The changing spectrum of pulmonary disease in patients with HIV infection on antiretroviral therapy

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\section*{Introduction}

The pulmonary manifestations of HIV disease in 2005 can be divided into two sets of presentations. For patients who do not have access to care, and who are not taking antiretroviral or chemoprophylactic drugs, opportunistic infections and neoplasms continue to occur. Pulmonary disease caused by \textit{Streptococcus pneumoniae}, \textit{Pneumocystis carinii} (now known as \textit{Pneumocystis jiroveci pneumonia}; PCP), \textit{Mycobacterium tuberculosis}, lymphoma, and Kaposi's sarcoma present much as they did in the 1980s. Management has improved in terms of new diagnostic, therapeutic, and preventive strategies, as reviewed in guidelines issued jointly by the National Institutes of Health, Centers for Disease Control and Prevention, and Infectious Disease Society of America (available online at http://www.aidsinfo.nih.gov).

Patients in the United States who are taking combination antiretroviral therapy (ART) and specific chemoprophylaxis demonstrate very different manifestations compared with patients in the 1980s who were receiving no ART or chemoprophylaxis. Some of these new manifestations are caused by the augmented immune response that occurs soon after ART is instituted, i.e. immune reconstitution syndromes. Other new manifestations are facilitated by prolonged patient survival at both high and low CD4 T-lymphocyte counts that result from ART. This prolonged survival has allowed other processes to occur after long periods of immunosuppression, e.g. neoplastic processes such as lymphoma and perhaps various solid tumors, and other entities such as pulmonary hypertension. This review will focus primarily on changing pulmonary manifestations in the populations in the United States and western Europe that have access to ART.

\section*{Current causes of pulmonary morbidity and mortality in the USA: epidemiological trends}

The causes of mortality and morbidity in patients with HIV have drastically changed over the past few years as a result of the use of ART. Before the use of potent antiretroviral drugs, pulmonary disorders caused an enormous percentage of the overall mortality from HIV. In one autopsy study from 1982 to 1988, all 75 patients had one or more pulmonary processes at the time of death. Opportunistic infections were responsible for 76\% of these pulmonary processes [1].

In a prospective multicenter trial investigating respiratory complications from 1988 to 1994, HIV-infected patients

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Fig. 1. Mortality and HAART use over time in HIV Outpatient Study (HOPS) cohort, fourth quarter, 2003 update.  
- Deaths per 100 person-years;  
- pulmonary deaths per 100 person-years;  
- percentage of patients on HAART.

had higher rates of both upper and lower respiratory infections than HIV-uninfected controls [2]. Respiratory infections were more common at all CD4 T-cell strata than for HIV-uninfected controls. Over 98% of respiratory complications were infectious [2]. The most frequent respiratory complications were acute bronchitis, bacterial pneumonia and PCP [2].

Since the introduction of ART, the overall mortality of HIV-infected patients, and the mortality caused by pulmonary processes, has dropped dramatically (Fig. 1). An analysis of the Center for Disease Control and Prevention’s HIV Outpatient Study (HOPS), in which over 7300 patients have been followed in over 180,000 visits since 1993, found reductions in overall pulmonary mortality and morbidity between 1994 and 2003 (Fig. 2, Fig. 3, Fig. 4).

Data from the HOPS study also demonstrate that pulmonary disease has declined as a cause of hospitalization for HIV-infected patients compared with other causes (Fig. 2). The increasing percentage of hospitalizations for cardiac etiologies also highlights the need to recognize the potential for chest complaints to represent atherosclerotic disease. A large, prospective study demonstrated that cardiovascular events increase with each year of ART [3].

The rates and causes of hospitalizations associated with pulmonary disease from the HOPS cohort have also

Fig. 2. Pulmonary, cardiovascular, and hepatic hospitalizations as percentage of total hospitalizations of HIV Outpatient Study (HOPS) participants, fourth quarter, 2003 update.  
- Total pulmonary diagnoses;  
- total cardiovascular diagnoses;  
- total hepatic diagnoses;  
- total renal diagnoses.

Fig. 3. Specific pulmonary processes as a percentage of total hospitalizations in the HIV Outpatient Study (HOPS) cohort, fourth quarter, 2003 update.  
- All pulmonary conditions;  
- Pneumocystis jiroveci pneumonia (PCP);  
- non-PCP pneumonia;  
- asthma, bronchitis, chronic obstructive pulmonary disease;  
- tuberculosis;  
- lung cancer.
Antiretroviral therapy as a cause of respiratory disease

There are four specific issues regarding ART that deserve special attention regarding respiratory manifestations. First, patients may present with unexplained tachypnea and dyspnea in the absence of pulmonary pathology. Clinicians must recognize that the tachypnea and dyspnea may be caused by nucleoside-induced lactic acidosis [9]. This lactic acidosis can be reversed by discontinuing the offending agents if the clinician recognizes the etiological link before end-organ damage is irreversible.

Second, enfuvirtide, or T-20, has been associated with an increased incidence of bacterial pneumonias [10]. The biological basis of the observation has not been explained. There is little guidance available as to the need to stop enfuvirtide if a bacterial pneumonia occurs in patients taking this drug.

Third, abacavir can produce a hypersensitivity reaction, with fever, rash, and myalgias. Patients can manifest dyspnea (13%), cough (27%), and pharyngitis (13%) [11]. In approximately 20% of patients, pulmonary infiltrates are seen [12]. If patients stop abacavir, and then restart it, distributive shock and death can occur [13–15]. Clinicians thus need to consider this syndrome in their differential diagnosis so that patients are not rechallenged with abacavir, leading to disastrous consequences.

Fourth, antiretroviral agents can produce intense immunological reactions (immune reconstitution syndromes) that can be clinically important, or life threatening.

![Antiretroviral therapy as a cause of respiratory disease](image-url)

Fig. 4. *Pneumocystis jiroveci* pneumonia deaths, hospitalizations, and total cases per 100 person-years, HIV Outpatient Study (HOPS) cohort, fourth quarter, 2003 update. □ Total *Pneumocystis jiroveci* pneumonia (PCP) cases; □ PCP hospitalizations; □ PCP deaths.

![Antiretroviral therapy as a cause of respiratory disease](image-url)

Fig. 5. Chest computed tomography of *Pneumocystis jiroveci* pneumonia at initial diagnosis and after 20 days of therapy.
Should antiretroviral therapy be initiated or continued when patients develop pulmonary disease?

When patients present with acute pulmonary disease, healthcare practitioners must decide how to manage ART. Initiating ART could be beneficial for patients with acute pulmonary disease: improving immunological and inflammatory responses could hasten recovery. However, there are several reasons to consider withholding ART. First, as described below, intense inflammatory responses can exacerbate lung dysfunction. Second, antiretroviral agents are all associated with toxicities. When patients with acute pulmonary processes develop rash, liver function abnormalities, or cytopenias, for example, clinicians often have difficulty determining whether the toxicity is caused by HIV, the acute pathogenic process, the specific therapy for the pulmonary process, or the newly prescribed ART.

Third, many antiretroviral agents cause drug interactions. The protease inhibitors and the non-nucleoside reverse transcriptase inhibitors have complex interactions with the cytochrome p-450 system, making serum concentrations of concurrent drugs unpredictable, and making their own pharmacokinetics difficult to anticipate. Withholding antiretroviral agents may thus be a safer option than initiating them in terms of avoiding undesirable drug–drug interactions. If such patients are administered ART and have unpredictable pharmacokinetics, irreversible HIV drug resistance may be promoted. Stopping drugs does not promote resistance, and may be a preferable strategy for patients who may not have predictable absorption or kinetics. Such a strategy also prevents drug toxicities and drug interactions from becoming problems superimposed on the issues being acutely managed.

In addition, most antiretroviral agents (except zidovudine and enfuvirtide) are only available as oral agents. Therefore, if patients are seriously ill, e.g. with respiratory failure, they may not be able to absorb oral drugs adequately. There are thus many reasons to adopt a conservative strategy and withhold ART from patients with acute respiratory processes, and to initiate or continue ART only if there is clear and well thought out benefit, and if the drug pharmacokinetics are carefully considered.

Immune reconstitution syndrome

When ART is initiated, patients with HIV infection may demonstrate new clinical manifestations as a result of enhanced immune response, i.e. immune reconstitution syndrome. Much of the current information about this syndrome is based on small case series. The true incidence of immune reconstitution syndrome is not yet clear, although it will presumably differ in various populations depending on the pathogens the patient has been exposed to and the degree of immune deficit when ART was initiated. It appears that the patients most likely to develop this syndrome are patients with low CD4 T-cell counts (e.g. < 50 cells/μl) and high viral loads (> 100 000 copies/μl) who have had a good virological response to ART. At least one retrospective review found that 31.7% of patients with known underlying opportunistic infections who received ART developed immune reconstitution syndrome [16].

The syndrome may manifest in the first few days after the initiation of ART when the viral load has fallen but before the CD4 T-cell count has increased as a result of an improvement in qualitative T-cell function as CD4 T cells become less activated. This improved qualitative T-cell function leads to a more robust response against organisms or antigens [17].

The range and severity of manifestations is wide, as indicated in Table 1. Some patients have clinically apparent but trivial syndromes, such as the appearance of an asymptomatic pulmonary nodule or mediastinal lymph node, whereas other patients develop extensive organ dysfunction (Fig. 6). Many of the listed syndromes are clearly related to recognized microbial pathogens. However, some are related to tumors or to syndromes of uncertain cause. As there is not a clear case definition for immune reconstitution syndrome, it is difficult to determine if all of the listed syndromes are true examples of immune reconstitution syndrome, or if some are unrelated coincidental occurrences.

There is no consensus or specific laboratory marker regarding the optimal method for diagnosing these immune reconstitution syndromes. When patients starting ART develop new manifestations, they merit a methodical evaluation to determine whether the syndrome represents a new, active, infectious process, a new neoplastic process, or some other disease entity in need of specific intervention. The distinction between a new opportunistic infection and an immune reconstitution syndrome can be subtle. The histology of immune and inflammatory response does not distinguish the acute opportunistic infections from immune reconstitution syndromes: responses to either may be composed of lymphocytes and monocytes with or without granulomas and necrosis. Negative cultures can be useful, although there is inconsistency in the published literature, emphasizing the lack of consistency in defining this syndrome.

In the absence of data to direct the optimal management approach, clinicians are left to make a clinical judgement about when to use anti-infectious therapy, how long to
continue the therapy, and when to use non-steroidal anti-inflammatory agents or corticosteroids. This decision should be influenced by the severity of the syndrome, the robustness of the virological and CD4 T-cell response to ART, and the specific pathogen identified.

**Pneumocystis jiroveci pneumonia**

Immune reconstitution syndromes can occur in patients with active infectious processes such as PCP [18,19]. In one small case series, three patients presented with PCP (median CD4 T-lymphocyte count of 26 cells/µl), improved on conventional anti-PCP therapy, and started ART therapy within 15–18 days of PCP diagnosis [18]. All three developed acute respiratory failure within a median of 5 days (range 3–17 days) [18]. Histopathological findings of alveolar inflammatory infiltrate with a few persistent *Pneumocystis* cysts were thought to be consistent with an immune reconstitution syndrome [19].

How often this occurs when ART is initiated soon after PCP is unknown, but there are enough such cases to make concern over an immune reconstitution syndrome one reason to consider delaying ART for many weeks after PCP therapy. The optimal time to wait has not been defined, i.e. enough time to diminish the likelihood that an immune reconstitution syndrome will occur, but not an excessive amount of time such that other opportunistic processes are likely to occur.

**Mycobacterium tuberculosis**

Immune reconstitution syndrome is especially common in patients with untreated tuberculosis, or patients with tuberculosis who have initiated antituberculosis therapy in the past few weeks or months [20]. In one prospective study of patients with active tuberculosis treated with antituberculosis therapy [21], 36% of HIV-infected patients treated with ART versus 7% of HIV-infected patients not taking ART developed clinical exacerbations consistent with immune reconstitution syndromes after the initiation of therapy. These syndromes occurred 2–40 days after the initiation of ART. In another retrospective study [22], transient radiographic worsening occurred during the first 1–5 weeks of ART in 45% of 31 HIV-positive patients who had received at least two initial weeks of antituberculosis therapy. A similar series from Spain reported transient exacerbations in 35% of 17 patients [23]. These exacerbations appeared to be particularly likely in those patients who had a substantial fall in HIV viral load (2.4 log drop in patients with immune reconstitution syndrome versus 0.4 log drop in HIV-RNA copies/µl in those without an exacerbation) and a larger median increase in CD4 T-lymphocyte counts.
(71 cells/μL for those with a clinical exacerbation versus 51 cells/μL in those without an apparent immune reconstitution syndrome).

The timing of ART initiation also affects the incidence of immune reconstitution reactions. In a retrospective study [24], seven out of 13 subjects starting ART less than 6 weeks after starting tuberculosis therapy developed immunological reactions, whereas only one out of 15 subjects developed such reactions when starting after a delay of more than 6 weeks.

For physicians treating patient populations in which tuberculosis is common, the potential for immune reconstitution syndromes poses a dilemma. It would clearly be desirable to start ART promptly to enhance the response to antituberculosis therapy and to prevent other opportunistic infections from occurring. Until larger studies are completed, there are no data-driven recommendations regarding when to start antituberculosis treatment in the absence of active tuberculosis. However, one reasonable approach would be if a patient is simultaneously diagnosed with tuberculosis and HIV, the antituberculosis therapy should be started first. Most clinicians delay the initiation of ART for 4–8 weeks after the start of antituberculosis therapy [25]. Patients with lower CD4 T-lymphocyte counts should be considered for early therapy with ART. Patients with higher CD4 T-lymphocyte counts should delay therapy; those with CD4 T-lymphocyte counts greater than 200 cells/μL can probably defer until antituberculosis therapy is completed [25,26].

Immune reconstitution syndrome and paradoxical reactions can also be associated with other mycobacterial infections, such as focal pulmonary Mycobacterium avium complex (MAC) infection [27] (Fig. 7). Immune reconstitution syndromes may occur in patients with latent MAC, i.e., those who have never had a clinically apparent syndrome as a result of MAC. In contrast, as noted above, it would appear that immune reconstitution syndromes caused by Mycobacterium tuberculosis occur predominantly in those who have recently had active infection.

**Neoplastic complications of HIV disease**

In the United States and western Europe, Kaposi’s sarcoma has been a hallmark cancer for HIV-infected individuals; however, the incidence has markedly decreased with the use of ART [28]. In the Swiss HIV Cohort study, non-users of ART had a much higher standardized incidence ratio (SIR) of Kaposi’s sarcoma than users of ART [SIR 239, 95% confidence interval (CI) 211–270 versus SIR 25.3, 95% CI 10.8–50.1] [29]. The EuroSIDA study, with over 9000 participants, demonstrated similar findings; the incidence of Kaposi’s sarcoma among patients receiving ART decreased with the increasing time since the initiation of ART [28]. Overall, there was an estimated 39% reduction (95% CI 35–43%, P < 0.0001) in the incidence of Kaposi’s sarcoma between 1994 and 2003 in the EuroSIDA population [28].

In patients with pulmonary Kaposi’s sarcoma, the mean CD4 T-lymphocyte count is 19 cells/μL, although the range was 0–520 cells/μL [30]. In one series, only 5% of patients with Kaposi’s sarcoma had a CD4 T-lymphocyte count greater than 200 cells/μL, emphasizing that most cases occur at low CD4 T-cell counts [30].

Patients with pulmonary Kaposi’s sarcoma generally present with cough, shortness of breath, and chest pain. Fever also occurs, probably because of blood in the air spaces. In a series of symptomatic pulmonary Kaposi’s sarcoma, all 30 patients (100%) presented with dyspnea, and 24 (80%) with cough. Chest pain was noted in 14 patients (47%), hemoptysis in nine patients (30%), and fever in four patients (13%) [31].

Most patients have mucocutaneous involvement. In one series, only 15.5% of 142 patients had isolated lung involvement without mucocutaneous involvement [30].

Chest X-rays typically show patchy infiltrates; unilateral effusions are sometimes present. In one case series, 24 patients (80%) had pleural effusions, 27 (90%) had a diffuse interstitial pattern and 11 (37%) had nodules on the chest radiograph [31]. Chest computed tomography scans usually demonstrate nodules or consolidation in a peribronchovascular distribution [32] (Fig. 8).

A diagnosis of Kaposi’s sarcoma is often suspected because of the cutaneous or endobronchial lesions. The red or
purple nodules are quite characteristic and are not easily mistaken for other pathological manifestations [31–33]. A bloody pleural effusion is also suggestive [33]. Cytology is not useful for establishing the diagnosis. Transbronchial biopsy is also not helpful because the crush artifact can easily be confused with the spindle cells of Kaposi’s sarcoma. A definitive diagnosis usually depends on video-assisted biopsy or open-lung biopsy.

For patients with Kaposi’s sarcoma, the median survival in the pre–ART era was approximately 6 months, although patients often died of processes other than Kaposi’s sarcoma [31]. With ART and combination chemotherapy regimens, such as those with liposomal doxorubicin, bleomycin, or vincristine, the response rates have improved [34–36]. ART therapy is also associated with a markedly reduced risk of death (hazard ratio 0.09) in HIV-positive patients with pulmonary Kaposi’s sarcoma receiving chemotherapy [37]. There is thus a reason for cautious optimism in offering chemotherapy to patients with clinically important Kaposi’s sarcoma using current treatment modalities.

Immune reconstitution syndromes have been reported in association with Kaposi’s sarcoma treated with ART [38,39].

**Non-Hodgkin’s lymphoma**

Non-Hodgkin’s lymphoma (NHL) has been the second most common HIV-associated malignancy. Most studies indicate a decrease in the incidence of systemic NHL in the past few years since the introduction of ART [29,40–44]. In the Swiss HIV Cohort study, the risk of developing NHL, compared with the general population, was much higher for non–ART users (SIR 99.3, 95% CI 85.8–114) compared with patients on ART (SIR 24.2, 95% CI 15.0–37.1) [29]. In one retrospective study [40], the rate of NHL decreased from 61.8 per 1000 reported AIDS cases in 1988 to 35.9 per 1000 AIDS cases in 2000. Another study from Australia [42], found a decrease in the incidence of NHL from 1994–1996 to 1996–1998 from 7.5 to 4.3 cases per 1000 person-years. Therefore, for systemic NHL, the incidence appears to be decreasing. However, given the longer duration of patient survival, the lifetime risk of systemic lymphoma may not be declining as impressively.

NHL occurs in patients at all CD4 T-lymphocyte counts, although the relative risk of NHL is higher at lower CD4 T-lymphocyte counts [45]. The median CD4 T-lymphocyte count has been noted to be lower in patients with pulmonary involvement than in those without such involvement. In a small series of patients with pulmonary involvement [46], the mean CD4 T-lymphocyte count was 67 cells/µl.

Most patients with pulmonary NHL present with cough (71%) and dyspnea (63%) [46]. The chest radiographs usually demonstrate isolated or multiple peripheral nodules [46,47]. In a case series of 38 patients [46], pleural effusions occurred in 68% and thoracic lymphadenopathy in 54% of the cases. Infiltrates and masses with cavitations have also been reported [47]. There are no major differences in the diagnostic approach to suspected NHL in patients with HIV compared with patients without HIV: a diagnosis of non-Hodgkin’s disease may be made with a pleural cytological study, transbronchial biopsy, percutaneous transthoracic needle biopsy or open-lung biopsy, whereas bronchial brushings are not usually helpful [46–48].

The most important change in the ART era has been the recognition of the importance of aggressive chemotherapy treatment for HIV-positive patients. During the pre–ART era, patients were often treated with a conservative low-dose chemotherapy regimen. More recently, treatment for HIV-infected patients has approximated regimens for high-grade NHL of HIV-non-infected populations [49–51].

As chemotherapy has become more successful, other aggressive modalities of therapy for lymphoma are being assessed. Peripheral blood stem cell transplantation is being investigated in some centers [52–54].

There has been some debate as to whether to continue ART during chemotherapy. In one study of 39 patients [55], holding antiretroviral therapy while patients underwent chemotherapy with EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) was associated with high response rates, with complete remission in 74% of patients, but tolerable toxicities. The median CD4 T-lymphocyte cell count returned to the baseline value in the 30 patients followed within 12 months after therapy [56]. Another trial demonstrated similar response rates with simultaneous ART and CHOP.
Primary effusion lymphoma

Primary effusion cell lymphoma is a human herpes virus 8 (HHV-8)-associated B-cell lymphoma, which occurs in body cavities. Pleural effusions are the most common manifestations; peritoneal and pericardial effusions also occur [59,60] (Fig. 9). At the time of presentation, patients’ CD4 T-lymphocyte cell counts are usually less than 150 cells/μl, but can range from 2 to 291 cells/μl [59,60]. Primary effusion lymphoma is diagnosed by cytology or biopsy [61]. The detection of HHV-8 by in-situ hybridization or in-situ polymerase chain reaction provides supportive evidence for this diagnosis [61].

Primary effusion lymphoma has a very poor prognosis. It is not yet clear what therapy is most likely to be effective. In one series of 11 patients, two of the three patients with complete remission were treated with both chemotherapy and ART, and one patient treated with ART alone also had a complete response [59]. In that series, the five patients treated before ART had a much poorer survival rate (survival time range 0.5–4.5 months) compared with those treated after ART therapy (survival time range 1–35 months) [59]. Another series of 28 patients with primary effusion cell lymphoma [60] found that the absence of ART before primary effusion cell lymphoma diagnosis was an independent predictor of shorter survival by multivariate analysis (hazard ratio 3.26, 95% CI 1.14–9.34). Several different chemotherapy regimens have been attempted [60]. Rituximab has also been used [62].

Multicentric Castleman’s disease

Multicentric Castleman’s disease (MCD) is an HHV-8-associated lymphoproliferative disorder associated with IL-6 dysregulation [63,64]. MCD presents at any CD4 T-lymphocyte count: patients have presented with counts ranging from 56 to 1086 cells/μl [65]. Patients can present with fever and cough and interstitial infiltrates, often with polyadenopathy, splenomegaly, hepatomegaly, and weight loss [63]. Pulmonary imaging may demonstrate diffuse mediastinal lymphadenopathy, as well as pleural effusions and bronchovascular nodularity [66]. Diagnosis can be difficult to establish, but is usually established by lymph node or bone marrow biopsy in conjunction with HHV-8 testing [63–66].

MCD has been treated with a variety of regimens, including various combinations of zidovudine, interferon, ganciclovir,cidofovir, and thalidomide [67–70]. ART appears to improve survival. In a case series of seven patients, the mean survival was 48 months, compared with a historical pre-ART median survival of 14 months [63,64]. Anti-CD20 monoclonal antibody has also been successful in inducing prolonged remission, possibly by decreasing the IL-6 and TNF-α levels [71–74].

Patients with MCD often also develop NHL as well as other HHV-8-related diseases [75]. In one prospective study of 60 patients with HIV and MCD [75], 14 patients developed NHL 0–76 months after the diagnosis of MCD, with a median follow-up of 20 months. MCD is also associated with a high rate of concurrent Kaposi’s sarcoma [64,66]. Therefore, much needs to be learned about the ultimate prognosis of patients with this disorder, and the optimal approach to therapy.

Bronchogenic carcinoma

Patients with HIV infection may have an increased risk of bronchogenic carcinoma [5–8,76–87]. When a
population of 7893 HIV-infected patients in Chicago was compared with general population databases, the adjusted relative risk of lung cancer for HIV-infected patients was 3.63 for the years 1992–2002 [76]. Another study of 26,861 HIV-infected patients found an observed/expected ratio of 6.5 for primary lung cancer for the years 1990–1995 [8]. What factors other than HIV might have contributed to this increased risk, such as an increased use of tobacco, have not been carefully assessed [76].

Bronchogenic carcinoma has occurred at CD4 T-lymphocyte counts ranging from 3 to 835 cells/µl [77,78]. There is thus not a definite association between CD4 T-lymphocyte counts and occurrence. It is also not clear what effect ART has on the epidemiology of lung cancer. In one prospective database comparing HIV-infected patients with the general population in southeast England [79], there was a dramatic increase in the incidence of HIV-related lung cancer from 0.8 per 10,000 patient years (95% CI 0.2–3.2) in the pre-ART period to 6.7 per 10,000 patient years (95% CI 3.1–13.9) in the post-ART period (post-1996). The relative risk of HIV-infected patients in the post-ART period was 8.93 (95% CI 4.92–19.98) compared with the control population [79]. Another retrospective study comparing HIV-infected patients in France with the observed rate in the French general population [80], found a twofold increase in the risk of lung cancer between the pre-ART period (1992–1995) and the ART era (1996–1999) (SIR 2.05, 95% CI 1.62–2.65). Strikingly, in the same study, the risk for women increased from 1992–1995 (SIR 1.08, 95% CI 0.01–5.98) to 1996–1999 (SIR 6.59, 95% CI 3.40–11.52) [80]. However, a similar study from the United States [44] found an increased risk of lung cancer compared with the general control population in HIV-infected women both pre-ART (SIR 6.8, 95% CI 0.8–18.9 from 1994 to 1995) and post-ART (SIR 6.2, 95% CI 2.3–12.1 from 1997 to 2001).

A large percentage of HIV-infected patients with bronchogenic cancer smoke tobacco, similar to the non-infected population with lung cancer [78,81–83]. Some experts have speculated that smoking accounts for the risk of lung cancer [76]. Adenocarcinoma has been the most common histology accounting for 36–80% of cases [8,77,78,84–86]. The mean or median age at diagnosis of bronchogenic carcinoma for HIV-positive patients is much younger (38–49 years) than expected in HIV-negative patients [77,86]. Survival has been noted to be significantly shorter for HIV-infected patients compared with HIV-uninfected individuals with similar stages of lung cancer [77,85,87].

No literature has suggested that therapy for HIV-infected patients with bronchogenic carcinoma should differ from that for non-HIV-infected individuals. It would seem logical to treat patients with ART as well as chemotherapy, possibly holding ART during the period of active chemotherapy administration, as with lymphoma above.

In a large retrospective study from New York City [88], the 24-month survival in patients with lung cancer and HIV did not significantly change from the time periods 1980–1989 (5%) to 1996–2000 (10%) (death hazard 2.2 and 2.5, respectively). In comparison, the 24-month survival for a non-HIV-infected population was much higher at 31% [88].

**Pulmonary hypertension**

There is an increasing suspicion that pulmonary hypertension is overrepresented in patients with HIV infection. It has been difficult to dissect out other risk factors such as methamphetamine abuse and chronic obstructive pulmonary disease. Therefore, until large prospective studies with appropriate controls are completed, the role of HIV in causing or predisposing to pulmonary hypertension is unclear.

The incidence of pulmonary hypertension in HIV-infected patients is estimated to be 0.5%, compared with 0.02% in the general population [89–91]. Pulmonary hypertension occurs at all CD4 T-lymphocyte counts [89–91]. In 82% of 131 cases reviewed from the literature, HIV was the sole identified cause of the pulmonary hypertensive occlusive disease [92].

It is not clear what the clinical importance of pulmonary hypertension is in this setting. There is yet no evidence that patients are dying as a result of pulmonary hypertension, but what will happen as patients live longer will have to be determined [91–95]. The pathological findings are similar to primary pulmonary hypertension, and are generallyplexogenic pulmonary arteriopathy and occasionally thrombotic pulmonary arteriopathy and pulmonary veno-occlusive disease [89,94,96,97].

In one small prospective study of long-term echocardiographic follow-up in 13 patients [91], the right ventricular systolic pressure decreased by 3.2 mmHg in six patients treated with either zidovudine or didanosine, and increased by 19 mmHg in the seven untreated patients (P = 0.026). A retrospective analysis of 47 patients found a decrease in right ventricular systolic pressure of 21 mmHg in 14 patients receiving HAART compared with an increase of 25 mmHg in nine patients not receiving ART [98]. In that analysis, the use of HAART also significantly decreased mortality by multivariable Cox regression analysis (hazard ratio 0.075, 95% CI 0.02–0.28, P < 0.001) [98]. Another series of 82 patients with HIV and primary pulmonary hypertension [99] also found that combination antiretroviral therapy,
including the use of a protease inhibitor, was associated with improved survival on univariate analysis; however, this was not validated in multivariate analysis or in subgroup populations with concurrent epoprostenol. Another retrospective study [100] found a higher risk of pulmonary artery hypertension in patients treated with ART (including a protease inhibitor) than in patients treated with ART (with only one or two nucleoside reverse transcriptase inhibitors; 2.0 versus 0.7%, \(P = 0.048\)). Whether HIV is directly linked to pulmonary artery hypertension, and whether effective and durable ART therapy will reduce the morbidity potentially caused by this condition remains to be determined.

A prominent report linked pulmonary hypertension in HIV-uninfected patients to HHV-8 [101]. This was particularly intriguing because HHV-8 is sexually transmitted, and causes neoplastic disease in HIV-infected patients (Kaposi’s sarcoma, multicentric Castleman’s syndrome, and primary effusion cell lymphoma). This observation needs to be confirmed before a link between HHV-8 and pulmonary hypertension is definitively established [102].

Conclusion

Over the next decade in the United States and western Europe, as more patients have access to ART and chemoprophylaxis, the pulmonary manifestations of HIV will continue to evolve. How much impact pulmonary hypertension, neoplastic processes such as lymphoma and bronchogenic carcinoma, and atherosclerosis will have on morbidity and mortality remains to be defined.

An unfortunate reality of the healthcare system in the United States is that there will continue to be large numbers of individuals who do not know they have HIV, or who cannot access care. Healthcare providers will thus continue to play an important role in managing pulmonary complications in patients receiving ART and in those who present without previous therapeutic intervention.

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