Imaging of thoracic pathology in patients with AIDS

C Lacombe (1), M Lewin (1), L Monnier-Cholley (1), J Pacanowski (2), JL Poirot (3), L Arrivé (1) and JM Tubiana (1)

Abstract

The imaging features of infectious and non-infectious pathologies in HIV patients with AIDS (less than 200 CD4/mm$^3$) are illustrated. Opportunistic infections, tumors and vascular pathologies have variable appearances based on the degree of immunosuppression and patient compliance with opportunistic infection prophylaxis. Because of advances in retroviral treatments and wider use of anti-infectious prophylaxis, thoracic pathologies in AIDS patients are less frequent but must nonetheless be recognized, and diagnosis should be suggested in patients with unknown serological status.

Key words: AIDS. Lung. Infection. Lung. Malignancy.

The appearance of antiretroviral therapies in 1996 has allowed many HIV-infected patients to rebuild their immune system, thus prolonging their life expectancy. A substantial reduction in death, opportunistic infections, and Kaposi sarcoma in responder patients has therefore been observed, with in parallel the emergence of noninfectious complications contributing significantly to these patients’ morbidity and mortality (1).

In addition, it should be remembered that there remain a large number of HIV-infected patients who are not treated with antiretroviral multitherapy, not only in developing countries but also in France, in certain underprivileged milieus or in cases where the patient is in denial of the disease. Acquired resistance to antiretrovirals also exists in a significant number of patients. The objective of this iconographic review was therefore to present the range of thoracic, infectious, and noninfectious diseases encountered in HIV-infected patients in our department between 2003 and 2006, whether or not they were on antiretroviral treatment.

Progression in the frequency of pulmonary complications in HIV patients

The improvement in immune functions in patients taking powerful antiretroviral multiple therapy has reduced the prevalence of opportunistic infections in responder patents by approximately 80% (2).

It is recommended to start antiretroviral treatment beyond a CD4 level varying from 200 to 350/mm$^3$ depending on the case; therefore, the complications occurring at modest immunodepression levels (200-500 CD4/mm$^3$) such as tuberculosis and bacterial lung infections are only moderately reduced (2).

Pneumocystosis remains a current problem, since in 2001 in France it was the most frequent inaugural disease of AIDS (20.4%), occurring above all in patients who had not been screened or were not treated (2).

Bacterial lung disease (fig. 1, 2)

Given their possible occurrence at modest degrees of immunosuppression, the incidence of acute community-acquired lung infections has dropped by only half since the antiretroviral multiple therapies have come onto the scene, decreasing from 316 to 167 cases for 10,000 person-years between 1996 and 2001 (2). These are the most frequent lung infections in the HIV subject, before tuberculosis and pneumocystosis.

The bacteria most frequently to blame are Streptococcus pneumoniae, followed by Haemophilus influenzae, Staphylococcus aureus, and Pseudomonas aeruginosa. Streptococcus pneumoniae can be accompanied by an initial shock. S. aureus lung infections preferentially infect subjects with intravenous drug addiction.

Other rarer bacteria can occasionally be found, responsible for opportunistic infections: Klebsiella, Rhodococcus equi, Nocardia asteroides, Pasteurella multocida, Corynebacterium, Legionella pneumophila, etc.

The radiographic signs of pulmonary disease severe in HIV subjects are the same as in non-HIV subjects, i.e., single or multiple alveolar areas of condensation that are confluent, whether systematized or not, with an air bronchogram. They can be complicated with pleural involvement, showing as pleural pneumonia. Their radiological and CT signs are nonspecific, and the bacterium responsible generally cannot be identified.
Current guidelines recommend antipneumococcal vaccination when a patient presenting more than 200 CD4/mm$^3$ is discovered to be HIV-positive; one can therefore assume that pneumococcal infections will continue to decline.

**Tuberculosis (fig. 3, 4)**

Tuberculosis can occur at a moderate stage of immunodepression (CD4 < 300/mm$^3$); therefore its incidence has only moderately decreased since the advent of antiretroviral treatments. The presentation is slightly different than that observed in the HIV-negative patient, particularly if the CD4/mm$^3$ level is less than 200: apical predominance is less pronounced, condensations and excavations are less prevalent, and hematogenic disseminations are less frequent (miliary parenchyma, mediastinal lymph node involvement, pleural and extrathoracic involvement) (3). However, typical images of micronodules distributed in a centrilobular branching structures resembling a budding tree can also be found.

**Atypical mycobacteria (fig. 5)**

The most frequent atypical mycobacteria encountered in the HIV subject was Mycobacterium avium intracellulare. Mycobacterium kansasii and Mycobacterium xenopi are rarer. Atypical mycobacteriosis occurs in a context of extreme immunodepression (CD4 < 50/mm$^3$). Their incidence has sharply declined since the start of antiretroviral triple therapies, dropping from 176 cases per 10,000 person-years in 1996 to 14 cases per 10,000 in 2001 (2). Mycobacterium kansasii is a respiratory tropism, whereas the pulmonary involvement of the other two comes within disseminated involvement. Mycobacterium kansasii gives CT imaging close to what is found with pulmonary tuberculosis.
Pneumocystosis (fig. 6, 7)

_Pneumocystis jiroveci_ (new nomenclature for _Pneumocystis carinii_) is a saprophyte fungus of humans responsible for the most frequent lung disease in AIDS patients who are not receiving specific prophylaxis.

Pneumocystosis, which occurs at a CD4 level under 200/mm$^3$ is the most frequent inaugural disease of AIDS. However, its incidence has greatly declined since the start of triple therapies, decreasing from 165 cases per 10,000 person-years in 1996 to 38 cases per 10,000 in 2001 (2).

Fig. 3: Lymph node and pulmonary tuberculosis in a 36-year-old patient at the AIDS stage (20 CD4/mm$^3$) on antiretroviral treatment.

- a CT with injection in mediastinal windows demonstrating necrotic precarinal adenopathy (T).
- b The same CT in parenchymal windows demonstrating an area of centrilobular micronodules of the left inferior lobe resembling a budding tree and right hilar adenopathy (T). Note the absence of excavation.

Fig. 4: Miliary tuberculosis with lymph node mediastinal involvement in a 40-year-old HIV-positive patient (200 CD4/mm$^3$).

- a Chest CT scan in parenchymal windows showing multiple millimeter-sized micronodules with clear borders seated in all areas, with random distribution (centrilobular and along the peribronchovascular axes). This aspect is characteristic of hematogenic dissemination.
- b Enlargement of Fig. 4a, with better visibility of micronodules.
- c Same CT scan in mediastinal windows, showing a large interaortopulmonary adenopathy, also related to the hematogenic dissemination of the tuberculosis.
Histoplasmosis (fig. 8)

In France, histoplasmosis is an imported mycosis. The agent responsible is the American histoplasmosis caused by *Histoplasma capsulatum* (presence also in a few endemic areas in South America, the West Indies, Guyana, Africa, and India, but the African histoplasmosis from *Histoplasma duboisii* is not responsible). Its incidence is very rare in France. Present in soils rich in bird droppings, its spores are inhaled and deposited in the alveoli, producing lung infection and spreading through the blood circulation to regional lymph nodes and viscera. In the immuno-depressed patient, the primary infection presents as a flu-like syndrome and is manifested radiologically by alveolar condensation that is sometimes migratory, with mediastinal adenopathy; in the healthy subject it can go undetected.

Spread through the circulation can involve the liver, the spleen, and the digestive tract, but can also involve the lungs in a more less dense miliary form. In the AIDS patient, the clinical symptoms can be very severe, with septicemia, and on the thoracic CT scan a very fine miliary appearance, which can be complicated by diffuse alveolar syndrome. Nodules larger than 3 mm and thick septal lines have also been described.

In the resolution phase, the appearance of granulomas (histoplasmomas) from 5 mm to 3 cm, calcified in 25% of cases, can be observed in the alveolar areas. Likewise, in all the organs involved in the hematogenic spread small granulomas that can calcify also appear. The most classical sequelae group chronic fibrous mediastinitis, granulomas, and calcified apical lesions (resembling those in tuberculosis).

Cryptococcosis (fig. 9)

In France, cryptococcosis is the second most frequent opportunistic mycosis after pneumocystosis: it infects 6%-13% of patients with a CD4 level less than 100/mm³ (2). Its frequency has declined since the generalization of antiretroviral treatments. Involvement is most often disseminated, and lung involvement is the most frequent of visceral locations after meningeval involvement.

CT images are variable, but they generally show infection in both lungs. Several nodules, septal thickening, and alveolointerstitial infiltrates can be observed, as well as cavity and even mililiary images. Mediastinal infiltrates, sometimes necrotic, can also be present. Subclinical pulmonary involvement can exist, discovered systematically in the disseminated cryptococcosis workup.

Invasive pulmonary aspergillosis (fig. 10)

Invasive aspergillosis is rare in the HIV-positive patient. For the most part, it is observed in patients presenting other risk factors (corticotherapy, neutropenia, etc.) or highly immunodepressed patients (< 50 CD4/mm³). The appearance of antiretroviral treatments has again reduced its incidence since 1996.

With invasive aspergillosis in a patient who has not yet been treated with antiretrovirals, initiating this treatment can increase the CD4 levels and potentiate the antifungal treatment.

From a radiologic point of view, the most frequent images are excavated opacities. However, areas of more or less nodular condensation can also be found. The halo sign is always present. The form invading the airways or aspergillar bronchopneumonia can also be found, showing up as peribronchial condensations and centrilobular micronodules.

Other infectious complications

Many other pathogenic agents can be responsible for opportunistic lung infections in AIDS patients, but they are extremely rare in France, particularly since the
Fig. 6: **Inaugural pneumocystosis of the lung in an untreated patient at the AIDS stage (23 CD4/mm³), who was not aware of his HIV-positive status.**

- **a** Frontal chest x-ray showing bilateral and symmetrical ground glass opacities predominating in the parahilar regions and in the base of the lungs.
- **b** Thoracic CT scan showing areas of bilateral perihilar and symmetrical confluent butterfly wing areas. The absence of vascular and bronchial structure effacement is characteristic of ground glass and differentiates it from alveolar condensation.

Fig. 7: **Inaugural pulmonary pneumocystosis in a 37-year-old AIDS patient (54 CD4/mm³).** Thoracic CT showing diffuse ground glass aspect with multiple biapical cysts. Later, this severe hypoxia-inducing pneumocystosis was complicated by pneumothorax, resulting in death.

Fig. 8: **Lung involvement of histoplasmosis spread during treatment of a 45-year-old, severely immunodepressed AIDS patient (15 CD4/mm³).** Thoracic CT scan showing multiple micronodules with clear borders distributed randomly, reflecting hematogenous spread (miliary pattern with low density).

Fig. 9: **Disseminated cryptococcosis lung involvement in a 48-year-old AIDS patient (56 CD4/mm³) treated with antiretrovirals.**

- **a** Thoracic CT scan showing a biapical infiltrate associating septal thickening and a small alveolar condensation.
- **b** Same CT scan a few slices lower showing regular bilateral perihilar areas of septal thickening associated with fine ground glass in the right superior lobe, demonstrated by the dark sign of the anterior bronchus in the right superior lobe (↑).
generalization of antiretroviral therapies. They often involve co-infections, with several bacteria found in the bronchoalveolar lavages.

Mycoses
Coccidioidomycosis is rare but classic. It infects subjects who have travelled to an endemic zone (North America) and manifests most often as alveolar condensations.
Symptomatic pulmonary candidoses are exceptional. The presence of *Candida* in the bronchoalveolar lavages most often comes from oropharyngeal contamination (2).

Parasitoses
The most frequent parasitosis described is pulmonary toxoplasmosis, occurring in the highly immunodepressed patient (< 100 CD4/mm³) presenting disseminated toxoplasmosis, most often with cerebral location. It is most often accompanied by high fever and high blood LDH; the prognosis is serious in absence of early specific treatment (2). Diagnosis is based on demonstrating *Toxoplasma gondii* in the bronchoalveolar lavage. Radiologically, bilateral areas of aspecific alveolar condensation are observed. It can go undetected in cases of co-infection with *Pneumocystis jiroveci*, with treatment of pneumocystosis also effective on the toxoplasmosis.
Cases of pulmonary cryptosporidiosis have been described in terminal-stage AIDS, often associated with other opportunistic infections. The pleuropulmonary locations of visceral Leishmanioses are exceptional; they have only been reported in subjects who have lived in endemic zones.

Virosis
Cytomegalovirus (CMV) is very frequently found in the bronchoalveolar lavage of AIDS patients, but in the vast majority of cases, it is associated with other pathogens and has no clinical incidence, whether or not the patient receives a specific anti-CMV treatment. The rare cases of documented CMV lung infections date from before the advent of antiretroviral treatments and are detected on the CT scan by ground glass areas (6).
A few other cases of virosis have been reported in AIDS patients (*Adenoviruses, Herpes simplex virus*, Epstein-Barr virus, etc.), but their responsibility in pulmonary manifestations has only rarely been proven. Viroses are therefore exceptionally blamed in pulmonary infections during AIDS.

Kaposi sarcoma (fig. 11, 12)
The incidence of Kaposi sarcoma is in sharp decline since the appearance of antiretroviral treatments, with an incidence per 10,000 person-years dropping from 192 to 30 between 1996 and 2001 (2). Its etiological agent is human herpesvirus 8 (HHV-8). In the United States and Europe, women are exceptionally infected, with the sex ratio in the neighborhood of 14. In industrialized countries, Kaposi sarcoma reaches essentially homosexual males, rarely heterosexual males, contrary to Africa (2). It occurs most often in untreated patients.
Pulmonary involvement generally occurs in severely immunodepressed patients who already have cutaneous mucous or digestive involvement. The initial symptoms are most often discrete (persistent cough and moderate fever).
Two CT forms can co-exist:
• The nodular form consisting of multiple irregular spiculated nodules, with a perihilar predominance and peribronchovascular distribution, with frequent air bronchogram (fig. 11b, 11d). A perinodular ground glass halo sign can also exist in cases of perilesional hemorrhage (fig. 11b, 11c, 11d);
• The infiltrating form consisting of peribronchovascular thickening and septal thickening that are sometimes nodular (fig. 12).
Pleural involvement can complicate the two forms with easily hemorrhagic pleural effusion (fig. 11d). In 30%-50% of patients, mediastinal or hilar adenopathy can be found (fig. 12b) (7).
Confirmation of the diagnosis is most often obtained endoscopically with demonstration of flattened or rounded red lesions of the carina tracheae. To begin treatment when these lesions are absent, one must sometimes use thoracoscopy or a minithoracotomy to confirm these lesions.
Treatment of visceral Kaposi sarcoma associates cytotoxic chemotherapy with antiretroviral treatment. A clinical response is usually observed in less than 12 weeks, but complete remissions rarely exceed 1 year.

Aggressive lymphoid proliferations
Aggressive lymphoid proliferations should be differentiated from generalized lymphadenopathy, which does not present a negative outcome (cervical and particularly axillary superficial adenopathy) (fig. 13).

Non-Hodgkin lymphomas (fig. 14)
As in other congenital or acquired immune deficiencies, lymphomas are frequent
**Fig. 11:** Progressive follow-up of pulmonary involvement of multivisceral Kaposi sarcoma in its nodular form occurring in a 44-year-old AIDS patient (5 CD4/mm³).

- **a** Beginning stage: initial thoracic CT scan at diagnosis, showing multiple nodules and spiculated micronodules in the peribronchovascular area.
- **b** Thoracic CT scan 6 months later, showing unfavorable progression despite cytotoxic chemotherapy: increase in size and number of nodules with appearance for some of them of a ground glass halo related to a perinodular hemorrhage (arrowheads). The air bronchogram showing the peribronchial involvement is more clearly visible than at the beginning stage (↑).
- **c** Same CT scan as in Fig. 11b, going through a slightly lower slice, showing substantial ground glass area.
- **d** Terminal stage. Thoracic CT scan done 3 months after the scan in Fig. 11b and c. Substantial increase in nodule size and number, with appearance of pleural effusion related to pleural involvement. Despite their confluence, the nodules have the same aspect, with ground glass halo and air bronchogram (↑).

**Fig. 12:** Lung involvement of multivisceral Kaposi sarcoma in its infiltrating form in a 37-year-old AIDS patient (210 CD4/mm³).

- **a** Thoracic CT scan in parenchymal windows demonstrating peribronchovascular thickening, clearly visible along the anterior bronchi of the right superior lobe and the culmen (↑), sometimes nodular septal thickening and disseminated peribronchovascular nodules throughout the parenchyma.
- **b** Same CT scan in mediastinal windows showing right hilar adenopathy and subcarinal adenopathy (↑).
Differential diagnosis of aggressive lymphoid proliferations in an AIDS patient: angiofollicular mediastinal lymph node hyperplasia

Considered benign in its localized form, lymph node hyperplasia is a well-known entity in healthy subjects. It is therefore most of- ten seen in HIV-infected subjects than in healthy subjects. Although Hodgkin’s disease is not recognized as one of the manifestations of AIDS, its incidence appears five to ten times more in HIV-infected subjects than in healthy subjects. It is therefore most often disseminated with a poor prognosis.

Angiofollicular mediastinal lymph node hyperplasia

Considered benign in its localized form, angiofollicular mediastinal lymph node hyperplasia, classic in AIDS, is close to lymphoma in its clinical presentation (hepatosplenomegaly and polyadenopathy) and its poor prognosis. It is treated with chemotherapy.

Other pulmonary neoplasias

Since antiretroviral treatments were begun, with the resulting decline in opportunistic infections, a significant increase in the incidence of cancers not related to HIV in the AIDS patient treated with antiretroviral drugs has been noted, particularly bronchopulmonary cancer, higher than the incidence in the rest of the French population. In a study conducted in 2000 on 964 AIDS patients’ deaths, 12% were related to cancers not related to HIV, 39.8% of which were lung cancers (8). The histological types encountered (adenocarcinoma followed by epidermoid carcinoma and small-cell carcinoma) and the radiological presentation are the same as in the rest of the general population, but rarer lesions can also be found, benign or malignant, such as Epstein-Barr virus leiomyoma (fig. 15) (4).

Lymphoid interstitial pneumonia (LIP) (fig. 16)

The definition of LIP is histological: lymphocyte infiltration of the lung parenchyma with peribronchovascular lymphocyte aggregates.

Pulmonary hypertension (PHT) (fig. 17)

Since the incidence of primary PHT is higher in the HIV+ patient, HIV-related PHT is described, even though HIV, DNA or viral RNA, or the P24 antigen are found in the pulmonary arteries of HIV-infected patients presenting with PHT. In December 2004, 279 cases were reported in the literature (1). The usual manifestations are the same as for dyspnea. The mechanisms of action are poorly known but suggest an indirect effect of cytokines and chemokines produced by the infected lymphocytes and alveolar macrophages on endothelial cells (1). Standard x-ray or CT images are the same as those found in primary PHT, i.e., dilatation of the trunk of the superior pulmonary artery to 29 mm, more or less associated with dilatation of the left and right pulmonary arteries and right cardiomegaly that varies depending on the involvement (10).
**Fig. 14:** Mediastinal involvement of cervicothoracic non-Hodgkin lymphoma in a 46-year-old AIDS patient.

a Thoracic CT scan in mediastinal windows through the right paratracheal space: large number of right paratracheal and anterior mediastinal adenopathic lymph nodes.

b Same CT scan through the carina tracheae: precarinal adenopathy.

**Fig. 15:** Epstein-Barr virus leiomyoma in a 44-year-old AIDS patient (64 CD4/mm³). This benign smooth muscle tumor is rare in the general population but classic in pediatrics in children at the AIDS stage. Thoracic CT scan showing a single multilobed nodule of the culmen, with clear borders. The mediastinal windows show no adenopathy.

**Fig. 16:** Asymptomatic lymphoid interstitial pneumonia (LIP), spontaneous remission, in a 40-year-old AIDS patient. Thoracic CT scan in millimeter-thick slice showing fine diffuse ground glass, predominating in the left superior lobe, as seen by the dark sign of the bronchus in the superior segment of the lingula (↑). Fine septal thickening can also be seen in the periphery (arrowheads). The other views showed no cysts.

**Fig. 17:** HIV-related pulmonary hypertension in a 43-year-old AIDS patient (166 CD4/mm³), on antiretroviral treatment for 7 years and presenting exercise dyspnea. The parenchymal windows are normal.

a Thoracic CT scan with injection showing a large increase in the caliber of the pulmonary trunk measuring 49 mm. Dilatation of the left and right pulmonary arteries is less pronounced.

b Same CT scan through cardiac cavities showing right ventricle dilatation with paradoxical septum: deviation of the interventricular septum on the left (↑).
The pulmonary parenchyma is most often normal at diagnosis. Treatment with pulmonary artery vasodilators is generally effective.

The advent of antiretroviral treatments has unmasked this disease by decreasing mortality and the incidence of opportunistic infections, but the relation between taking antiretroviral drugs or not and the emergence of PHT remains to be demonstrated. Nevertheless, a study on a series of 82 HIV-related PHT patients showed a better prognosis in patients on antiretroviral treatment (1).

**Other diseases**

Other thoracic diseases can be encountered during the course of AIDS, particularly cardiomyopathies of varying etiology. These are most often related to viral myocarditis or another opportunistic infection but can also stem from drug toxicity.

When antiretroviral treatment is started for cryptococcosis, tuberculosis infection, or a *Mycobacterium avium* infection, immune reconstitution inflammatory syndrome (IRIS) can be observed. This is an exacerbation of clinical, biological, and radiological symptoms, whereas the CD4 level rises and viral replication declines, associated with the appearance of varied autoimmune disorders, explaining the sarcoid-like reactions in the chest cavity. It responds most often to corticoid therapy.

**Conclusion**

Despite the drop in the incidence in France of opportunistic infections during AIDS, stemming from the generalization of antiretroviral treatments and anti-infectious prophylaxis, the infectious pulmonary diseases of AIDS remained a daily occurrence as of 2006. This phenomenon is related on the one hand to drug noncompliance, to unawareness or denial of the disease, frequently observed in AIDS patients, and on the other hand to the emergence of subjects who do not respond to antiretroviral treatments. In addition, these opportunistic lung diseases are often observed in foreign-born patients from developing countries, whether or not they know their HIV status.

In parallel, lengthening the life expectancy of patients treated with antiretrovirals has allowed new noninfectious lung diseases to emerge in AIDS patients such as pulmonary hypertension and lung cancers. In practice, with an HIV+ patient presenting with cough, whether febrile or not, dyspnea, or a change in general health, a chest x-ray remains indispensable. Nonetheless, whatever the result may be, in highly immunodepressed patients, an initial CT scan is more and more frequently requested to detail the aspect of lesions, to suggest an etiologic diagnosis, and to search for complications: excavation or pleural extension in pneumonias, the presence of bubbles in interstitial diseases (pneumocystosis), which should alert the clinician to the possible appearance of pneumothorax. Furthermore, the CT scan can orient bronchoalveolar lavage toward the segments involved and improve bacteriological diagnosis. Follow-up of opportunistic infections is radiological, except when there is no response to therapy. Tumors are better followed by CT.

Diagnostic ranges can be proposed and should be adjusted depending on the CD4 level and whether the patient is on antiretroviral treatment. With alveolar condensation, whether or not it is excava
ted, community-acquired or opportunistic bacterial pneumonia, tuberculosis, atypical mycobacteriosis, aspergillosis, toxoplasmosis, or lymphoma are possible. With radiological interstitial syndrome, pneumocystosis, tuberculosis miliary formations, cryptococcosis, infiltrating Kaposi sarcoma, and more rarely LIP or histoplasmosis are suggested if the subject has lived in an endemic area. With a large mediastinum, PHT or adenopathy are suggested in a context of tuberculosis lymphoma, angiofollicular hyperplasia, Hodgkin’s disease, or more rarely a sarcoïd-like reaction (immune restitution syndrome when starting antiretroviral treatment). Finally, the appearance of several nodules should call to mind the preliminary hypothesis of Kaposi sarcoma or lymphoma.

**References**