

- HIV infects lung lymphocytes and alveolar macrophages, and tropic strains infect lung lymphocytes and alveolar macrophages using distinct chemokine coreceptors.
- Lung CD4+ T cells are reduced in number, but demonstrate impaired proliferative and cytokine responses, despite expression of activation signals. Lung CD8+ T cells are increased in number and cause lymphocytic alveolitis, but do not lyse target cells appropriately.
- Specific antibody responses and opsonization of microorganisms are impaired.
- Alveolar macrophages demonstrate intact phagocytosis and killing, enhanced antigen presentation, and increased tumor necrosis factor elaboration. Despite these findings, pulmonary infections *in vivo* may result from impaired activation signaling from T cells.
- Further investigation is needed to clarify discrepant results regarding pulmonary neutrophils' capacities for chemotaxis and phagocytosis.

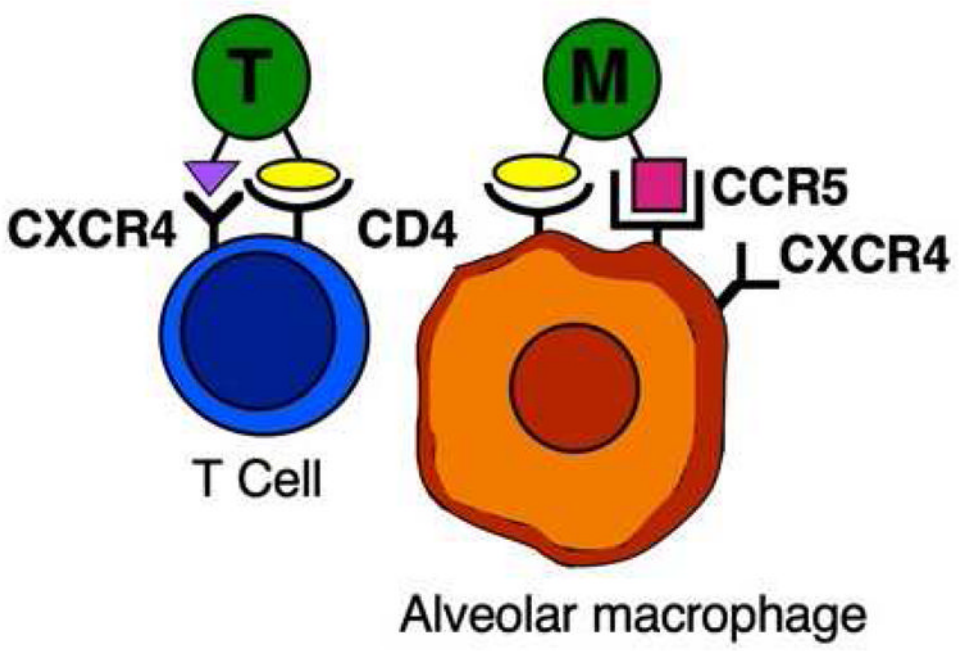

Figure 1.
HIV tropism for T cells and alveolar macrophages. T-tropic HIV strains interact with CD4 and CXCR4 (fusin) on T cells for entry. In contrast, M-tropic HIV strains interact with CD4 and CCR5 on alveolar macrophages, although CXCR4 is also present.