Lung transplantation in HIV-positive patients: a European retrospective cohort study

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To the Editor:

Steady progress in antiretroviral therapy, with the introduction of new medications and the earlier institution of more aggressive treatment regimens, has markedly improved the outcomes of HIV infection [1]. The longer life expectancy provided by optimal management is associated with an increased risk of eventually developing chronic medical conditions, including lung diseases and pulmonary arterial hypertension (PAH), many of which can be treated but not cured [2, 3].

Transplantation of organs from HIV-positive donors was a federal crime in the US until the HIV Organ Policy Equity (HOPE) Act was signed into law in 2013 to allow transplantation between HIV-positive individuals. In Europe, legislation varies across countries, but transplantation from HIV-positive donors to HIV-positive recipients is usually allowed [4]. Nonetheless, HIV infection has often been considered to contraindicate organ transplantation [5]. Recently, improvements in the outcomes of both HIV infection and transplantation have prompted several centres to adopt a case-by-case approach to patients with controlled HIV infection. Over the past decade, acceptable outcomes have been reported in 11 lung transplant (LTx) recipients and one heart-LTx recipient [6–8]. However, data on LTx in HIV-positive patients remain limited.

The objective of this multicentre retrospective study was to obtain further information on key transplantation- and HIV-related outcomes of HIV-positive patients treated with LTx. We identified 68 LTx centres in 22 European countries *via* the International Society for Heart and Lung Transplantation (ISHLT) registry and by personal knowledge. Each centre received a 54-item questionnaire seeking information, including outcome data, about consecutive HIV-positive patients who underwent LTx in 2007–2021. For each patient, data were recorded until 1 September 2021. Performance status was rated on the World Health Organization scale (0, fully active; 5, death) [9]. Baseline variables were described as median (25th–75th percentiles) if continuous, and as percentages if categorical, and were compared by applying Fisher's exact test or the Kruskal–Wallis test, as appropriate. Median follow-up was 25 months and the Kaplan–Meier method was applied to assess survival. Our institutional review board (*Groupe Hospitalier Paris-Saint Joseph*) and the local ethics committees for each participating centre approved the study protocol (*Groupe Éthique Recherche Médicale*, IRB 00012157). The requirement for informed consent was waived in compliance with legislation about retrospective studies of anonymised data.

Among the 68 centres, 25 returned the completed questionnaire, allowing the identification of 22 HIV-positive LTx recipients (table 1). The viral load was negative in all patients at listing and did not change significantly after transplantation. At transplantation, no patient was receiving protease inhibitor therapy. A change in the antiretroviral regimen before LTx was deemed necessary in three (15%) patients, due to osteoporosis, renal insufficiency, and an unknown reason, respectively. Interestingly, PAH, a condition associated with HIV infection [10], was the main reason for LTx in our cohort. Median follow-up was 25 (6–52) months after transplantation. Of the eight (40%) patients with post-LTx infections requiring admission, six had bacterial pneumonia, one pulmonary invasive aspergillosis, and one gastroenteritis. Seven patients received induction therapy, consisting in anti-thymocyte globulin in two and basiliximab in five. During follow-up, acute cellular rejection, antibody-mediated rejection, and chronic allograft dysfunction developed in 7/19 (37%), 2/19 (11%), and 5/19 (26%) patients, respectively. None of

Shareable abstract (@ERSpublications)
In selected HIV-positive patients, lung transplantation provided good transplant and patient survivals, without more infections than reported in HIV-negative patients. Further work is needed to determine the best immunosuppressive regimens. https://bit.ly/3kyLnDL

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TABLE 1 Main features of the 22 study patients

	Overall (n=22)	p-value
Baseline characteristics		
Male	14 (64)	
Recipient age (years)	49 (45–55)	
Caucasian	13 (59)	
Transplantation indications		
Pulmonary arterial hypertension	7 (32)	
Fibrosis	5 (23)	
COPD	4 (18)	
Cystic fibrosis	3 (14)	
Other	3 (14)	
Transplantation procedure		
Double	20 (91)	
Single	2 (9)	
Induction therapy	7 (32)	
HIV characteristics		
CD4 T-cell count (cell·mm^{-3})		0.91
Before transplantation	514 (351–670)	
After transplantation[#]	484 (229–622)	
RNA viral load (copies·mL^{-1})		0.99
Before transplantation	0	
After transplantation[#]	0	
History of opportunistic infection[¶]	2 (9)	
History of acquired immunodeficiency syndrome[¶]	2 (9)	
Hepatitis B surface antigen positivity	6 (27)	
Hepatitis virus C antibody positivity	4 (18)	
Antiretrovial therapy regimen at transplantation		
Nucleoside reverse transcriptase inhibitors/integrase inhibitors	13 (62)	
Non-nucleoside reverse transcriptase inhibitors/integrase inhibitors	4 (19)	
Nucleoside reverse transcriptase inhibitors/non-nucleoside reverse transcriptase inhibitors	3 (14)	
Integrase inhibitors	1 (5)	
Antiretrovial therapy change before transplantation (n=20)	3 (15)	
Post-operative outcome		
Infections requiring hospitalisation during first year (n=20)	8 (40)	
Acute cellular rejection (n=19)	7 (37)	
Antibody-mediated rejection (n=19)	2 (11)	
Chronic lung allograft dysfunction at last follow-up (n=19)	5 (26)	
Malignancy (n=21)	3 (14)	
Estimated glomerular filtration rate (mL·min^{-1} per 1.73 m^2)		0.02
Before transplantation	90 (80–111)	
After transplantation[+]	73 (53–90)	
Last known status		
World Health Organization scale		
0	9 (41)	
1	4 (18)	
2	4 (18)	
3	5 (23)	
Last known immunosuppressive regimen		
Tacrolimus + steroids + MMF	15 (67)	
Cyclosporine + steroids + MMF	2 (10)	
Tacrolimus + steroids + everolimus	2 (10)	
Other	3 (13)	

MMF: mycophenolate mofetil. [#]: evaluated at last follow-up; [¶]: the two patients with a history of opportunistic infection are the same as the two with acquired immunodeficiency syndrome; [+]: evaluated 1 year after transplantation.

the patients with rejection episodes had received induction therapy. The malignancies diagnosed during follow-up consisted of one case each of colonic adenocarcinoma, Kaposi's sarcoma, and squamous cell carcinoma of the skin. The estimated glomerular filtration rate decreased significantly over the first post-transplantation year. Four patients died during follow-up, including two within the first three post-operative months, from haemorrhagic shock and grade-3 primary graft dysfunction, respectively. Post-transplant survival rates after 1, 3 and 5 years were 79%, 79% and 79%, respectively. At last follow-up, 13 (59%) patients were fully active and independent.

To date, this is the largest case series of LTx in HIV-positive recipients. The good outcomes in highly selected patients validate and expand upon previous reports. A multicentre study by Koval *et al.* [6] included 29 HIV-positive patients who underwent heart (n=21), lung (n=7), or heart–lung (n=1) transplantation in 2000–2016. In the eight LTx recipients, 1-, 3- and 5-year survival rates were 86%, 80% and 75%, *i.e.*, similar to those in the overall LTx population in the ISHLT registry.

The 1-year acute cellular rejection rate in HIV-positive patients was 37%, whereas the rejection rate in an overall population of patients who underwent LTx in 2005–2018 was 26% [11]. Nonetheless, these early rejections did not translate into decreased graft survival during the first 5 years [11]. Higher rejection rates in HIV-positive recipients have been reported in several studies [5, 11, 12]. The impact of HIV-associated immune activation has been under-recognised and remains insufficiently understood, notably in the transplant arena. Cautious immunosuppression aimed at avoiding an unacceptable risk of infection has long been blamed for the higher rejection rates in HIV-positive recipients. Thus, according to the Scientific Registry of Transplant Recipients, HIV-positive kidney and heart recipients were less likely to undergo induction immunosuppression and to receive anti-thymocyte globulin or alemtuzumab [5, 13]. In our cohort, only 32% of patients received induction therapy. In contrast, the proportion of ISHLT-registry patients given induction therapy has risen steadily, reaching 80% in 2017 [11].

Drug interactions, chiefly involving protease inhibitors, may affect maintenance immunosuppressive therapy, thereby contributing to the higher rejection rate in HIV-positive patients [14]. Of note, three (15%) of our patients required a change in their antiretroviral regimen before LTx, but in none was the change motivated by concern about interactions with calcineurin inhibitors. Overall, the main regimen at LTx was a combination of nucleoside reverse transcriptase inhibitors and integrase inhibitors, without pharmacological boosters.

HIV infection remained controlled in all the study patients, with stable $CD4^+$ T-cell counts and no instances of viraemia or AIDS-related events. The 40% frequency of infectious episodes after LTx was not different from that reported in the overall LTx population [15]. Last, although four patients received tenofovir disoproxil, a drug potentially associated with renal tubulopathy, the significant decrease in the estimated glomerular filtration rate during the first post-transplant year was consistent with results in HIV-negative LTx recipients [16]. Of note, this finding suggests good patient selection and may also be related to the more cautious approach to immunosuppression.

The general applicability of our findings deserves discussion. Only 25 of the 68 invited centres returned the completed questionnaire, and we cannot rule out selection bias towards patients with better outcomes. Although this is the largest study of LTx in HIV-positive patients, the sample size remains small, limiting the ability to draw definitive conclusions. As the population with well-controlled HIV infection grows, so, too, will the number of HIV-positive LTx candidates who might be included in prospective studies.

In summary, LTx is a successful treatment modality in selected HIV-positive patients with advanced lung disease. Until further data become available, the high rejection rates in HIV-positive LTx recipients support the use of immunosuppressive regimens similar to those given to HIV-negative patients. Information from prospective studies is needed to optimise the care of this specific population.

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