Research Article ISSN 2771-5906

Trends in Internal Medicine

Mixed Pulmonary Hypertension: HIV Infection as an Underlying Cause

Ricardo Donado-Botero[1,2*], Ingrid Tibocha-Gordón[1,2], Mario Montoya-Jaramillo[1,2], Isabella Mesa-Beltran[2,3], Karol Mendoza-Leottau[3], Karina Ibañez-Sanchez[3], Maria Camila Benitez-Escobar[3], Andrea Jimenez-Petro[3], Elían Macias-Posada[3], Mari Rosa Salaiman-Serpa[4], María Auxiliadora Cuello Rojas[4] and Orlando Naranjo-Lorduy[4]

[1]*Department of Internal Medicine, Faculty of Health Sciences, Universidad del Sinú, Cartagena Campus, Cartagena, Colombia.*

[2]*MEDISTAR, Research Group in Internal Medicine, Faculty of Health Sciences, Universidad del Sinú, Cartagena Campus, Cartagena, Colombia.*

[3]*General Medicine, Universidad del Sinú, Cartagena Campus, Cartagena, Colombia.*

[4]*General Medicine, Universidad Metropolitana, Barranquilla, Colombia.*

[5]*General Medicine, Universidad del Sinú, Montería, Colombia.*

***Correspondence:**
Ricardo Donado Botero, Department of Internal Medicine, Faculty of Health Sciences, Universidad del Sinú, Cartagena Campus, Cartagena, Colombia.

Received: 05 Aug 2025; **Accepted:** 19 Sep 2025; **Published:** 27 Sep 2025

Citation: Donado-Botero R, Tibocha-Gordón I, Montoya-Jaramillo M, et al. Mixed Pulmonary Hypertension: HIV Infection as an Underlying Cause. Trends Int Med. 2025; 5(3): 1-5.

ABSTRACT

In the context of HIV infection, pulmonary hypertension (PH) represents an uncommon but clinically significant complication, particularly when mechanisms corresponding to Groups 1 and 4 coexist. We present the case of a 50-year-old male patient with well-controlled HIV and a history of pulmonary tuberculosis, who presented with progressive dyspnea, initially suspected to be a tuberculous reactivation. A chest CT scan revealed a cavitary pulmonary lesion and an organized lobar thrombus, findings later confirmed by right heart catheterization, which showed parameters consistent with precapillary PH. Catheter-directed thrombolysis was performed using the EKOS® system, resulting in favorable clinical evolution without adverse events. Subsequently, initiation of targeted vasodilator therapy was planned. To our knowledge, this is the first case reported in Colombia describing the use of the EKOS® system in an HIV-positive patient with mixed PH. This therapeutic approach offers a safe and effective alternative in complex clinical settings with limited resources, such as those in the Caribbean region. The case highlights the importance of early hemodynamic assessment and of therapeutic strategies tailored to regional contexts.

Keywords

Pulmonary Hypertension, HIV Infections, Thrombosis, Endothelium, Vascular, Thrombolytic Therapy, Catheter-Directed.

Introduction

Within the spectrum of diseases affecting pulmonary circulation, pulmonary hypertension (PH) is defined as a functional alteration of the pulmonary vascular bed and a progressive overload of the right ventricle. Its contemporary classification organizes it into five etiological groups based on pathophysiological mechanisms, hemodynamic profiles, and associated clinical conditions [1-3]. Particularly, groups 1 and 4 represent scenarios of special diagnostic and therapeutic complexity: the first, due to its relationship with uncommon diseases such as HIV infection; the second, due to its association with chronic thromboembolic disease, which may be susceptible to curative treatment through surgery or interventional techniques [1,4,5].

In individuals living with human immunodeficiency virus (HIV), pulmonary arterial hypertension (PAH) constitutes an unusual yet clinically relevant complication. It is attributed to processes of endothelial activation, immunoregulatory alterations, and

irreversible vascular remodeling, even when adequate virological control is achieved [6-8]. From a hemodynamic perspective, the presentation is usually of the precapillary type, with features indistinguishable from idiopathic PAH [9], and it has been associated with unfavorable clinical outcomes and survival in the absence of specific therapies [6,10].

On the other hand, chronic thromboembolic pulmonary hypertension (CTEPH) arises as a consequence of unresolved pulmonary thrombotic episodes, which induce persistent vascular obstruction, secondary angiopathy, and distal remodeling. This process gives rise to a mixed form of PH that can be definitively treated if diagnosed in early stages [11-13]. In this context, therapeutic tools such as ultrasound-assisted thrombolysis (EKOS®) have been developed, which are useful in selected cases with proximal disease or contraindications for surgery [14-16].

The diagnosis of these PH variants necessarily requires right heart catheterization, which allows confirmation of the patient's hemodynamic profile. In those living with HIV, a careful evaluation of vasoreactivity is essential, as well as consideration of potential interactions between antiretroviral therapy (ART) and pulmonary vasodilators [17,18].

Regarding treatment, HIV-associated PAH is approached with a therapeutic scheme similar to that used in other group 1 forms. This includes endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs, with personalized adjustments according to patient tolerance and clinical risk level [3,17,19]. Although intensive ART has been shown to improve clinical and hemodynamic parameters, its effect on the specific progression of PAH continues to be under investigation [6,20].

Against this background, we describe the case of a 50-year-old male patient with controlled HIV infection who developed a mixed form of PH corresponding to groups 1 and 4. Findings included organized thrombus, pulmonary infarction, vascular remodeling, and a partial hemodynamic response. Treatment involved an endovascular intervention with the EKOS® system and a complete hemodynamic characterization, thereby exemplifying the complexity of diagnosing and managing combined PH in immunocompromised patients, as well as highlighting emerging options for targeted treatment in challenging clinical contexts.

Clinical Case

A 50-year-old man, with a previous diagnosis of HIV infection under antiretroviral therapy with adequate virological response (viral load <200 copies/mL in September 2023 and CD4+ count of 378 cells/µL in December 2024), and a history of pulmonary tuberculosis treated eight years earlier, presented with progressive exertional dyspnea, orthopnea, right-sided pleuritic chest pain, desaturation episodes, and mild general symptoms such as asthenia and decreased appetite.

Chest computed tomography (Figures 1 and 2) revealed thickening of the interlobular septa in the right upper lobe, cystic bronchiectasis, peripheral consolidations of subpleural distribution, and areas with ground-glass pattern. These findings, in the patient's clinical context, initially raised suspicion of reactivation of pulmonary tuberculosis. Given this diagnostic possibility, empirical antimicrobial therapy was initiated, and bronchoscopy was scheduled for diagnostic purposes.

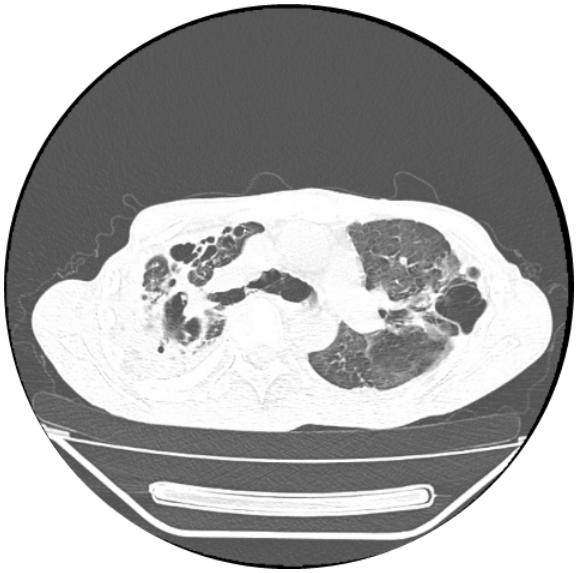

Figure 1: Non-contrast chest computed tomography, lung window, apical slice.

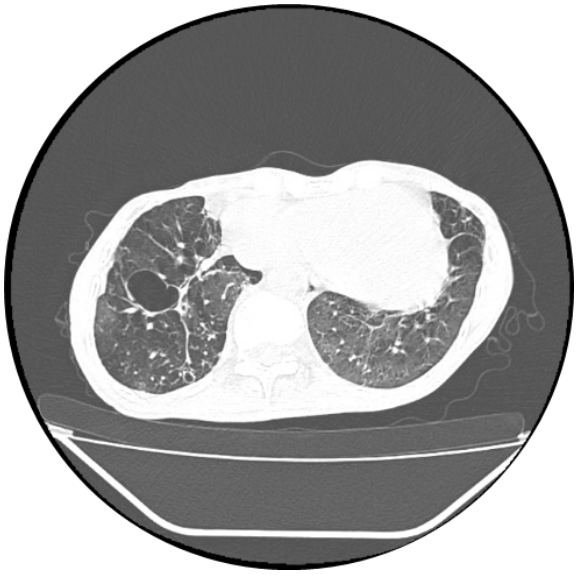

Figure 2: Non-contrast chest computed tomography, lung window, inferior slice.

During bronchoscopy, no findings compatible with active inflammation or endobronchial lesions were observed, nor were purulent secretions identified. The analysis of the bronchoalveolar lavage was negative for acid-fast bacilli (AFB) on Ziehl-Neelsen staining, as well as for the GeneXpert MTB/RIF molecular test, mycobacterial culture, and the viral panel. With these results, the possibility of tuberculous reactivation or bacterial coinfection was

ruled out, leading to the discontinuation of empirical antimicrobial therapy.

Given the persistence of dyspnea and hypoxemia, a transthoracic echocardiogram was requested, which revealed signs of right ventricular overload and elevated pulmonary artery systolic pressure (PASP). These findings led to the indication of a right heart catheterization complemented by bilateral pulmonary arteriography.

The hemodynamic study, performed on February 13, 2025, showed an abrupt filling defect with interruption of flow in the right upper lobar artery, compatible with a chronic organized occlusive thrombus. At the distal level, perfusion appeared irregular, with areas of segmental hypoperfusion, showing an angiographic pattern suggestive of chronic pulmonary thromboembolism.

Hemodynamic parameters revealed a mean pulmonary artery pressure of 23 mmHg, a transpulmonary gradient of 12 mmHg, and mildly elevated pulmonary vascular resistance (2.4 Wood units), without elevation of pulmonary capillary wedge pressure. Right atrial pressure was 12 mmHg, at the upper limit of normal. Taken together, these values defined a hemodynamic profile consistent with mild precapillary pulmonary hypertension, probably in the context of chronic thromboembolic pulmonary hypertension (group 4), with additional suspicion of HIV-associated pulmonary arterial hypertension (group 1), given the virological control and the absence of postcapillary or structural causes.

In view of the evidence of persistent functional impairment and the angiographic finding of an organized thrombus, the multidisciplinary team opted to perform an endovascular intervention using the EKOS® system (EkoSonic Endovascular System) on February 12, 2025. This technique combines the local administration of a fibrinolytic agent with the application of low-frequency ultrasound, which enhances drug penetration and promotes thrombus dissolution, allowing more effective thrombolysis with lower drug doses. The subsequent angiographic control showed partial persistence of the filling defect, suggestive of a partially recanalized chronic thrombus, although with subjective improvement of the perfusion pattern.

During hospitalization, the patient presented a single episode of paroxysmal atrial fibrillation without hemodynamic compromise, which was managed conservatively. Echocardiography showed preserved left ventricular ejection fraction (60%) and mild signs of right ventricular dysfunction.

The patient experienced a favorable clinical course, with progressive improvement, normalization of arterial blood gases, and resolution of type 2 respiratory failure. He was discharged with oral anticoagulation, outpatient follow-up in specialized pulmonology, and short-term functional evaluation. Initiation of specific vasodilator therapy for pulmonary arterial hypertension (group 1) was considered, depending on clinical evolution and reassessment of risk parameters at subsequent follow-up visits.

Discussion

In patients living with HIV, highly complex cardiovascular complications may occur, among which the form of pulmonary hypertension (PH) linked to group 1 of the Nice hemodynamic classification stands out. Although its frequency is low, its coexistence with other forms such as chronic thromboembolic pulmonary hypertension (CTEPH, group 4)—as evidenced in this case—poses relevant clinical challenges [1]. The pathophysiology of HIV-associated PH (HIV-PH) is heterogeneous and multifactorial, involving phenomena such as endothelial dysfunction, persistent systemic inflammation, prolonged immune activation, and structural remodeling of the pulmonary vasculature. These processes are driven by the action of viral proteins and proinflammatory cytokines, even in patients receiving effective antiretroviral therapy (ART) with undetectable viremia [2-4]. The final consequence is a vascular damage pattern similar to that observed in idiopathic pulmonary arterial hypertension (PAH), which supports the application of analogous diagnostic and therapeutic strategies, adapted to the particularities of the viral context.

Within the therapeutic approach, high-efficacy ART constitutes the cornerstone. However, when functional alterations, evidence of right ventricular dysfunction, or hemodynamic deterioration are detected, it is necessary to consider the use of specific pulmonary vasodilators. The BREATHE-4 clinical trial, one of the few prospective studies focused exclusively on patients with HIV-PH, evaluated the use of bosentan in individuals with PAH in NYHA functional classes III and IV. The results showed improvement in functional performance, increased cardiac index, and reduction of pulmonary vascular resistance, without the occurrence of severe adverse effects or relevant interactions with ART [21]. Subsequent research reinforced these findings, with reports of sustained long-term benefits, including improvements in the six-minute walk test distance and favorable hemodynamic parameters during follow-up periods of up to 29 months [22,23].

Due to the hepatotoxicity profile associated with bosentan, alternatives such as macitentan and ambrisentan have been proposed. However, the low representation of patients with HIV infection in the pivotal trials of these drugs limits the possibility of making definitive recommendations and compels their use to be based on careful clinical extrapolation [24]. For their part, phosphodiesterase-5 inhibitors (PDE5i), such as sildenafil and tadalafil, have shown therapeutic usefulness in observational studies and case reports. Nevertheless, caution is needed when prescribing them, due to the potential for pharmacological interactions with protease inhibitors used in some ART regimens [25,26].

In high-risk scenarios or in the absence of an adequate clinical response to initial treatment, a combination therapy strategy may be considered, integrating endothelin receptor antagonists and PDE5i, following the management model used in idiopathic PAH. New molecules such as riociguat or selexipag have shown efficacy in other PH subtypes, but their experience in people with HIV is

scarce, so their use should be reserved for individualized cases with strict risk-benefit evaluation [6,27].

Regarding the management of CTEPH (group 4), pulmonary endarterectomy remains the treatment of choice in patients with operable disease. However, in those deemed unsuitable for surgery or with distal involvement, minimally invasive therapies such as catheter-directed thrombolysis have gained prominence. In this category, the EKOS® system (EkoSonic Endovascular System) has demonstrated efficacy by combining the local infusion of thrombolytic agents with low-intensity ultrasound, which enhances drug penetration and facilitates thrombus dissolution with lower doses and reduced bleeding risk.

The SEATTLE II and OPTALYSE PE clinical trials have been fundamental in establishing the role of the EKOS system in the management of submassive pulmonary embolism. These studies demonstrated significant reductions in mean pulmonary artery pressure, improvement in the right ventricle/left ventricle (RV/LV) ratio by echocardiography, and symptomatic clinical relief, all with a superior safety profile compared to conventional systemic thrombolysis [28-30]. Although there are no specific clinical trials in people with HIV and CTEPH, case reports have documented the efficacy of EKOS in complex clinical scenarios, with positive and well-tolerated results [31,32].

In Latin America, experience with this technique is still limited and usually described through individual reports in high-complexity centers. In the Colombian context, despite having been previously used, no clinical series have been published in HIV-positive populations, which makes the present report one of the first documented experiences in the country [33].

This case highlights the importance of a comprehensive diagnostic evaluation that incorporates clinical, imaging, and hemodynamic data to accurately characterize the etiology of PH, especially in situations of possible mixed etiology. The successful application of the EKOS system in a patient with HIV, organized thrombus, and probable combined PH (groups 1 and 4), together with the planning of specific vasodilator therapy, underscores the need for individualized, interdisciplinary approaches guided by the best available scientific evidence. Only through such strategies is it possible to optimize clinical outcomes in vulnerable populations traditionally excluded from research, such as people living with HIV.

Conclusions

This clinical experience, developed in the Caribbean region of Colombia, highlights the inherent difficulties in diagnosing and treating patients with combined forms of pulmonary hypertension in a context of limited access to specialized therapies. The intervention with the EKOS® system facilitated a safe and effective resolution of the organized thrombus, with evident clinical benefits and no hemorrhagic complications. The use of right heart catheterization as a central diagnostic tool, as well as the consideration of initiating specific vasodilator therapy, exemplify an individualized, contextualized, and evidence-based approach. This case reinforces the need to promote the implementation of emerging technologies in local settings and to generate local data supporting their efficacy and safety in complex and underrepresented populations such as HIV-positive patients.

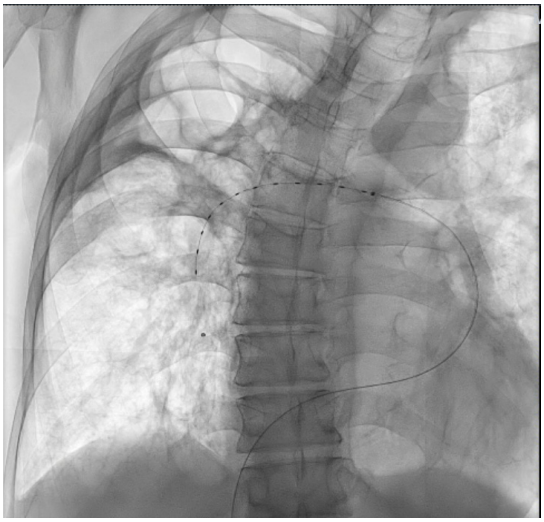

Figure 3: Endovascular catheter designed for ultrasound-assisted thrombectomy, such as the EKOS system (EkoSonic Endovascular System).

Endovascular procedure with the EKOS® system. Visualization of the catheter positioned in the right pulmonary artery, used for low-frequency ultrasound-directed thrombolysis.

References

1. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022; 43: 3618-3731.
2. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019; 53: 1801913.
3. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J. 2019; 53: 1801889.
4. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019; 53: 1801915.
5. Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. Circulation. 2014; 130: 508-518.
6. Janda A, Shah R, Finkel K, et al. HIV and pulmonary arterial hypertension: a systematic review. HIV Med. 2010; 11: 620-634.
7. Zuber JP, Calmy A, Evison JM, et al. Pulmonary arterial hypertension related to human immunodeficiency virus infection: a case series. Clin Infect Dis. 2004; 38: 1740-1749.
8. Graham BB, Bandeira AP, Morrell NW, et al. Pathogenesis of HIV-associated pulmonary hypertension: a review. Am J Respir Crit Care Med. 2017; 195: 709-716.

9. Sitbon O, Lascoux-Combe C, Delfraissy JF, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med. 2008; 177: 108-113.
10. Degano B, Yaici A, Le Pavec J, et al. Long-term outcome of HIV-associated pulmonary arterial hypertension. Eur Respir J. 2009; 33: 376-383.
11. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension: advances in diagnosis and treatment. Eur Respir Rev. 2017; 26: 160112.
12. Tapson VF. Chronic thromboembolic pulmonary hypertension: the overlooked subset of pulmonary hypertension. Am J Med Sci. 2008; 335: 286-290.
13. Lang IM, Madani MM. Surgical treatment of CTEPH. Semin Respir Crit Care Med. 2013; 34: 645-655.
14. Tapson VF, Sterling K, Jones N, et al. A randomized trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the ULTIMA trial. J Am Coll Cardiol. 2014; 64: 2481-2490.
15. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary embolism response teams: multidisciplinary approach to pulmonary embolism treatment. Circulation. 2019; 139: 823-830.
16. Engelberger RP, Kucher N. Ultrasound-assisted thrombolysis for acute pulmonary embolism: a systematic review. Eur Heart J. 2014; 35: 758-764.
17. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002; 40: 780-788.
18. Swigris JJ, Olson AL, Huie TJ, et al. Ethnicity in pulmonary arterial hypertension: confounding or causative? Respir Med. 2012; 106: 730-737.
19. Gall H, Felix JF, Schneck FK, et al. Genetics of pulmonary arterial hypertension: an update. Eur Respir J. 2019; 53: 1801899.
20. Nunes H, Humbert M. HIV-associated pulmonary arterial hypertension: a changing landscape. Eur Respir J. 2019; 53: 1802555.
21. Sitbon O, Gressin V, Speich R, et al. Bosentan for the treatment of human immunodeficiency virus–associated pulmonary arterial hypertension. Am J Respir Crit Care Med. 2004; 170: 1212-1217.
22. Degano B, Yaici A, Le Pavec J, et al. Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. Eur Respir J. 2009; 33: 92-98.
23. Nunes H, Humbert M, Sitbon O, et al. Prognostic factors for survival in human immunodeficiency virus–associated pulmonary arterial hypertension. Am J Respir Crit Care Med. 2003; 167: 1433-1439.
24. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013; 369: 809-818.
25. Badesch DB, Hill NS, Burgess G, et al. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. J Rheumatol. 2007; 34: 2417-2422.
26. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005; 353: 2148-2157.
27. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015; 373: 2522-2533.
28. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014; 129: 479-486.
29. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: The SEATTLE II study. JACC Cardiovasc Interv. 2015; 8: 1382-1392.
30. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in patients with acute intermediate-risk pulmonary embolism: The OPTALYSE PE trial. JACC Cardiovasc Interv. 2018; 11: 1401-1410.
31. Choi JH, Kim NH, Kim HJ, et al. Ultrasound-assisted catheter-directed thrombolysis in patients with submassive pulmonary embolism. Korean Circ J. 2019; 49: 647-658.
32. Patel N, Patel NJ, Agnihotri K, et al. Utilization of catheter-directed thrombolysis and outcomes in patients with pulmonary embolism: A nationwide analysis. J Invasive Cardiol. 2015; 27: 327-332.
33. Restrepo MI, Reyes LF, Rivera R, et al. Pulmonary embolism and innovative therapies in Latin America: advancing in high-risk settings. Colomb Med (Cali). 2021; 52.