



Review

Updating Our Understanding of Pulmonary Disease Associated With HIV Infection[☆]

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ABSTRACT

The introduction of highly active antiretroviral therapy (HAART) has resulted in a reduction of opportunistic infections associated with cellular and humoral immunosuppression. However, what is still unclear is the impact of HAART on the development of other diseases not associated with AIDS, such as lung cancer and COPD. The aim of this paper is to review the most innovative and relevant aspects of lung pathology in patients infected with HIV.

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Actualización en la patología pulmonar relacionada con la infección VIH

RESUMEN

La introducción del tratamiento antirretroviral de gran actividad (TARGA) ha supuesto una disminución de las infecciones oportunistas asociada a la inmunodepresión celular y humoral. Sin embargo, no está claro el impacto del TARGA en el desarrollo de otras patologías no asociadas a sida, como el cáncer de pulmón y la enfermedad pulmonar obstructiva crónica (EPOC). El objetivo del presente artículo es revisar los aspectos más novedosos y relevantes de la patología pulmonar en pacientes infectados por el virus de la inmunodeficiencia humana (VIH).

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Introduction

Lung pathologies associated with HIV infection are currently an important cause for comorbidity despite the immunological recuperation associated with HAART (highly active antiretroviral

therapy). In this article, we will review the most current aspects of the most prevalent lung diseases in patients with HIV infection.

Lung Cancer

The incidence of AIDS-defining neoplasms, such as Kaposi's sarcoma and non-Hodgkin lymphoma (NHL), has significantly decreased in the HAART era when compared with the pre-HAART era (before 1996). However, the incidence of non-AIDS-defining

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neoplasms, such as lung cancer, has increased since the introduction of HAART.^{1–5} Lung cancer currently represents the first cause of mortality due to non-AIDS-associated neoplasm among the population with HIV infection.⁶ The increased risk for lung cancer associated with HIV infection observed in two recently published meta-analyses was 2.7 (95% CI, 1.9–3.9)⁷ and 2.6 (95% CI, 2.1–3.1)⁸, respectively.

The causes for the increased risk for non-AIDS-defining neoplasms are not well defined.⁹ In the case of lung cancer, it seems that smoking is the most important risk factor.¹⁰ It is not clear whether a greater prevalence in tobacco habit among patients with HIV than in the general population¹¹ explains all of the increased risk, or whether there is an independent effect of the HIV infection.

Kirk et al.¹² analyzed the factors associated with the development of lung cancer in a prospective cohort study made up of patients addicted to parenteral drugs who were HIV negative and HIV positive. The recruitment of the patients was begun in 1988; therefore, the patient follow-up included both the pre-HAART era as well as the HAART era. In the multivariate analysis, adjusted for smoking, HIV infection was an independent risk factor for lung cancer; however, neither the CD4 count nor the viral load in blood of the HIV subjects was significant.

The mechanisms by which HIV itself can increase the development of neoplasms are not clearly identified. On the one hand, in *in vitro* studies it has been observed that the product of the HIV *tat* gene may have an oncogenic role¹³; however, no evidence has been found of HIV genome in tumor tissue.¹⁴ The epidemiological studies that evaluate whether the degree of immunosuppression can favor the development of lung cancer does not offer conclusive results,¹⁵ and there are doubts about whether the use of HAART protects against the development of lung cancer.^{13–16}

As for the clinical and demographic characteristics of lung cancer in the population infected with HIV, there are no important differences with the HIV-negative population. The age at presentation is younger than in the general population, and it has a predilection for the male sex (9–10:1). The majority of the patients are symptomatic at the time of diagnosis. In 75%–90% of cases, the diagnosis is of locally advanced or metastatic disease, similar to what is observed in the control groups paired for age.⁸

The distribution of the histological varieties of lung cancer is similar to the HIV-negative population. Non-small-cell lung cancer represents 86%–94% of lung cancers¹⁶ in the HIV-infected population. Adenocarcinoma and squamous cell carcinoma are the most frequent histologic varieties.⁸ The prognosis of lung cancer in the HIV population seems to be worse than in the general population, probably because the disease is in a more advanced stage at the time of diagnosis. When compared by TNM classification, no significant differences are observed between the HIV population and the general population.^{17,18} Makinson et al.¹⁹ evaluated the factors associated with an increase in survival of the patients with HIV infection and non-small-cell lung cancer in a French cohort (the Dat'Aids cohort). The study included 52 patients. These authors found that a performance status (PS) of less than 2, a CD4 count ≥ 200 cells/ μ l at the time of the cancer diagnosis and the use of HAART after the cancer diagnosis were independent factors associated with increased survival in the multivariate analysis. Neither the use of cytotoxic chemotherapy nor the stage of the neoplasm was significant. Hessol et al.²⁰ also observed an increase in the survival of non-AIDS-associated cancer with the use of HAART for at least 6 months.

Patients with HIV infection and lung cancer should be treated following the standard protocols for the general population based on surgery, chemotherapy and radiotherapy according to the stage of the neoplasm, regardless of the CD4 count.¹⁹ However, one must take into account the possible pharmacological interactions between the chemotherapy agents and the antiretroviral agents

due to the risk for severe hematological toxicity. Makinson et al.¹⁹ found that the use of antiretroviral treatment guidelines that included a protease inhibitor (PI) with chemotherapy increased the risk for grade 4 hematological toxicity. PIs, whether ritonavir-enhanced or not, may alter the metabolism of antineoplastic agents by inhibiting CYP450 3A4. The anti-neoplastic agents indicated for the treatment of non-small-cell lung cancer that are metabolized by this pathway are taxanes, vinca alkaloids, etoposide and the anilinoquinazolines erlotinib and gefitinib. In addition, AZT can promote the risk for myelosuppression secondary to antineoplastics, and its use should therefore be avoided.

Pneumonia Due to *Pneumocystis jirovecii*

Pneumonia due to *Pneumocystis* is one of the most frequent opportunistic infections in patients with HIV infection. The introduction of HAART has resulted in a drastic decrease in the incidence of this infection.^{21,22} In the EuroSIDA study, the incidence of pneumonia due to *Pneumocystis* dropped from 4.9 cases per 100 persons/year before 1995 to 0.3 cases per 100 persons/year after 1998.²³

Infection by *Pneumocystis* associated with HIV infection typically appears when the CD4 lymphocyte count is lower than 200 cells/ μ l. The role of the CD4 lymphocytes in the defense against *Pneumocystis* has been confirmed in studies based on CD4 *Knockout* animal models.²⁴ Nevertheless, the lung damage and the clinical severity are related more with the degree of pulmonary inflammation than with the direct effect of *Pneumocystis*.²⁵ The clinical benefit of corticosteroids in cases of hypoxemia supports these observations.

The clinical presentation of pneumonia due to *Pneumocystis* in patients with HIV infection differs from that associated with other forms of immunosuppression. In HIV patients, the clinical presentation is typically subacute with less affectation of alveolar oxygenation. The bronchoalveolar lavage samples (BAL) present a significantly greater number of *Pneumocystis* organisms and less neutrophils than the patients without HIV infection, which means a greater diagnostic performance of the induced sputum and the bronchoalveolar lavage in patients with HIV infection.²⁶ The classic symptoms of pneumonia due to *Pneumocystis* are fever, dry cough and exertion dyspnea. Physical examination may be normal. The typical radiological pattern is the presence of diffuse bilateral interstitial infiltrates. Other less frequent radiological patterns are: solitary nodule or multiple nodules, infiltrates in the upper lobes in patients who received pentamidine aerosol, pneumatoceles, pneumothorax, or radiography may even be normal. In the cases of normal radiography, high-resolution computed tomography (CT) may show evidence of a ground glass pattern.²²

Pneumocystis cannot be cultured; therefore, the microbiological diagnosis has traditionally been based on the demonstration under optical microscope of the cysts and/or trophozoites in clinically relevant samples (induced sputum, BAL or lung tissue). The diagnostic performance of the induced sputum is 50%–90%.²⁷ In the cases of negative results, it is necessary to resort to an invasive procedure, such as bronchoscopy with BAL. These diagnostic difficulties have promoted the development of molecular diagnostic techniques.

Several studies have evaluated the performance of PCR techniques with non-invasive samples, such as induced sputum and samples from oral rinsing as well as BAL samples. The detection by DNA PCR of *Pneumocystis* in the respiratory samples does not give information about the infectivity of the organism, as DNA is relatively stable after cell death. RNA, especially mitochondrial RNA, is quickly degraded by the endogenous RNase after cell death; therefore, its detection could indicate the viability of the organism.²⁸ The detection of *Pneumocystis* antigens by means of monoclonal

antibodies in induced sputum samples presents high sensitivity and specificity, and has the advantage of identifying cystic forms as well as trophozoites.²³

Hauser et al.²⁹ carried out a multicenter assay to evaluate the diagnostic performance of a qualitative real-time PCR (subunit mLSU) and of an IFI technique (Merifluor-Pneumocystis direct fluorescent antigen [MP-DFA] test) compared with the clinical diagnosis based on radiological studies, degree of hypoxemia, lactate dehydrogenase (LDH) level and local microscope technique. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the PCR were 93%, 91%, 59%, and 99%, respectively, and those of the MP-DFA test were 93%, 100%, 59%, and 98%, respectively. 92% of these samples were from the BAL. These authors suggested that the high NPV of PCR can exclude the diagnosis of *Pneumocystis* when given a negative result. However, a positive result without accompanying symptoms could result in over-treatment as it does not distinguish between infection and colonization. The results of the Chawla et al.³⁰ study about the diagnostic value of PCR (mtLSURNA) support these results.

Other groups of researchers have evaluated the role of determining serum biomarkers, such as LDH, KL-6 and (1→3) β-D-glucan. The KL-6 antigen (high molecular weight, mucin-like glycoprotein) is expressed in the type 2 alveolar pneumocytes and in bronchiolar epithelial cells. This marker is high in interstitial pneumonitis³¹ and in acute lung injury.³² β-D-Glucan is a component of the wall of most fungi; therefore, it has been used as a marker of organic mycosis. In 279 patients (16 with HIV infection) Tasaka et al.³³ evaluated the diagnostic value of LDH, KL-6 and β-D-glucan using a case-control study. A level of β-D-glucan higher than 31.1 pg/ml presented a sensitivity and specificity of 92.3% and 86.1%, respectively. The sensitivity and specificity of the determination of an LDH level higher than 268 UI/l was 86% and 45.3%, respectively. In this study, the LDH level correlated with the oxygenation index. The authors propose that the determination of β-D-glucan could be indicated in patients with respiratory insufficiency in whom bronchoscopy is poorly tolerated. These results have been supported by more recent studies.³⁴ Monitoring the levels of β-D-glucan has not been shown to be useful for evaluating the response to treatment.³⁵

The drug of choice for the treatment and prophylaxis of pneumonia due to *Pneumocystis* is trimethoprim/sulfamethoxazole. The oral administration reaches levels comparable with intravenous administration. In severe cases ($pO_2 < 70$ mmHg or alveolar-arterial gradient >35 mmHg), intravenous administration is preferred, associated with corticosteroids. The treatment should be prolonged up to 21 days. In the consensus document completed by the GESIDA panel of experts, different therapeutic options are described in detail.³⁶

Prophylaxis should be initiated when T helper cell levels are lower than 200 cells/ μ l, or whenever there is some AIDS-defining illness, oral candidiasis or unexplained fever for more than 20 days (AI recommendation).³⁷

There is certain concern about the emergence of *Pneumocystis* resistance to trimethoprim-sulfamethoxazole, although it still is not clear if the existence of mutations in dihydropteroate synthase (DHPS) correlates with a poorer prognosis.³⁸ One study in a Spanish population³⁹ evaluated the existence of mutations in patients with HIV infection in the pre-HAART era (previous to 1996) and in the HAART era (2001–2004). The authors observed that 33% of the genotyped samples from the pre-HAART era and 5.5% of the genotyped samples from the HAART era presented mutations in the DHPS gene. The factors that were found to be significantly related with the presence of mutations were the pre-HAART period, having received previous prophylaxis for *Pneumocystis* with trimethoprim-sulfamethoxazole or another sulfa drug, and homosexuality. In this study, the presence of mutations was not related

with a poorer prognosis despite having received treatment with trimethoprim-sulfamethoxazole.

COPD

HIV infection has been related with the early development of pulmonary emphysema. Several observational studies have shown a greater prevalence of respiratory symptoms, obstructive pattern on spirometry, decrease in DLCO and emphysematous changes on CT in the HIV population.^{39,40} In a cross-sectional study done in the pre-HAART⁴¹ era in patients with HIV infection, without a previous history of AIDS-associated pulmonary complications, it was found that 41.6% presented dyspnea, 40% cough and 41.9% expectoration. The prevalence of these symptoms in the control group, with similar age and smoking habit, was significantly lower. In this study, tobacco was the most important predictor for respiratory symptoms. George et al.⁸³ evaluated the impact of HAART in the development of COPD.³⁷ In this study, 83.3% of the 234 patients included received HAART and 59.8% had a history of smoking. The prevalence of cough, dyspnea upon exertion and dyspnea at rest was 23%, 16%, and 3%, respectively. The factors that were independently associated with the appearance of respiratory symptoms were smoking, the viral load and a reduction in the FEV₁/FVC ratio. The prevalence of an FEV₁/FVC value less than 0.7 was 6.8%. 62.5% of the patients with obstructive pattern had grade I of the GOLD stage. The predictive factors for presenting an obstructive pattern on spirometry were age, smoking history (pack-years), history of bacterial pneumonia and the use of HAART. Gingo et al.⁴² found a greater prevalence of alterations on spirometry. 21% of the patients evaluated presented an obstructive pattern on spirometry, and 64.1% presented alteration in diffusion. The factors that were independently associated with irreversible airway obstruction were tobacco habit (pack-years), the use of intravenous drugs and antiretroviral treatment. The prevalence of obstructive pattern among the HIV patients who have never smoked is also higher than what is described in controls without HIV with a history of smoking (13.6% versus 3.2%, $P=.003$).⁴³

The etiopathogeny of the predisposition to develop COPD in HIV infection is still not clear.⁴⁴ The greater prevalence of the risk behaviors in the population with HIV infection, such as tobacco habit, smoking marijuana and parenteral drug use is one of the main hypotheses proposed. The greater susceptibility to infections and colonizations may perpetuate the structural damage favored by tobacco use. Pneumonia and colonization by *P. jirovecii* have been related with the accelerated development of emphysema.⁴⁵ The HIV infection itself is associated with lymphocytic alveolitis and an increase in CD8+ lymphocytes. In animal models, it has been observed that the CD8+ lymphocytes secrete IFN- γ and favor the development of emphysema.⁴⁶ A decrease in the levels of antioxidants has also been observed as well as an increase in the oxidants at the systemic and pulmonary levels.^{47,48}

Cohort studies have found an association between antiretroviral treatment and COPD. However, the mechanisms of this relationship are not known. It has been proposed that endothelial dysfunction of the pulmonary capillaries could bring decreased diffusion.⁴⁹ On the other hand, the start of the antiretroviral treatment could favor the development of a subclinical inflammatory response in organisms that colonize the airway (such as *Pneumocystis*, mycobacteria) or against autoantigens.⁴⁰

Tuberculosis and HIV

HIV infection is an important risk factor for the development of tuberculosis. The introduction of HAART has led to a reduction in the risk for tuberculosis in 70%–90%. However, the incidence is still

higher than expected, even in patients with high CD4 counts.^{50,51} In a cohort study done in countries with a low prevalence for tuberculosis in North America and Europe, there was an observed global incidence of tuberculosis of 4.69 cases per 1000 persons/year in the first years of the study after starting HAART.

The diagnosis of tuberculosis in HIV patients requires high clinical suspicion, as the sensitivity of the diagnostic tests is lower in this group of patients. Chest radiography can be normal in up to 22% of the cases of pulmonary tuberculosis,^{52,53} and the performance of the sputum smear is lower in patients with HIV when compared with HIV-negative patients.⁵⁴

In recent years, the implementation of molecular biology techniques for the diagnosis of tuberculosis has been a great advance in the clinical management of this infection. GeneXpert, a real-time PCR, can confirm the diagnosis with a sputum sample on the same day the sample is taken and identify whether the mycobacteria is resistant to rifampicin. The study by Boehme et al.⁵⁴ found a sensitivity of 90% and a specificity of 99% compared with the sputum culture. In comparison, the sensitivity and the specificity of the sputum smear (in 2–3 sputum samples) were 67% and 99.5%. In this paper, patients were stratified according to the state of HIV and it was observed that the sensitivity of the GeneXpert technique, unlike the sputum smear, did not decrease in patients with HIV infection.

The diagnosis of tuberculosis in a patient with HIV infection has important therapeutic implications. One of the main uncertainties which has attempted to be answered by developing observational studies and clinical assays is when the antiretroviral treatment should be initiated in *naïve* patients diagnosed with tuberculosis. Pharmacological interactions, risk for drug toxicities and the development of immune reconstitution inflammatory syndrome associated with the establishment of antiretroviral treatment are the main factors that condition the decision to initiate anti-retroviral treatment. In a retrospective cohort study developed in Spain, it was observed that the patients who initiated antiretroviral treatment in the first 2 months after the initiation of tuberculostatic treatment presented less mortality than the patients who were administered HAART later on.⁵⁵ Three recent clinical assays^{56–58} support these results. The SAPIT study⁵⁶ demonstrates that in patients with less than 500 CD4/ μ l, the start of antiretroviral treatment while receiving tuberculostatic treatment (integrated treatment) is associated with less all-cause mortality than when the anti-retroviral treatment is initiated after completing the tuberculostatic treatment (sequential treatment). In order to better specify the time to begin HAART, in the CAMELIA clinical assay⁵⁷ (Cambodian Early versus Late Introduction of Antiretrovirals), the patients were randomized to receive HAART either 2 weeks or 8 weeks after the start of tuberculostatic treatment. The patients included in this clinical assay had less than 200 CD4/ μ l. The early introduction of HAART significantly lowered mortality compared with the late-treatment scenario. The ACTG 5221⁵⁸ STRIDE study also demonstrated that starting with HAART in the first 2 weeks was associated with lower mortality than delaying the start of HAART some 8–12 weeks afterwards in patients who presented less than 50 CD4/ μ l. Based on these results, the British HIV Association⁵⁹ recommends starting HAART as soon as possible in patients who present less than 100 CD4/ μ l. In those with between 100 and 350 CD4/ μ l, it is recommended to start as soon as possible, although a delay of treatment initiation of 2 months after the onset of the tuberculostatic treatment is acceptable if there are problems with pharmacological interactions, toxicity or adherence. Lastly, in patients with more than 350 CD4/ μ l, the decision is left to the specialist.

The second consideration in the treatment of tuberculosis-HIV co-infection is possible pharmacological interactions. Rifampicin reduces the levels of protease inhibitors; therefore, this family

of drugs is not recommended. The administration of high doses of lopinavir/ritonavir can surpass the metabolic induction of rifampicin, but this option has a high risk for hepatitis. In this context, the treatment of choice is a non-nucleoside analog reverse transcriptase inhibitors, preferably efavirenz.⁶⁰ A recent clinical assay⁶¹ compared 600 mg efavirenz/day with 400 mg nevirapine administered once a day, both in association with didanosine and lamivudine. The treatment group with nevirapine presented significantly more virologic failure than the efavirenz group.

Rifampicin reduces the levels of maraviroc and raltegravir and these are therefore not recommended in this scenario.⁶⁰ In case they are used, the doses of these antiretroviral drugs should be doubled.⁵⁹

Pneumococcal Vaccine

Invasive pneumococcal disease has declined since the introduction of HAART, probably secondary to the immunological recovery and the use of antibiotic prophylaxis. However, the incidence continues to be higher than that of the non-HIV population.⁶² Health authorities, CDC and HIV Medicine Association recommend vaccinating adults and children with more than 200 CD4 in cases that have not been vaccinated in the last 5 years. The 23-valent polysaccharide vaccine is generally recommended for adults with HIV or other comorbidities. The efficacy of this vaccine has been previously demonstrated in HIV populations in observational studies.⁶³ In a prospective cohort study⁶⁴ done in Taiwan in HIV patients who were receiving HAART, the group of vaccinated patients presented an incidence of pneumococcal disease of 2.1 cases per 1000 persons/year versus 21.8 cases per 1000 persons/years in the unvaccinated patients. In this study, immunization was not seen to affect the immunological recovery or virologic control.

In recent years, the efficacy of the 7-valent conjugate vaccine has been evaluated in HIV populations. In a clinical assay published recently,⁶⁵ the efficacy of this vaccine was evaluated as a secondary prophylaxis in patients with a previous history of invasive pneumococcal disease. In this study, the efficacy of the vaccine was estimated at 74%.

Influenza A in HIV Infection

Several observational studies have evaluated the susceptibility to infection by the H1N1 virus among patients with HIV infection. In seroprevalence studies, a similar percentage of seroconversion has been found, measured by specific antibodies against H1N1 among HIV patients compared with the HIV-negative group.⁶⁶ The studies that evaluate the state of HIV infection among patients with acute respiratory disease due to lab-confirmed H1N1 do not offer consistent data to support that HIV infection entails higher risk for H1N1 infection.⁶⁷ Smoking and older age are more prevalent among HIV patients with flu disease due to H1N1 than in the general population.

The studies that have evaluated whether the state of HIV infection entails a greater risk for severe disease when given H1N1 infection offer similar results to non-HIV patients.^{68–70} The majority of the patients included in these studies presented good immunological state, and the majority were receiving HAART. Some authors have found that advanced HIV infection and the presence of an opportunistic infection are associated with increased risk for severe flu disease caused by H1N1.⁷¹

The studies that evaluate immunogenicity against influenza A (H1N1) vaccine of HIV-positive patients present discordant results. In a prospective observational study, it was seen that patients with HIV infection (with a mean CD4 of 523 cells/ μ l) presented better seroconversion (69%) than the non-HIV patients after a dose

of the vaccine with AS03 adjuvant (79%–98%). The seroconversion after a vaccine dose without adjuvant in patients with HIV infection is around 50%.^{72,73} The administration of a second dose of non-adjuvant vaccine has not been demonstrated to increase the percentage of seroconversion in a recently published study.⁷⁴

Pulmonary Hypertension

The prevalence of pulmonary arterial hypertension (PAH) in the HIV population is approximately 0.5%. Since 1991, the prevalence of PAH has not modified despite the introduction of HAART.⁷⁵ PAH can appear at any stage of immunosuppression and it has been described in all types of HIV transmission. However, it seems more frequent among parenteral drug users.⁷⁶ There does not seem to be a significant correlation between the degree of immunosuppression associated with HIV infection and the severity of PAH.^{77,78}

The clinical presentation of PAH in patients with HIV infection is similar to that of the general population. The time interval between the onset of the symptoms until the diagnosis of PAH is significantly shorter in HIV-positive patients than in the HIV-negative population (6 months vs 2.5 years), probably due to a closer monitoring of the former group.

The presence of PAH is an independent risk factor for mortality in patients with HIV infection. The 3-year prognosis of the patients with grade III–IV functional class is 28%.⁷² In the French cohort, 72% of the causes of death in patients with PAH were secondary to PAH complications. The only factor in this study that was significantly associated with a poorer prognosis in the multivariate analysis was a CD4 count below 212 cells/ μ l upon diagnosis of PAH. Supporting these results, in a recent and retrospective review of 77 cases, a cardiac output of more than 2.8 l/min and a CD4 count of more than 200 cells/ μ l were the only parameters that were independent factors for survival in the multivariate analysis.⁷⁹

The treatment of PAH in patients with HIV infection duplicates, in general, the recommendations of the therapeutic guidelines for PAH treatment. Nevertheless, it must be taken into account that these recommendations are mainly based on the results of studies done in patients with idiopathic PAH or PAH associated with connective-tissue disease. In HIV patients, anti-coagulation is not recommended due to the pharmacological interactions and the potential risk for thrombopenia. PAH associated with HIV is characterized by a lack of response to vasodilators; therefore, calcium antagonists are not indicated.

There are few studies that evaluate the efficacy of the drugs aimed at specific or advanced treatment of PAH in the HIV population. The majority are observational studies with very small sample sizes, which makes it difficult to generalize the results. Intravenous epoprostenol has been shown to improve the hemodynamic and clinical parameters in patients with HIV infection. The main limitation for its use is the need for intravenous access, with the risk for secondary infection that this entails.^{80,81} The data for iloprost, beraprost and treprostinil in patients with HIV infection are insufficient. Studies on the use of oral bosentan are offering promising results.⁸²

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Conflict of Interests

The authors declare having no conflict of interests.

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