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Impact of Antiretroviral Therapy on Lung Immunology and Inflammation

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Synopsis

HIV infection causes profound changes in the lung compartment characterized by macrophage and lymphocyte activation, secretion of pro-inflammatory cytokines and chemokines, and accumulation of CD8 T cells in the alveolar space leading to a lymphocytic alveolitis. All of these changes impact pulmonary immunity, leading to a progressive loss in the ability to respond to pathogenic organisms, starting with a decreased ability to respond to common bacteria and mycobacteria and progressing to susceptibility to opportunistic pathogens. Since most of the changes seen in the lung can be attributed to a direct effect of HIV on immune cells, therapy to reduce the HIV burden should have significant beneficial effects. Indeed, ART rapidly reduces the viral burden in the lung, reduces the number of CD8 T cells in the alveolar space, and reduces the amount of pro-inflammatory cytokines and chemokines in BAL, thus returning the alveolar microenvironment towards normal. The clinical implications of these changes include the recognition of a new spectrum of HIV-related lung diseases in the ART era, including the immune reconstitution inflammatory syndrome (IRIS). Lastly, understanding the normal immunologic makeup of the lung and the kinetics of immune depletion in HIV infection, as well as immune restoration after starting ART, provide a conceptual framework for current recommendations on when to initiate antiretroviral therapy to minimize long term susceptibility to pulmonary complications in HIV-infected individuals.

Keywords

HIV; antiretroviral therapy (ART); pulmonary immune reconstitution

Introduction

In its 2010 report, the World Health Organization estimates that 34 million people worldwide are living with HIV ¹ Lung disease is a major source of morbidity and mortality

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in these patients and can be directly linked to progressive loss of pulmonary immunity. Typically, infections complications occur in an orderly fashion, with increased susceptibility to common pathogens occurring early in HIV infection and susceptibility to opportunistic pathogens appearing later after substantial losses of CD4+ T cells (**Figure 1**). The immunologic correlate of this progression is the loss of antigen-specific immune responses early in HIV infection, followed by the loss of alloantigen and finally mitogen responses. However, the development of combination antiretroviral therapy (ART) has greatly influenced the morbidity and mortality of HIV infection. This influence has generally been attributed to improvements in immunologic function, either by preventing the progressive loss of immunity in HIV infection or by actually promoting immune reconstitution. While the effects of ART are well described in the vascular compartment, their effects at the tissue level, including the lung, are just beginning to be understood. In this review, we will describe how ART has greatly improved the lung immunologic and inflammatory milieu in HIV-infected subjects. The consequences of this improvement will be discussed extensively by other authors contributing to this publication.

Effect of HIV on Pulmonary Immune Responses

The respiratory tract from the oropharynx to the alveoli serves as an interface between the host and the environment. Thus, pulmonary immune responses are felt to represent a form of mucosal immunity. Pulmonary immunity can be divided into innate and acquired responses. Most pathogens gaining access to the respiratory tract are phagocytized by alveolar macrophages (AM), the principal arm of innate immunity. Importantly, phagocytosis of most foreign material gaining access to the alveolar space does not result in an inflammatory response due to the general immunosuppressive properties of alveolar macrophages ². This results in a generalized paucity of lung inflammation under normal conditions, allowing gas exchange to occur unimpeded. Failure of innate host defenses leads to persistence of antigen in the respiratory tract and initiation of specific acquired immune responses. This process, which typically occurs in regional lung lymphoid tissue, results in the production of antigen specific effector T and B cells which traffic back to the site of initial challenge, in this case the alveolar space, under the control of local chemokine production in the lung ³. During the initial antigenic response, memory B and T cells are also created that allow the host to respond more rapidly upon re-exposure to the same antigen. Importantly, memory cells make up the predominant resident lymphocyte population in the normal lung ⁴.

HIV infection impacts all components of the pulmonary immune response and has been addressed in a prior chapter. Specifically, the alveolar environment in HIV infection is characterized by:

- Generalized alveolar macrophage activation ^{5,6}.
- Generalized CD4 T cell and CD8 T cell activation ^{7,8}.
- Preserved alveolar macrophage phagocytic function ^{6,9,10}.
- Increased concentrations of most macrophage and lymphocyte cytokines studied to date ¹¹.
- Mild decrease in absolute CD4 T cell counts and a large decrease in CD4:CD8 T cell ratio in the alveolar space ^{12,13}.
- Early preferential loss of antigen-specific memory CD4 T cells ¹⁴⁻¹⁶.
- Increase in the number and percentage of CD8+ cells resulting in a lymphocytic alveolitis ¹⁷.
- High immunoglobulin concentrations ^{18,19}, but poor opsonic activity ^{20,21}.

The end result of these changes is a generalized state of cellular activation and accumulation of immune cells and pro-inflammatory mediators in the alveolar space (**Figure 2A**). Since HIV is easily detectable in the lungs of HIV-infected individuals not on ART ²², it is reasonable to speculate that the virus itself can drive this response. In fact, very early studies recognized that HIV-infected individuals had an increase in lung CD8+ T cells consisting of HIV-specific cytotoxic T lymphocytes ¹⁷, a finding confirmed by later investigators ¹³. However, despite this apparent appropriate anti-HIV response and background “inflammatory” state, clearly defects in specific immunity are present as demonstrated by the increase in opportunistic infections. The challenge, and hope, of effective antiretroviral therapy is to return the alveolar compartment to a more “normal” state.

Effects of ART on Pulmonary Immunity

While there is extensive literature on effects of ART in controlling plasma viral load and improving immune responsiveness of peripheral blood mononuclear cells (PBMC), there is a paucity of data describing the effect of ART in tissue compartments, especially the lung. Much of the existing data on lung immunologic changes after starting ART pertain to IRIS which is a clinically recognized disease discussed later in this chapter. Less understood is the effect of ART on lung immune function and inflammation in individuals who are otherwise doing well after starting treatment. This type of analysis requires participation of HIV-infected individuals on ART in research protocols where studies such as bronchoscopy and chest imaging are performed in the absence of clinical symptoms. The existing literature on these types of studies is described here.

A. Effects on lung HIV viral load

If, as speculated above, the presence of HIV antigens in the lung drives the development of CD8+ lymphocytic alveolitis and induces generalized cellular activation in the pulmonary microenvironment, then control of the pulmonary viral load should return alveolar constituents towards a normal state. Thus, the first question to be addressed is whether ART can reduce the lung viral load. Cross-sectional studies had suggested that individuals on ART had decreased detection of HIV in BAL, compared with lavages obtained from individuals not on treatment ²². To address this question prospectively, a longitudinal study was conducted under the auspices of the Adult AIDS Clinical Trials Group in which blood and BAL were obtained from HIV-infected individuals starting ART and again after 4 weeks, and 24 weeks ²³.

At each time point, free virus (in plasma and acellular BAL fluid) as well as cellular HIV RNA and DNA (in PBMCs and alveolar cells) was measured. As expected, ART was associated with a significant decline in plasma viral load and a delayed, but significant decrease in the cellular viral load in peripheral blood cells. However, the decline in the lung viral load, both in the acellular compartment as well as in alveolar cells, was much more rapid and dramatic. At baseline, the ability to detect HIV in the lung and vascular compartments was similar. After four weeks of ART, the ability to detect HIV in BAL was significantly lower than the ability to detect HIV in plasma. After 6 months of therapy, the ability to detect HIV RNA in lung cells was significantly less than the ability to detect HIV RNA in PBMCs. Thus, the lung appears to respond to ART as well as, if not better, than the vascular compartment ²³.

B. Effects on BAL cell counts and activation.

If HIV is the antigen driving the CD8+ cytotoxic T cell response in untreated patients, then control of the antigenic load through ART therapy should theoretically decrease the lymphocytic alveolitis seen in these subjects. Indeed, ART was associated with a delayed,

but significant decrease in absolute number and percentage of alveolar lymphocytes. This decline was due exclusively to decreased numbers of CD8+ lymphocytes in the alveolar space ²³. As a result of the decline in CD8+ cells, the CD4:CD8 ratio in the lung returned towards normal much more rapidly than in the vascular compartment ²³.

When analyzed in more detail, ART was associated with increases in CD8+ naïve and central memory T cells and decreases in CD8+ effector memory T cells in the lung, suggesting the lung was repopulating its CD8+ lymphocyte pool from the peripheral circulation ²⁴. CD4+ lung lymphocytes were not changed, suggesting that longer therapy courses may be necessary to cause changes in this population. Indeed, in another longitudinal cohort, it was shown that after one month of ART there was a slight but significant increase in lung CD4+ T cells, and that this increase was significantly greater after one year of therapy ²⁵. Furthermore, the increase in CD4+ T cells at one month after starting therapy was associated with expression of the proliferation marker Ki67, suggesting the increase in the lung CD4+ T cell population was in part occurring through local expansion ²⁵. Given our understanding of how antigen specific T cells populate the lung under normal circumstances ³, it is likely that both recruitment of new T cells and local expansion of resident T cells contribute to the increase in lung CD4+ lymphocytes after starting ART.

In addition to causing changes in lung lymphocyte subsets, ART also significantly affects the activation status of alveolar cells. ART has been shown to reduce the activation state of peripheral blood lymphocytes ²⁶. Similarly, ART was associated with a significant decline in lung T cell expression of the activation markers CD38 and HLA-DR, most notably in the CD8+ T cell population ²⁴. Interestingly, this decline was limited to subjects who had demonstrable control of the lung HIV viral load (**Figure 3A**) ²⁴. Other work has shown that lung lymphocytes from HIV-infected individuals display polyfunctional responses as determined by intracellular cytokine production when stimulated with mitogens or HIV peptides ¹³. As part of a second longitudinal cohort study on lung immunity before and after starting ART, we analyzed lung T cell responses to mitogenic stimulation with the superantigen Staphylococcal Enterotoxin B (SEB). ART was associated with a significant decline in CD4+ and CD8+ T cell intracellular cytokine production (TNF- β , IFN- γ , IL-2) in response to SEB, again most notably in the CD8+ T cell population (**Figure 3B**).

C. Effects on lung cytokine and chemokine concentrations

It has long been appreciated that infection of macrophages with HIV leads to their activation and secretion of pro-inflammatory cytokines and chemokines ¹¹. If true, then treatment of HIV-infected subjects should result in a decline in lung inflammatory mediators. We have examined the change in BAL cytokine and chemokine levels in HIV-infected subjects starting ART. Antiretroviral therapy induces a significant decline in BAL concentrations of interferon (IFN)- γ and interleukin (IL)-6 ²⁷⁻²⁹. Even more striking, ART induces a dramatic decline in BAL concentrations of pro-inflammatory chemokines, especially the IFN- γ inducible ones ²⁷⁻²⁹, which may have significant implications for recruitment of inflammatory cells to the lung. Despite these decreases, both IFN- γ and the IFN- γ inducible chemokines (inducible protein [IP]-10, monokine induced by IFN- γ [MIG]) remained easily detectable in both HIV-infected subjects and normal volunteers. These chemokines contribute to the recruitment of memory cells to the lung ³⁰. Furthermore, there is a correlation between the number of lymphocytes in the alveolar space and the concentration of IP-10 and MIG, but not other chemokines such as IL-8 or RANTES. This correlation was weak in untreated subjects, but strengthened markedly with time on ART (**Figure 4**) ²⁷⁻²⁹.

D. Model of pulmonary immune reconstitution in HIV-infected individuals on ART

In summary, ART is associated with the following changes in the alveolar immunologic and inflammatory milieu:

- Significant decrease in the alveolar HIV viral load
- Significant decrease in alveolar CD8 T cells, returning the CD4:CD8 ratio towards normal.
- Mild increase in alveolar CD4 T cells resulting from recruitment of cells from the vascular space and *in situ* proliferation.
- Significant decrease in lymphocyte and macrophage activation.
- Significant decrease in inflammatory cytokines and chemokines, but persistence of detectable IFN- γ and the IFN- γ detectable chemokines.

Based on the above findings, we can propose the following model concerning HIV in the lung and the effect of ART on these changes (**Figure 2**). In untreated patients (**Figure 2A**), there is persistent HIV antigen in the lung leading to generalized cellular activation and augmented cytokine and chemokine secretion in response to pathogens and other particulate antigens, including those that would not induce an inflammatory response under normal circumstances. This response not only leads to further cellular activation, but also promotes influx of inflammatory cells to the alveolar space in a nonspecific manner, including B cells which are producing non-specific antibody. HIV-specific cytotoxic T lymphocytes (CTL) are also present in the alveolar space and are a rich source of IFN- γ , further leading to even higher concentrations. The large amount of non-specific cytokine and chemokine secretion lead to a relatively poor correlation between lung lymphocyte numbers and chemokine concentrations. With ART (**Figure 2B**), the pulmonary viral load decreases, reducing the antigenic load driving the nonspecific inflammatory pulmonary response. Less cellular activation is seen, and nonspecific cytokine secretion resolves. Persistent low level IFN- γ production from resident memory cells that inhabit the lung remains⁴, which in turn maintains the BAL concentration of IFN- γ inducible chemokines leading to the normal trafficking of these cells into the alveolar space rather than a massive influx of non-specific inflammatory cells. This change results in a much tighter relationship between chemokine concentrations in the lung and lung lymphocyte numbers. In summary, ART therapy is able to return the pulmonary environment towards normal, with normal cellular composition, reduced cellular activation, and normal inflammatory mediator concentrations.

Clinical implications of ART on pulmonary disease in HIV infection

While ART is clearly associated with a significant decrease in alveolar inflammation and return of the immunologic environment towards normal, it is not yet clear whether this translates into immunologic recovery. In this regard, there are three broad implications of the immunologic and inflammatory changes observed in HIV-infected subjects on ART which may impact patient care.

A. Change in the spectrum of lung disease in the ART era

One would posit the immunologic changes described should result in an enhanced ability to respond appropriately to infectious challenges. In the lung, ART has been associated decreased opportunistic infections³¹, decreased mycobacterial infections³², and decreased incidence of bacterial pneumonia³³. This improved immunologic milieu has led to the development of guidelines on when primary and secondary prophylaxis against opportunistic pathogens can be discontinued³⁴

With the decrease in pulmonary infections in HIV-infected subjects on ART, other pulmonary complications have become more frequently recognized, leading to a dramatic change in the spectrum of pulmonary disease in HIV infection. These complications include pulmonary hypertension³⁵, emphysema^{36,37}, and a variety of malignancies³⁸. HIV-related chronic obstructive pulmonary disease in particular is becoming more frequently recognized. A discussion of lung complications in the ART era is covered extensively by subsequent authors in this publication.

B. Immune reconstitution inflammatory syndrome

IRIS is perhaps the most intriguing complication in patients on ART because it is likely being mediated by the very immunologic improvements we seek when treating patients. IRIS is best defined as “a paradoxical deterioration in clinical status attributable to the recovery of the immune status during ART”³⁹. Currently it is estimated that between 10% and 25% of patients who begin ART will experience IRIS of varying intensity and severity⁴⁰.

IRIS can be categorized as either infectious or non-infectious. Infectious IRIS has been described for many different pathogens with a wide array of symptoms depending on the organ systems involved and pathogens identified^{38,41}. It occurs when subclinical or a partially treated infection persists prior to initiation of ART and provides the antigenic substrate necessary for an immunopathologic inflammatory response. Infectious IRIS can occur very rapidly (i.e. days after starting ART) and usually occurs within the first 3 months after initiating therapy⁴². Pulmonary IRIS is most often due to an ongoing or partially treated tuberculosis^{43,44} or atypical mycobacterial (ie: *Mycobacterium avium*) infection. The inflammatory response to these mycobacterial antigens can present as infiltrates or mediastinal lymphadenopathy and are responsible for about a third of IRIS cases reported⁴⁵. In the lung, early infectious IRIS is occurring at a time when antigen-specific memory cells are arriving the alveolar space. One can picture a scenario where antigen-specific memory cells against mycobacteria are released from lymph nodes after initiating ART. These cells traffic back to the lung where they encounter pre-existing mycobacterial antigens, leading to the inflammatory response characteristic of IRIS. Interestingly, when examining the cytokine milieu in subjects before and after starting ART, there is an initial slight increase in IFN- γ in BAL after four weeks of therapy before it starts to decline²⁷. One could speculate this increase represents antigen-specific memory cells encountering their targets as they traffic back to the lung.

Non-infectious IRIS is increasingly described and frequently occurs after 6 months of successful therapy. Late pulmonary IRIS may manifest as sarcoidosis (up to 3 years) after ART initiation⁴⁶. In the few studies that examined cell phenotype during sarcoid IRIS, a CD4+ alveolitis was seen; and in one study, a significant percentage of CD25+ cells were noted^{47,48}. Both HIV and sarcoidosis exhibit a state of peripheral lymphopenia, setting the stage for memory cell expansion by homeostatic proliferation⁴⁹. The role of the thymus and naïve cells in IRIS of any type is not defined.

The exact incidence of pulmonary IRIS is not known. To address this question, we recently completed a longitudinal study in which patients were studied with chest computed tomography before starting ART and at 4 weeks, 6 months, and 1 year after starting therapy. The incidence of asymptomatic radiographic abnormalities that could be consistent with IRIS (i.e. new or increasing infiltrates, new or increasing adenopathy) four weeks after starting ART was 10%⁵⁰. These changes were stable or had resolved by 6-12 months after starting therapy, always without intervention. Since the current clinical definition of IRIS requires “a paradoxical deterioration in clinical status”, one could argue that none of these subjects had IRIS as it is currently defined. However, these studies suggest there is

frequently some level of subclinical lung IRIS that occurs in HIV-infected individuals who start ART, and that in the absence of symptoms they can be safely observed without undergoing extensive evaluation.

Predictors of IRIS are for the most part limited to peripheral blood characteristics such as a low CD4+ cell nadir, CD4+ T cell increases after one month of therapy, rate of decrease in HIV RNA levels, CD8+ T cell numbers, and previous opportunistic infections^{43,51-53}. A recent investigation found that IRIS was associated with higher frequencies of blood effector memory cells, higher markers of blood CD4+ lymphocyte activation, and higher serum IFN- γ concentrations⁵⁴. There are very few studies of tissue predictors of IRIS, including in the lung. Preliminary data suggests that the influx of CCR5 memory cells into the alveolar space may predict radiographic IRIS⁵⁰. One of the most common settings of IRIS is seen in patients with tuberculosis, and studies have shown that the incidence of pulmonary IRIS is actually higher and more severe if antiretroviral therapy is started around the same time as tuberculosis treatment rather than waiting to start HARRT till after the initial intensive phase of tuberculosis treatment⁵⁵. Interestingly, the potential deleterious effect of early ART does not seem to be present in non-tuberculous opportunistic infections⁵⁶.

C. Timing of antiretroviral therapy

As discussed at the beginning of this paper, antigen specific responses are lost very early in HIV infection (**Figure 1**)¹⁴⁻¹⁶. Furthermore, memory T cells are more susceptible to HIV infection than other T cell subsets⁵⁷. Thus, one could argue that the loss of antigen specific memory T cells is the major contributor to many of the infectious diseases seen in HIV-infected individuals. This loss may be particularly important in mycobacterium tuberculosis infection, where there is clearly an increased incidence of disease relatively early in HIV infection despite a preserved ability of alveolar macrophages to ingest and kill the organism⁶.

There is evidence that 1) CD4 lymphopenia alone is not the sole mechanism of immune dysfunction, 2) A low CD4+ T cell nadir is a marker for suboptimal immunologic recovery after starting ART, and 3) increases in CD4+ T cells during ART do not predict successful restoration of immunologic responses to antigens⁵⁸⁻⁶⁰. When one considers that antigen specific CD4+ T cells are lost early in HIV subjects, the only way they can be repleted after treatment is if the few remaining cells undergo proliferative expansion or new antigen specific T cells are generated through stimulation of naïve T cells, an option that is less available as we grow older and the thymus undergoes involution. These speculations suggest that there is a CD4+ T cell threshold below which immune reconstitution after starting ART becomes suboptimal.

In support of this hypothesis, we previously demonstrated that while antigen-specific responses were decreased in HIV-infected individuals, enrichment for CD4+ T cells was able to “restore” the proliferative response to recall antigens in some individuals⁶¹. However, in HIV-infected individuals with low CD4+ T cell counts, proliferative responses to recall antigen remained poor even after CD4+ T cells were enriched to correct for low CD4+ counts. Furthermore, antigen specific responses were gradually lost in vitro after repeated stimulation by the same antigen in the presence of HIV, whereas in the absence of HIV the proliferative response just became more robust as a secondary immune response was generated. Taken together, these studies suggest T cell immune dysfunction cannot be solely ascribed to loss of CD4 T cell number and implicate deletion of antigen-specific T cells as an important mechanism of loss of T cell responses. Since lung CD4 T cells are almost all memory T cells, the timing of ART therapy may be especially important when considering optimal pulmonary immune reconstitution.

Conclusion

HIV infection causes profound changes in the lung compartment characterized by macrophage and lymphocyte activation, secretion of pro-inflammatory cytokines and chemokines, and accumulation of CD8 T cells in the alveolar space leading to a lymphocytic alveolitis. These changes impact pulmonary immunity, leading to a progressive loss in the ability to respond to pathogenic organisms, starting with a decreased ability to respond to common bacteria and mycobacteria and progressing to susceptibility to opportunistic pathogens once profound immunologic defects occur. Most of the changes seen in the lung can be attributed to a direct effect of HIV on immune cells. As such, therapy to reduce the HIV burden should have significant beneficial effects. Indeed, ART rapidly reduces the viral burden in the lung, reduces the number of CD8+ T cells in the alveolar space, and reduces the amount of pro-inflammatory cytokines and chemokines in BAL, thus returning the alveolar microenvironment towards normal. While these effects clearly have had the expected clinical benefit of reducing susceptibility to pulmonary infections, new complications have been discovered. The immune reconstitution inflammatory syndrome in particular is likely a direct effect of improved immunologic responsiveness, occurring when a recovering pulmonary immune system encounters residual pathogenic antigens still present in the lung. Consideration must also be given to the timing of initiation of ART, striving to control the lung viral load and promote immunologic recovery before irreversible immune defects have occurred. Thus, while the clinical outlook for HIV-infected individuals has greatly improved in the ART era, one still has to be vigilant for potential pulmonary complications.

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Key points

The lung alveolar compartment in HIV infection is characterized by the presence of HIV in alveolar fluid, accumulation of HIV-specific CD8 memory T cells, and a generalized increase in inflammatory cytokines and chemokines.

Highly active antiretroviral therapy (HAART) decreases the lung HIV viral load, reduces the number of CD8 T cells in the alveolar space, and decreases alveolar cytokine and chemokine levels, thereby returning the alveolar milieu towards a normal homeostatic baseline.

HAART decreases the infectious complications of HIV but may play a role in newly recognized pulmonary complications including pulmonary hypertension, emphysema, and immune reconstitution inflammatory syndromes (IRIS).

IRIS is a paradoxical deterioration in clinical status despite virological and immunological improvement during HAART. IRIS most often is due to an appropriate immune response against residual pathogens as host immunity improves on HAART.

New asymptomatic pulmonary abnormalities are commonly noted on CT scans in the first 4 weeks of HAART, but most often resolve spontaneously on radiographic followup.

Progression of Cellular Immunodeficiency in HIV Infection

1.

Progression of cellular immunodeficiency in HIV infection. There is early loss of antigen-specific immune responses and increased susceptibility to bacterial infections. Over time, there is progressive CD4+ T cell depletion, progressive loss of T cell responsiveness, and ultimately an increased risk of opportunistic infections.

2.

Effect of ART on the alveolar environment in HIV infection. A) In untreated patients, there is persistent HIV antigen in the lung leading to generalized cellular activation and augmented cytokine and chemokine secretion in response to pathogens and other particulate antigens. This response leads to further cellular activation and promotes influx of inflammatory cells to the alveolar space in a nonspecific manner, including B cells which are producing non-specific antibody. B) With ART, the pulmonary viral load decreases, reducing the antigenic load driving the nonspecific inflammatory pulmonary response. Less cellular activation is seen, and nonspecific cytokine secretion resolves. Low level IFN- γ and IFN- γ inducible chemokine production continues leading to the normal trafficking of memory cells into the alveolar space rather than a massive influx of non-specific inflammatory cells.

Decreased CD8 T Cell Activation After HAART

3.

ART decreases activation of alveolar CD8+ T cells. A) Alveolar T cells were stained with the lymphocyte activation markers CD38 and HLA-DR. After six months of ART, the percent of dual positive cells were significantly lower in HIV-infected individuals with a good virologic response in the lung. B) Alveolar T cells were stimulated with Staphylococcal Enterotoxin B. Intracellular IFN- γ , TNF- β , and IL-2 were measured. The percentage of CD8+ T cells expressing any of these cytokines decreased significantly with time on ART.

Correlation Between BAL IP-10 Concentrations and BAL Lymphocytes

4.

Correlation between BAL IP-10 concentrations and BAL lymphocytes. BAL was obtained from HIV-infected individuals prior to starting ART and again at 4 weeks, 6 months, and 1 year after starting therapy. The number of BAL lymphocytes was plotted against the BAL concentration of the T cell chemokine IP-10. With time on ART, there is a progressive increase in the correlation between these two variables.