

# Improvement of HIV-related pulmonary hypertension after the introduction of an antiretroviral therapy

To the Editors:

The potential impact of combination antiretroviral therapy (CART) on HIV-related pulmonary arterial hypertension (PAH) remains controversial [1–4]. We herein report the case of a dramatic improvement in PAH at the time of the inception of CART in a 19-yr-old female with HIV-1 infection due to mother-to-child transmission. HIV-related PAH was diagnosed in January 2006, when she was stable in stage A2 of the US Centers for Disease Control and Prevention classification without any antiretroviral therapy (table 1). Specific PAH therapy with bosentan was started in January 2006, in combination with oral anticoagulant and diuretic therapy. CART was indicated at that time, but not prescribed owing to patient refusal. Her clinical condition slowly deteriorated (onset of major bilateral lower limb oedema and functional New York Heart Association (NYHA) class IV) until June 2006, leading to hospitalisation: right heart catheterisation revealed further haemodynamic deterioration (table 1). Continuous intravenous epoprostenol therapy was added, and a dose of  $15 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  was reached in September 2006. At that time, it was decided to commence antiretroviral therapy, including lopinavir, ritonavir, emtricitabine and tenofovir disoproxil. Simultaneously, the epoprostenol dose was increased to  $25 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , reached in March 2007. A sustained improvement in her clinical condition was observed from the end of November 2006. Since January 2007, the viral load has been undetectable and the CD4 count has gradually risen to  $>500 \text{ cells}\cdot\text{mm}^{-3}$ . Treatments for PAH and HIV infection have remained unchanged and a right heart catheterisation, performed in September 2007, demonstrated a dramatic improvement (table 1). As the patient was in functional NYHA class I, it was decided to cautiously decrease the *i.v.* epoprostenol doses until its interruption, achieved in February 2008. Bosentan and CART were maintained unchanged. A right heart

catheterisation, performed a few weeks after epoprostenol interruption, confirmed the stable results (table 1).

This case report is remarkable, because first, in contradiction with previous reports on the effectiveness of these drugs in such a setting, a flare-up of PAH occurred despite the step-up in specific therapy with the combination of oral bosentan and *i.v.* epoprostenol. As an example, in the open-label study by SITBON *et al.* [2], which evaluated the administration of bosentan in HIV-related PAH, an improvement in the 6-min walk distance was observed in all patients at week 16. Secondly, a dramatic clinical and haemodynamic improvement paralleled the introduction of CART and, furthermore, the withdrawal of epoprostenol was achieved. Data on the impact of CART on PAH are scarce and conflicting, with reports of either improvement [5, 6] or worsening [7, 8]. One open-label 6-month study compared, in 36 previously untreated HIV-infected patients with PAH, the effect of the introduction of CART alone and the combination of CART and bosentan [9]: at week 24, a significant decrease in mean pulmonary artery pressure from baseline was observed in the subgroup receiving the combination of CART and bosentan; this was not observed in the subgroup receiving CART alone. As case reports point to variable therapeutic responses of PAH to antiretroviral therapies, larger studies including HIV-related PAH patients with high CD4 counts are needed [10].

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**TABLE 1** Evolution of main clinical, biological and haemodynamic parameters

Date	January 2006	June 2006	August 2006	September 2006 <sup>#</sup>	November 2006	January 2007	June 2007	September 2007	March 2008
NYHA class	III	III	IV	IV	III	II	II	II	I
6MWD m	324	328	257	278	350	424	534	563	623
CD4 cells·mm <sup>-3</sup>	454	471	316	404	657	268	480	510	850
Viral load copies log <sub>10</sub> mL <sup>-1</sup>	4.96	4.63	4.97	2.21	2.41	1.32	1.32	1.32	1.32
Pro-BNP pg·mL <sup>-1</sup>	4442	2533	3943	4763	4562	1890	124	192	157
$\bar{P}_{pa}$ mmHg	65	70						31	28
$P_{ra}$ mmHg	12	16						4	4
PVR Wood units	22.2	25						5	5.4
Cardiac index L·min <sup>-1</sup> ·m <sup>-2</sup>	1.8	1.8						3.1	2.9

<sup>#</sup>: introduction of combination antiretroviral therapy was performed closely after the September 2006 check-up. NYHA: New York Heart Association; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide;  $\bar{P}_{pa}$ : mean pulmonary artery pressure;  $P_{ra}$ : right atrial pressure; PVR: pulmonary vascular resistance.

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## Intravenous $\alpha_1$ -antitrypsin in a child with deficiency and severe lung disease

Hereditary  $\alpha_1$ -antitrypsin deficiency presents with symptomatic obstructive and suppurative lung disease usually in the fourth decade in individuals with a history of smoking [1, 2].

A mature neonate had prolonged icterus due to  $\alpha_1$ -antitrypsin deficiency (PiZZ-type). At 4 weeks of age she developed transient middle lobe atelectasis and persisting hyperinflation on chest radiographs. The patient was hospitalised for virus induced wheezing, bronchopneumonic episodes and atelectasis of the middle lobe many times throughout childhood. Chest computed tomography imaging showed basal emphysema and bronchiectasis in the middle lobe and lingula. Heavy passive smoke exposure was known to have occurred from infancy onward, with active smoking possibly occurring in adolescence for brief periods.

She attended our centre regularly from the age of 12.5 yrs. Cystic fibrosis, ciliary dyskinesia, structural bronchopulmonary abnormalities, gastroesophageal reflux-induced lung disease, immune deficiency states, allergies and allergic asthma were excluded. Treatment intensity remained high over the years. At age 14 yrs, weekly intravenous augmentation with 60 mg·kg<sup>-1</sup>·body weight<sup>-1</sup> of  $\alpha_1$ -antitrypsin (Prolastin; Bayer, Wuppertal, Germany) was started. Continuous treatment with bronchodilators, inhaled steroids and cefuroxime was left unchanged. Her overall condition improved markedly, and

the number of exacerbations, defined according to ANTHONISEN *et al.* [3], was reduced (fig. 1a) and lung function studies showed decreased airways obstruction and decreased hyperinflation (fig. 1b). Arrest of basal emphysematous changes and bronchiectasis was seen on computed tomography after 4 yrs of treatment. Before  $\alpha_1$ -antitrypsin therapy her bodyweight had been below or at the 3rd percentile for many years and we had encouraged her to take supplemental calories (fig. 1c). Her weight increased rapidly, in association with her improved pulmonary condition, although unintended weight gain subsequently occurred, with dietary intervention being successful only recently.

This is an example of the characteristic course of  $\alpha_1$ -antitrypsin lung disease, which is commonly observed in adults, occurring in a teenager. Among the reasons for such a precocious manifestation of this inherited disease may be as yet unknown endogenous factors and clearly exogenous factors. These included long-standing passive and later possibly active tobacco smoke exposure, frequent and severe lower respiratory tract infections, significant psychosocial family problems and, potentially, malnutrition.

Based on an urgent need for stabilisation of the lung disease and the experience in the adult population, *i.v.*  $\alpha_1$ -antitrypsin-augmentation therapy was started. According to current