



THE SCIENCE OF TOMORROW STARTS **TODAY**

AMERICAN TRANSPLANT CONGRESS

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Update on HIV-to-HIV thoracic transplant

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Update on HIV-to-HIV thoracic transplant

I have financial relationship(s) with:

Grant support, Merck

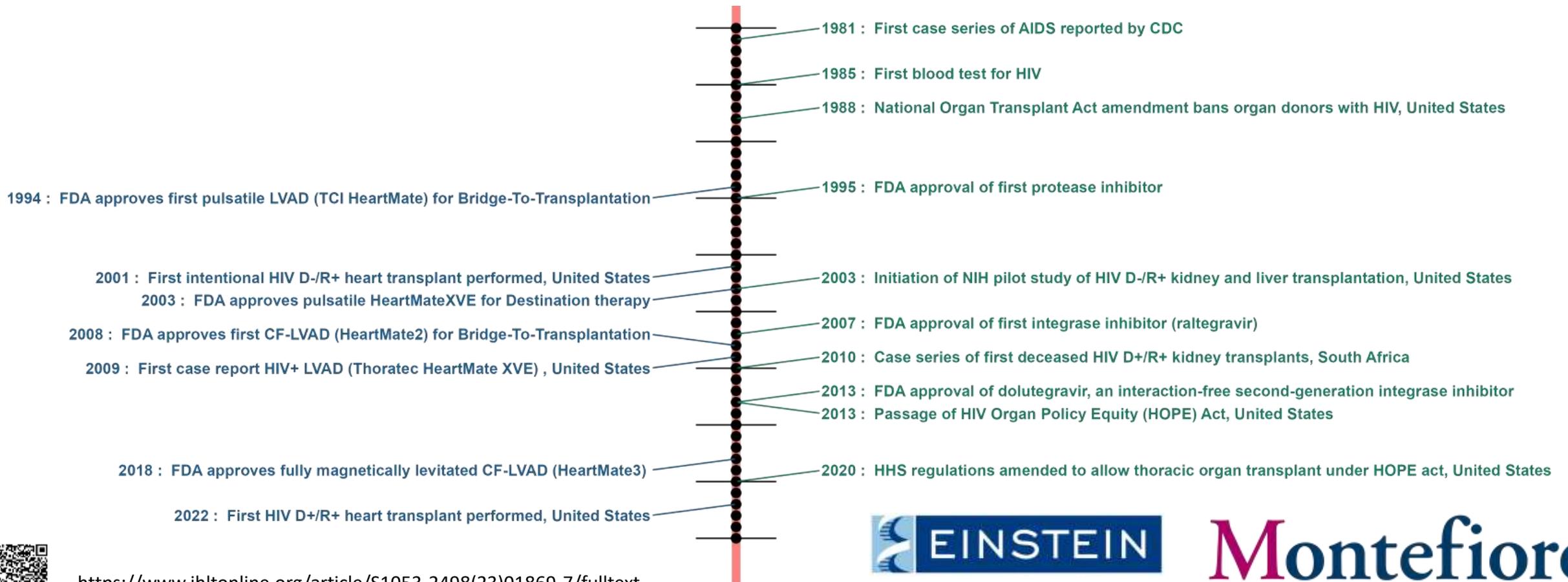
AND

My presentation does not include discussion of off-label or investigational use of pharmaceuticals.

Update on HIV-to-HIV thoracic transplant

- HIV D-/R+ heart transplantation
- HIV D+ heart transplantation
- HIV D-/R+ lung transplantation
- HIV D+/R+ lung transplantation

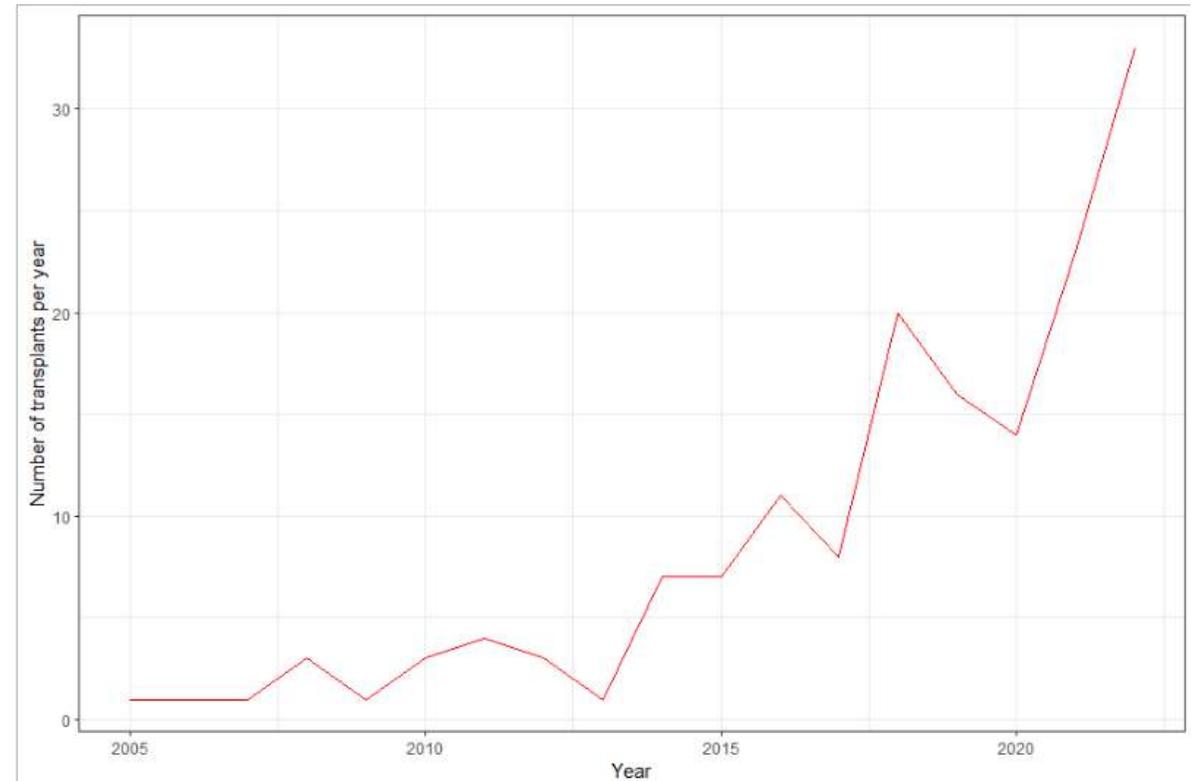
Progress in advanced heart failure care and in care for PLWH



[https://www.jhltonline.org/article/S1053-2498\(23\)01869-7/fulltext](https://www.jhltonline.org/article/S1053-2498(23)01869-7/fulltext)

Current state of HIV D-/R+ heart transplant

- Currently 158 HIV D-/R+ heart transplants to date performed in US, including 2 heart-lung recipients
 - Half of transplants performed at 16 centers; most have performed none
 - The UNOS database reached this number of D-/R+ kidney transplants in 2006 and D-/R+ liver transplants in 2009
 - Currently 30+ transplants/year



HIV D-/R+ heart outcomes

No
difference

- Survival
- Graft vasculopathy
- Malignancy

Higher rates
in PLWH

- Acute rejection prior to primary discharge (38.7% versus 17.7%)
- Antirejection treatment administration (26.7% versus 10.4%)

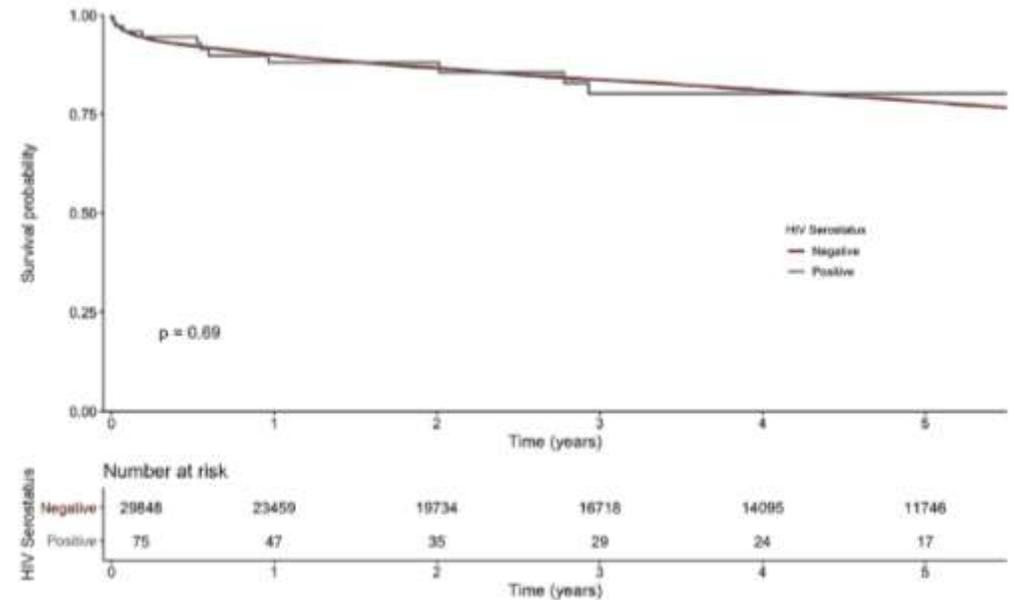
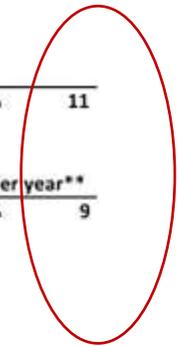
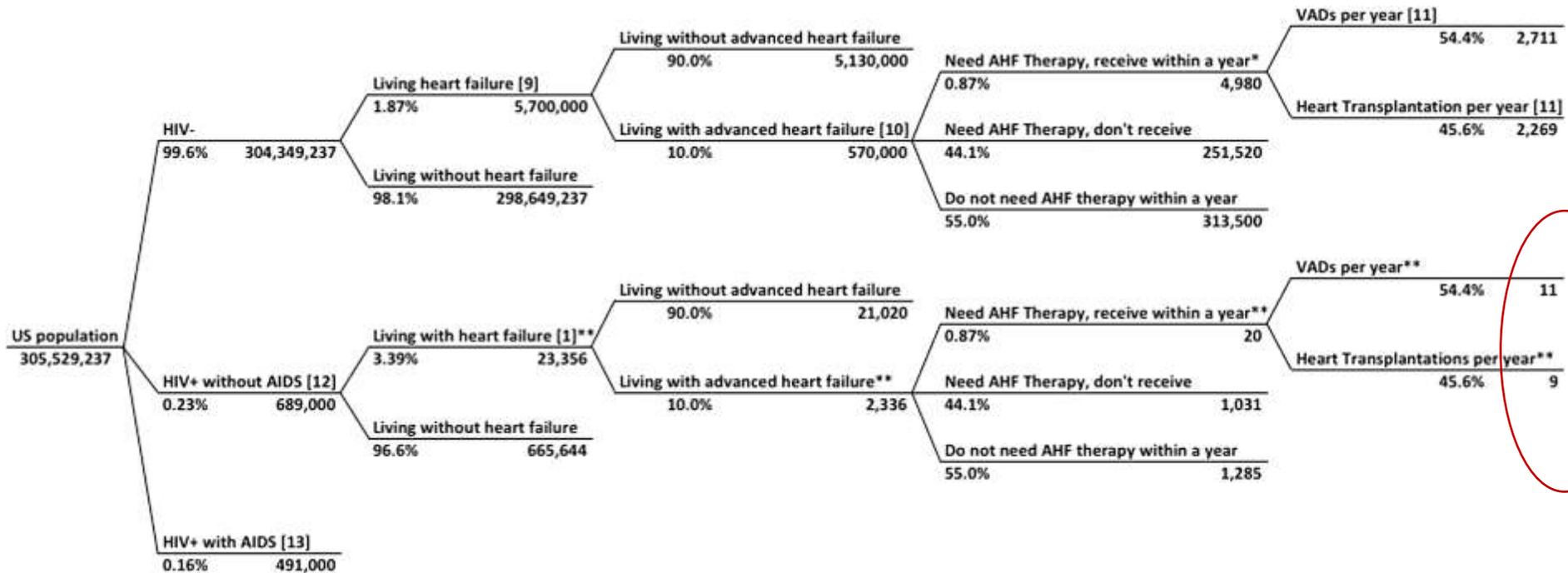


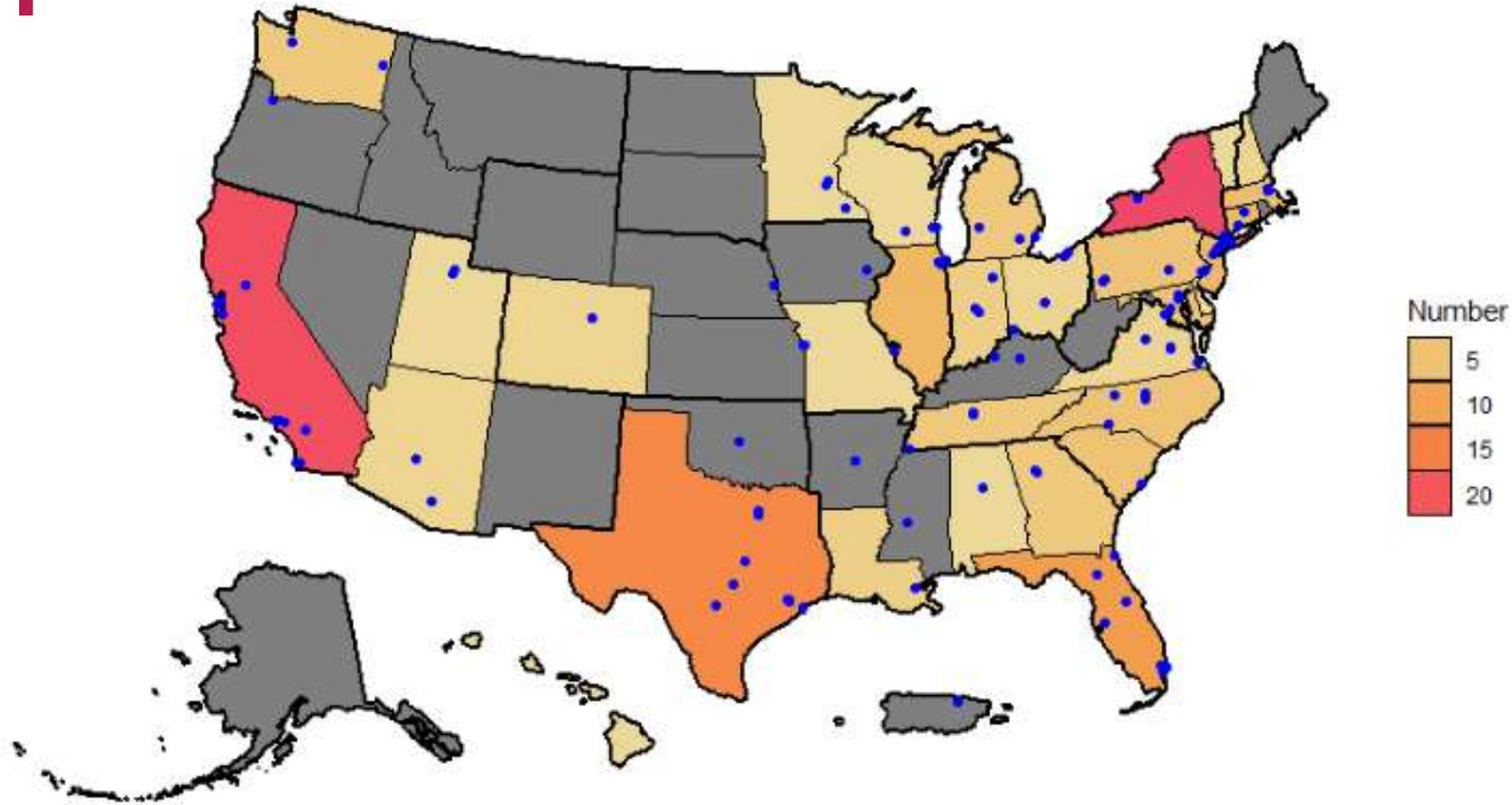
Figure 1. Kaplan-Meier curve for orthotopic heart transplant patients stratified by recipient HIV status: negative (red line), or positive (gray line). The P value represents the two-sided log-rank test. Numbers at risk are provided at the bottom of the graph.



Does the current rate and pattern of transplant meet the need?



Does the current rate and pattern of transplant meet the need?



HIV D+ donors: what are the concerns?

Systolic dysfunction/HFrEF

- Cumulative viremia
- Nadir CD4 count

Diastolic dysfunction/HFpEF

- Age
- Traditional risk factors
- Nadir CD4 count?

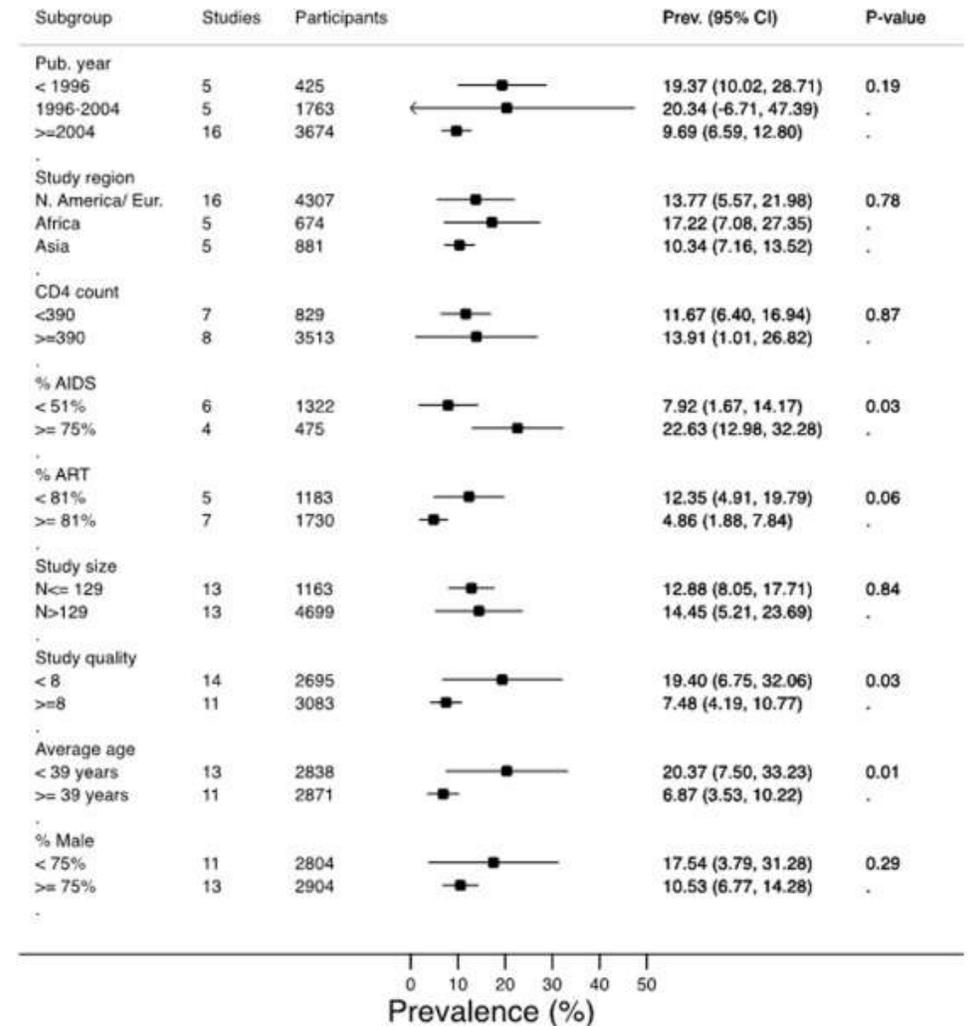
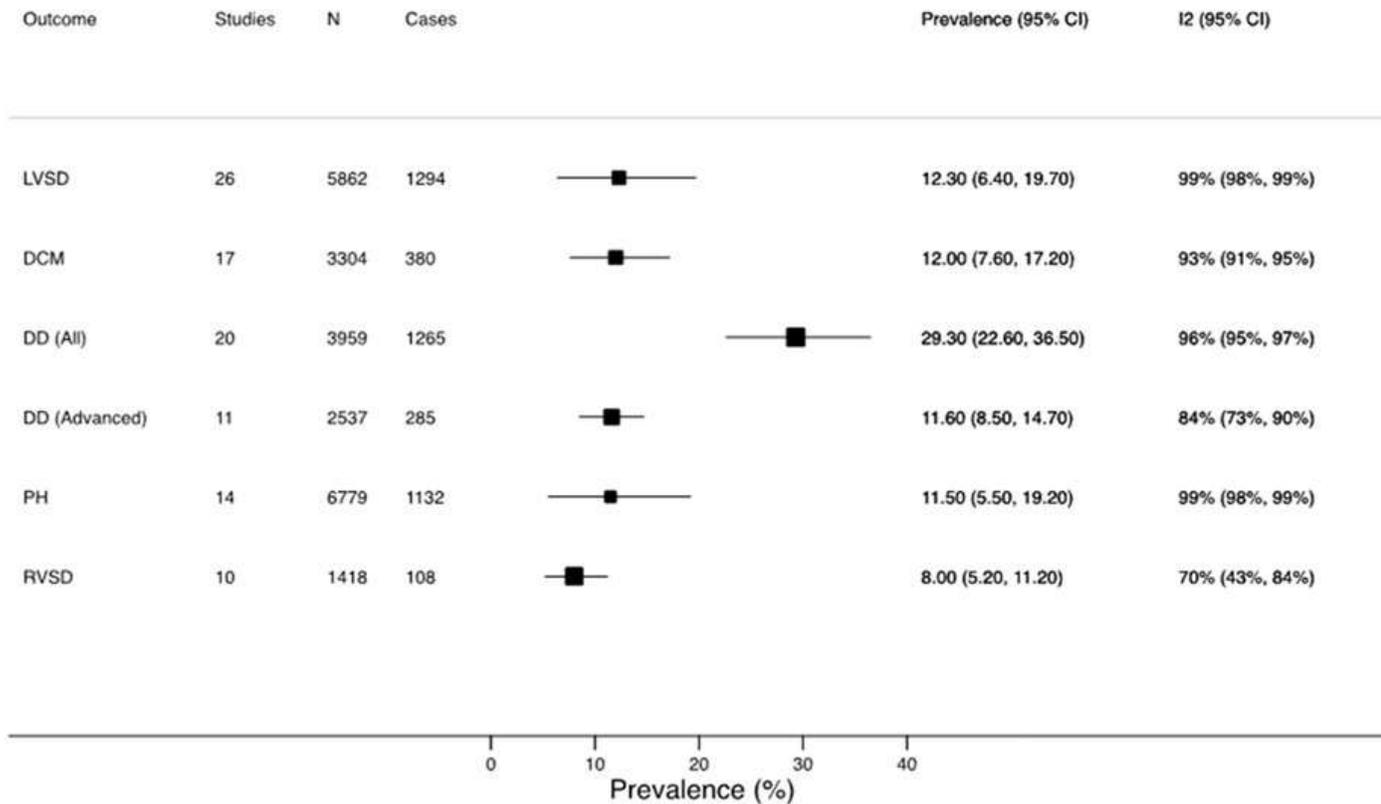
Premature coronary artery disease

- Cumulative viremia
- Tobacco
- Inflammation
- Specific ARVs?

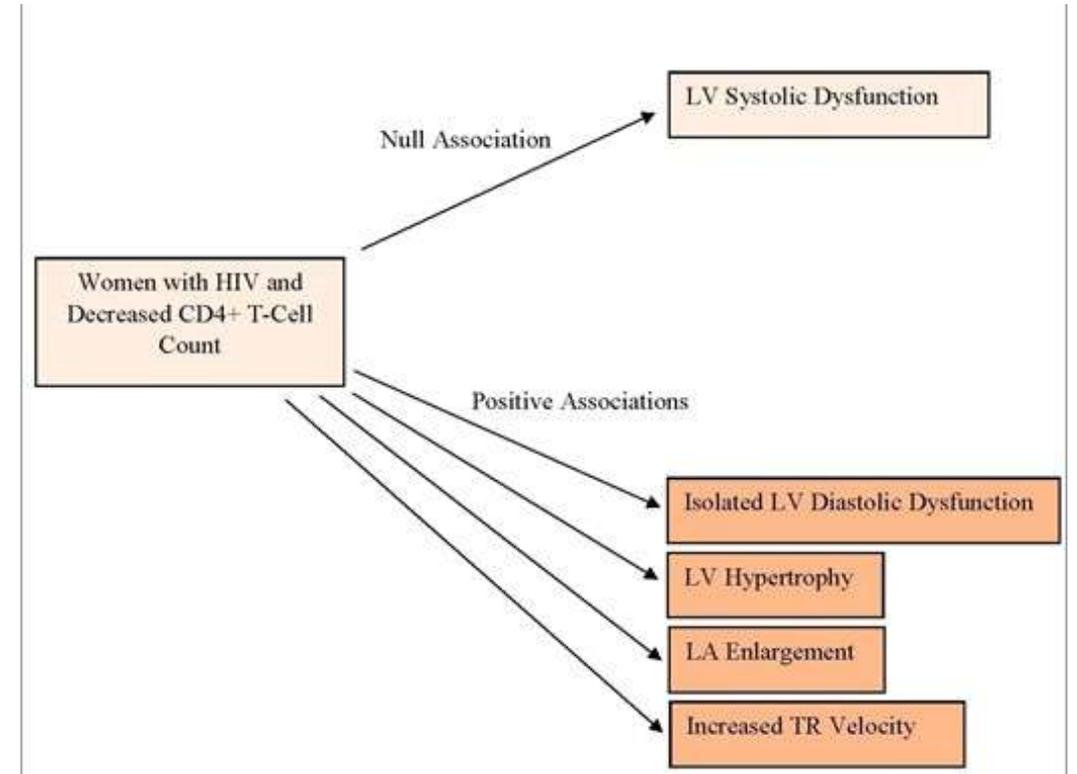
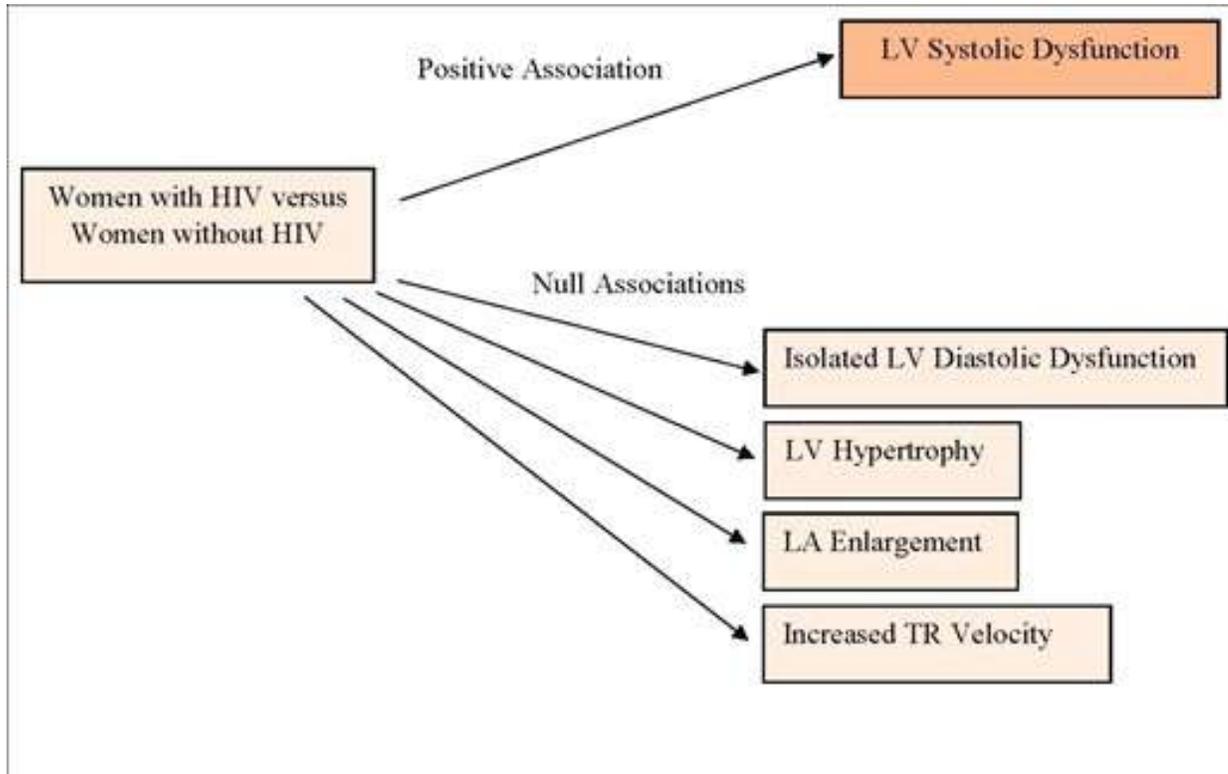
Epidemiology. 2019 Jan;30(1):69-74.
J Am Heart Assoc. 2016 Jun 27;5(6):e003371.



High prevalence

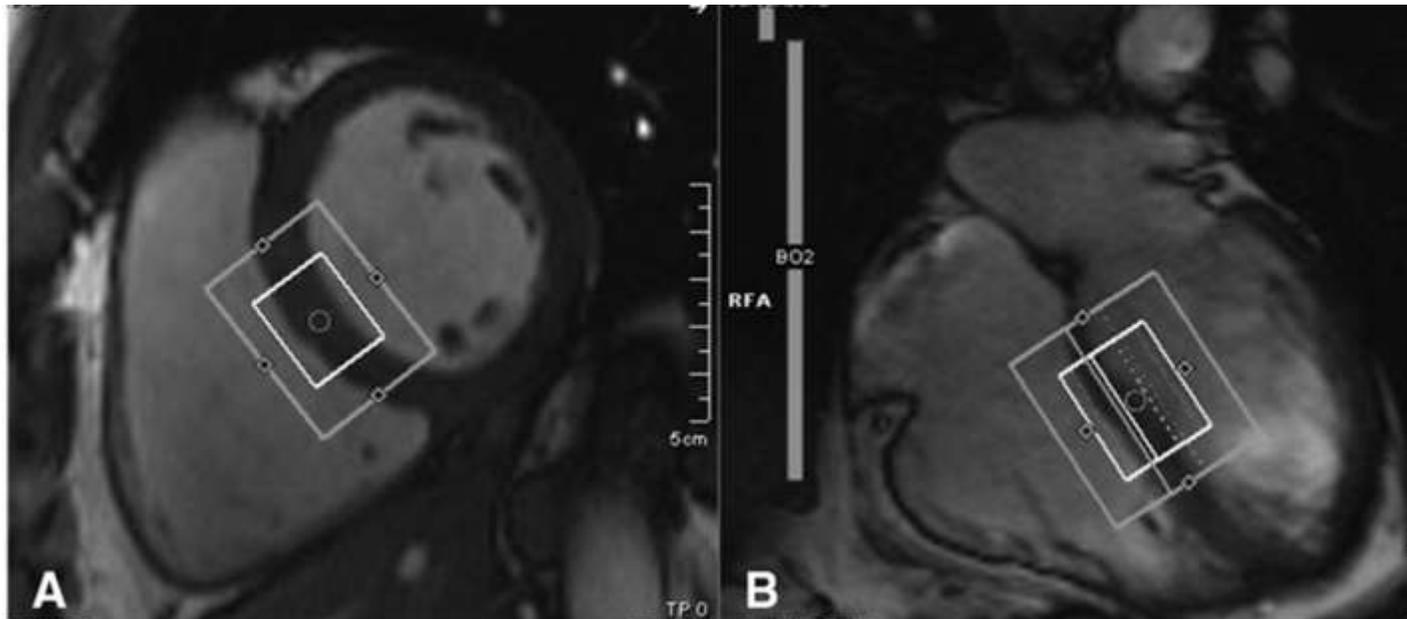


Systolic and diastolic dysfunction in women with HIV



Most people with HIV have abnormal cardiac MRI findings

- Myocardial fibrosis in 76% of asymptomatic PLWH compared with 13% of control subjects ($P < 0.001$)



Circulation. 2013 Aug 20;128(8):814-22.



HIV D+/R- heart transplants in the ARV era

Chicago, 2006	Survived three years Death due to non-adherence	Mild rejection treated with oral prednisone
Taiwan, 2012	Well-functioning graft four years-post transplant	Moderate rejection Coronary allograft vasculopathy

HIV D+/R+ transplant

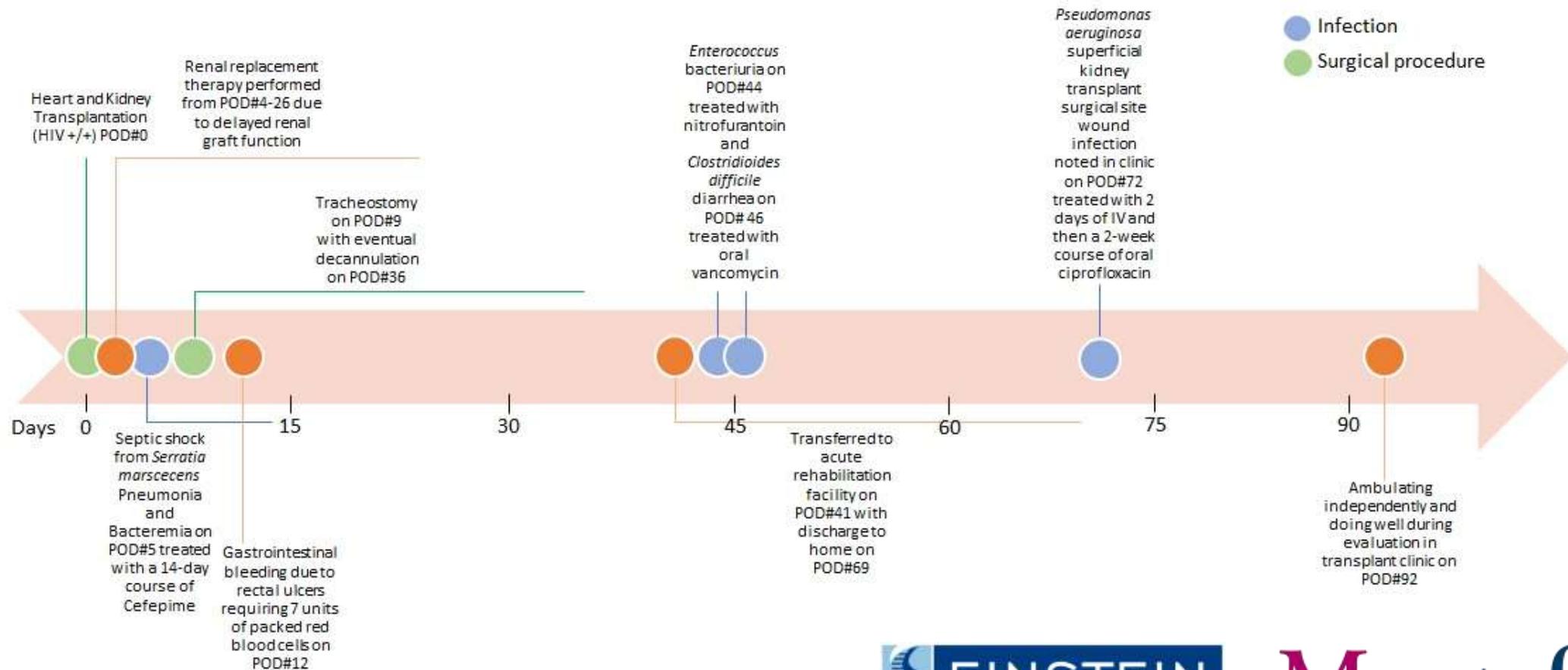


- Two centers approved to perform D+/R+ heart transplants

HIV D+/R+ transplant

- Our center established very strict donor criteria for our first D+/R+ transplant:
 - Age < 35
 - Normal angiography
 - Donor after brain death
 - Short ischemic time

HIV D+/R+ heart transplant



Work up of the HIV D+ donor

- Angiography indications for heart donors vary by center
 - **Age>40**
 - Hypertension
 - Diabetes
 - Tobacco
 - Hyperlipidemia
 - Family history of premature coronary artery disease
 - Cocaine use



HIV D+ donor evaluations

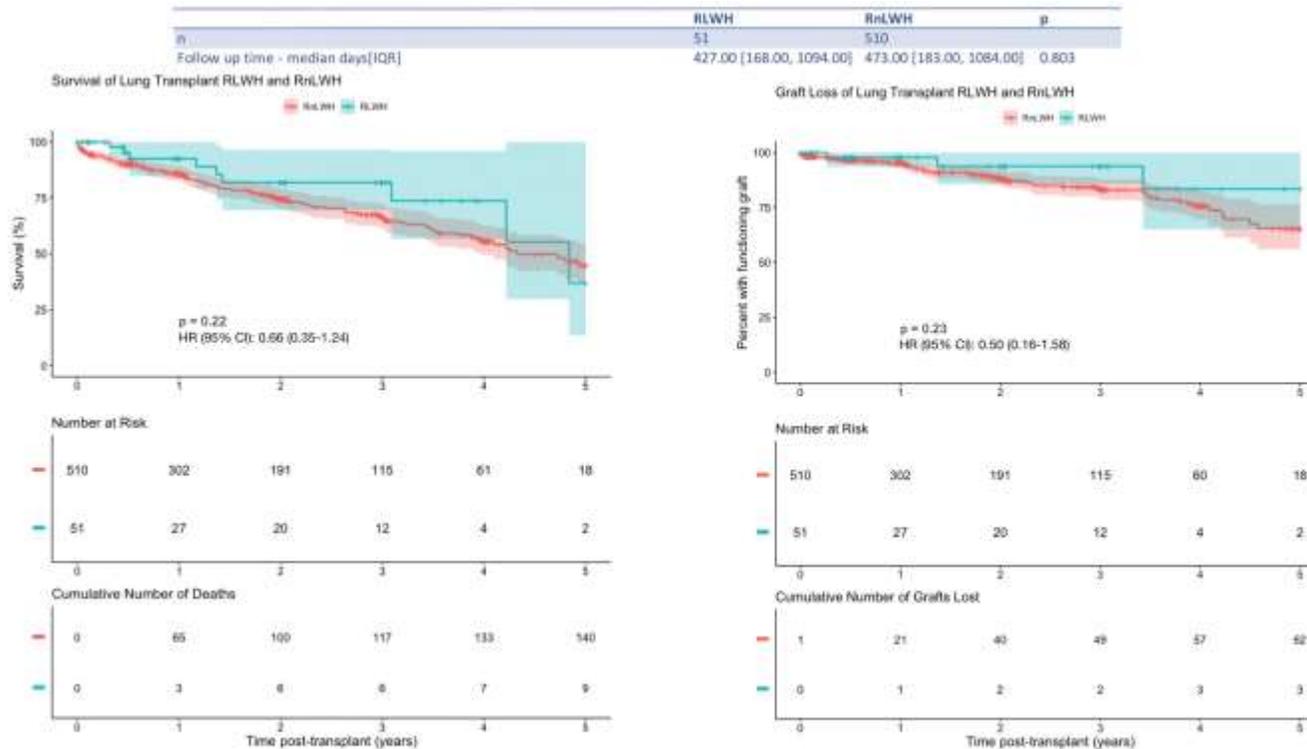
- The extent to which these criteria could be relaxed for future transplants will need be determined
- Should HIV be an indication for, or affect the age limit for, angiography?

HIV D-/R+ lung transplant

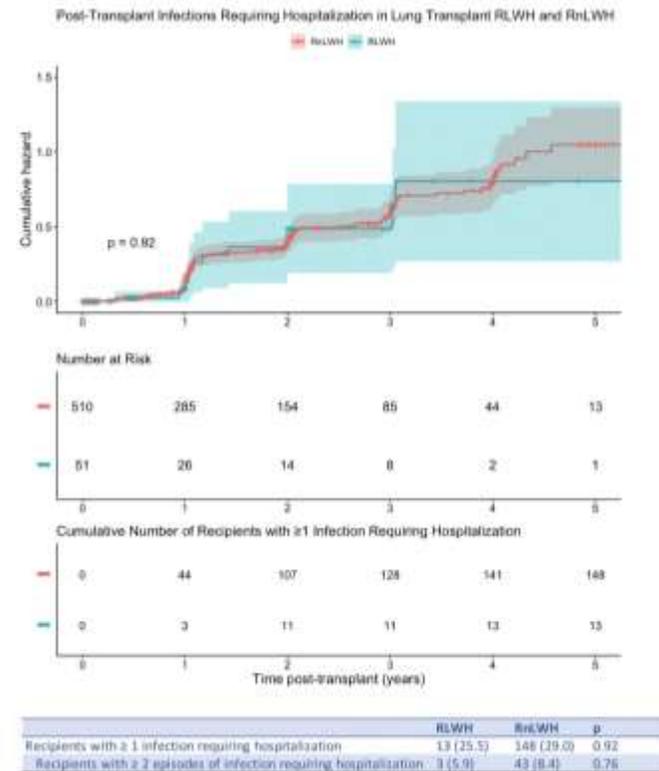
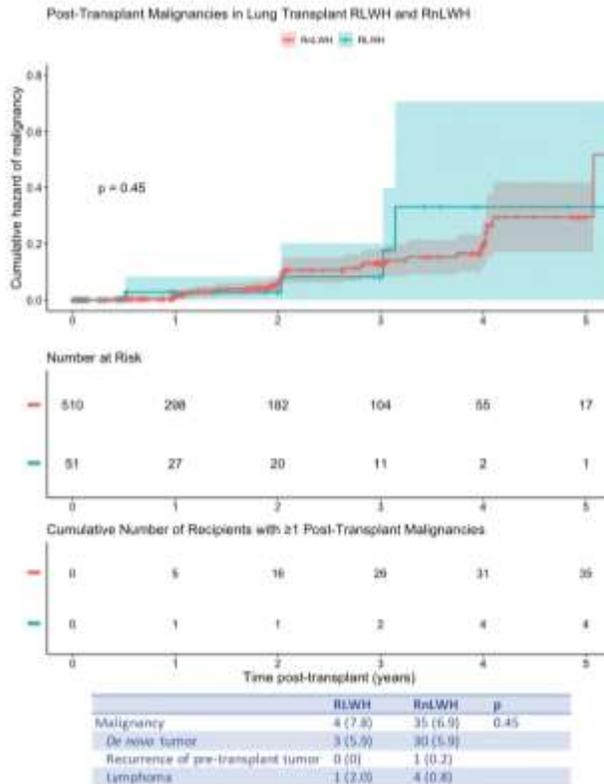
- Currently 70 HIV D-/R+ lung transplants to date performed in US as per the SRTR, including the two aforementioned heart-lung transplants
 - The UNOS database reached this number of D-/R+ kidney transplants in 2004 and D-/R+ liver transplants in 2005
- Well over half performed in last four years
- Four centers responsible for 50+% of transplants
- Recipient selection criteria an open question



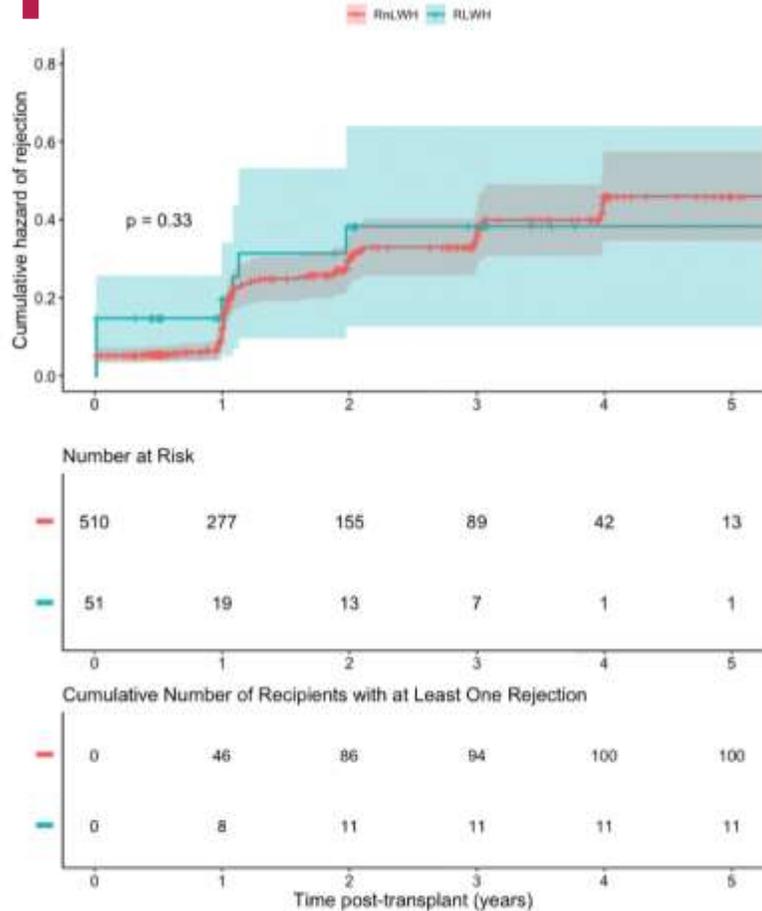
Equivalent survival in lung transplant recipients with HIV



Equivalent malignancy rate in lung transplant recipients with HIV



Increased rejection in lung transplant recipients with HIV



	RLWH	RnLWH	p
Recipients with ≥1 episode of acute rejection requiring changes in IS	11 (21.6)	100 (19.6)	0.33
Recipients with acute rejection during index admission	7 (13.7)	26 (5.1)	0.022
Recipients with two or more episodes of rejection	4 (7.8)	19 (3.7)	0.24

Immunosuppressant	RnLWH	RLWH	p
n	47	440	
Corticosteroids	44	387	0.338
Basiliximab	41	361	0.373
Thymoglobulin	0	24	
Rituximab	1	2	
Alemtuzumab	0	19	

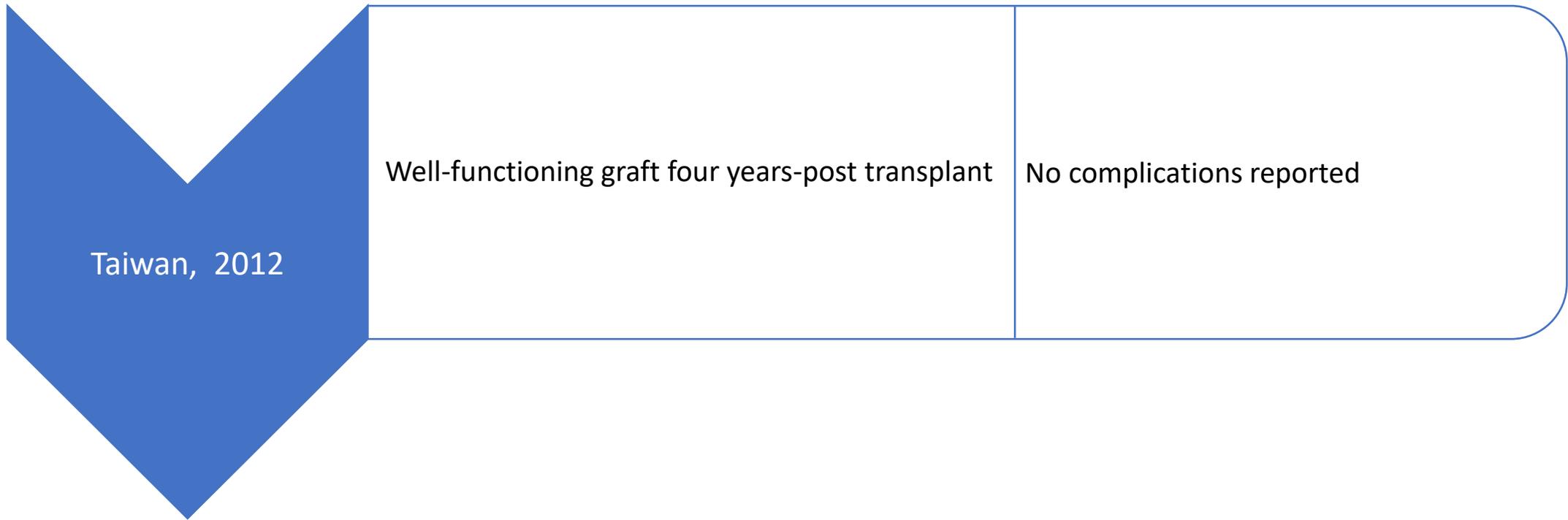


Similar outcomes in European experience

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)	



HIV D+ lung experience

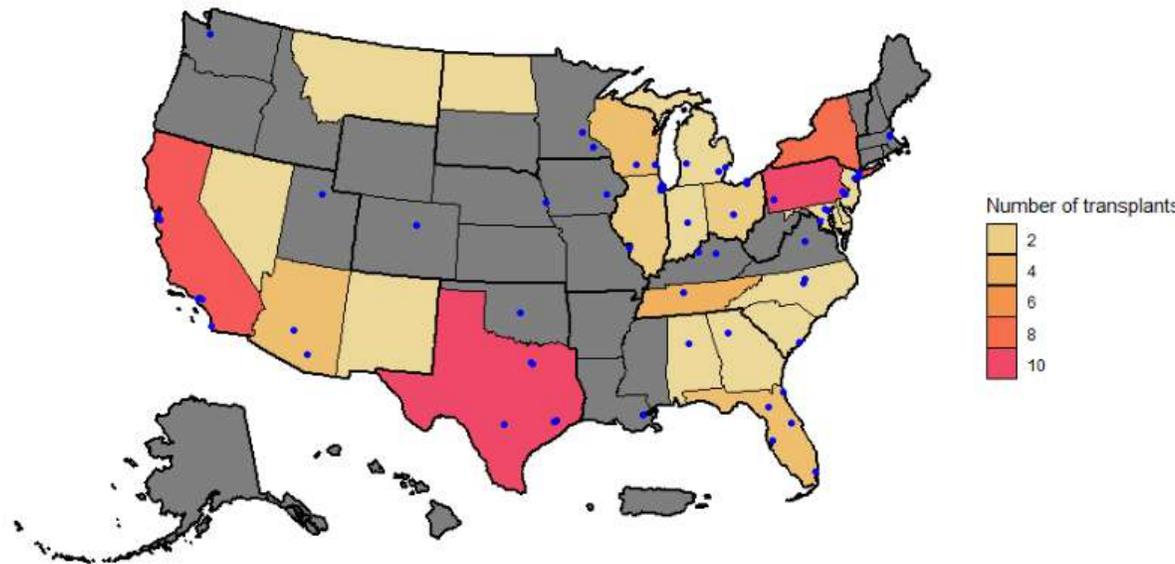


ATC 2016, abstract C292



HIV D+/R+ lung transplant not yet performed to date

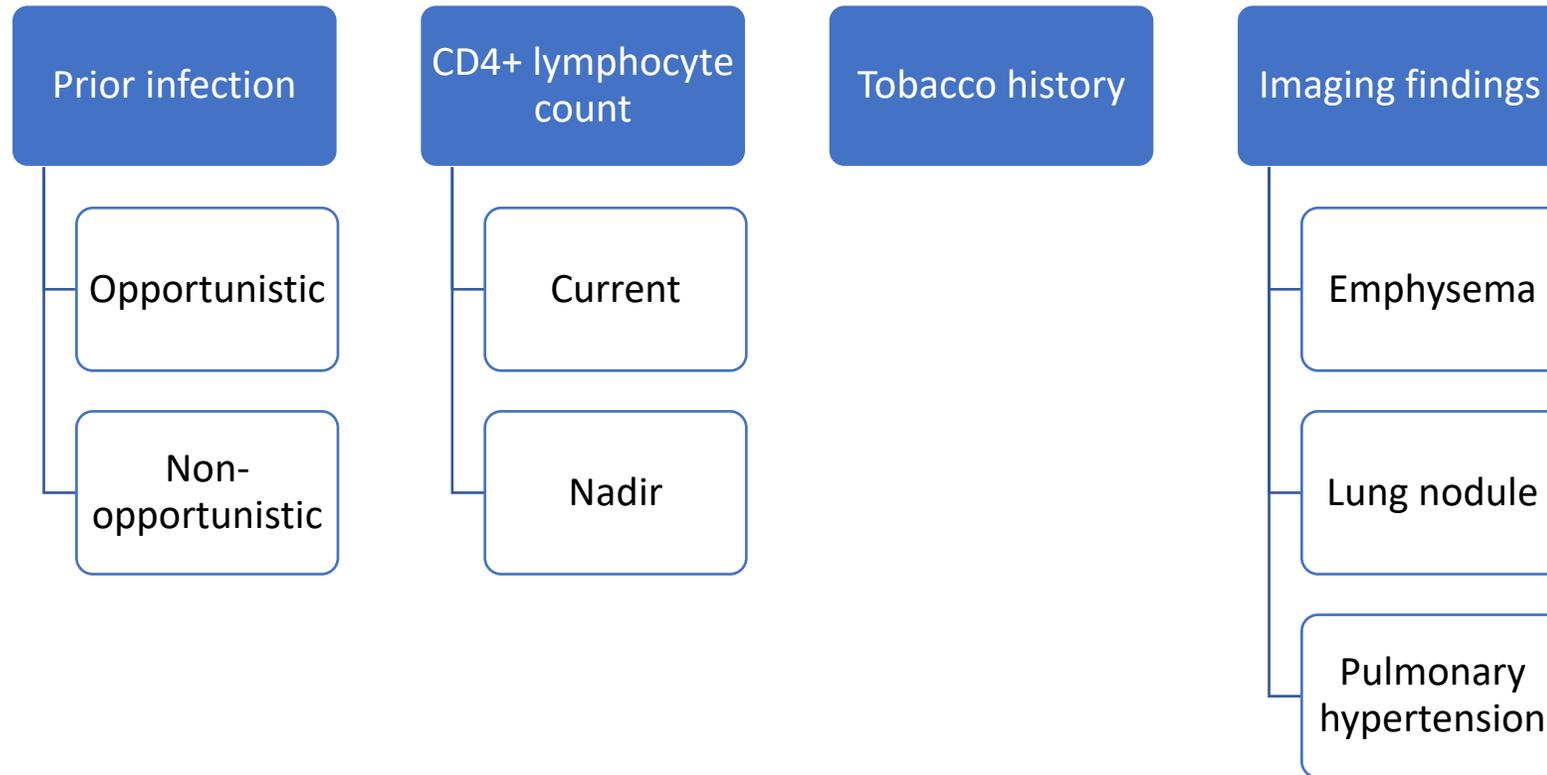
- Two centers as per SRTR meet current volume criteria
- More may meet relaxed criteria depending on final DHHS decision



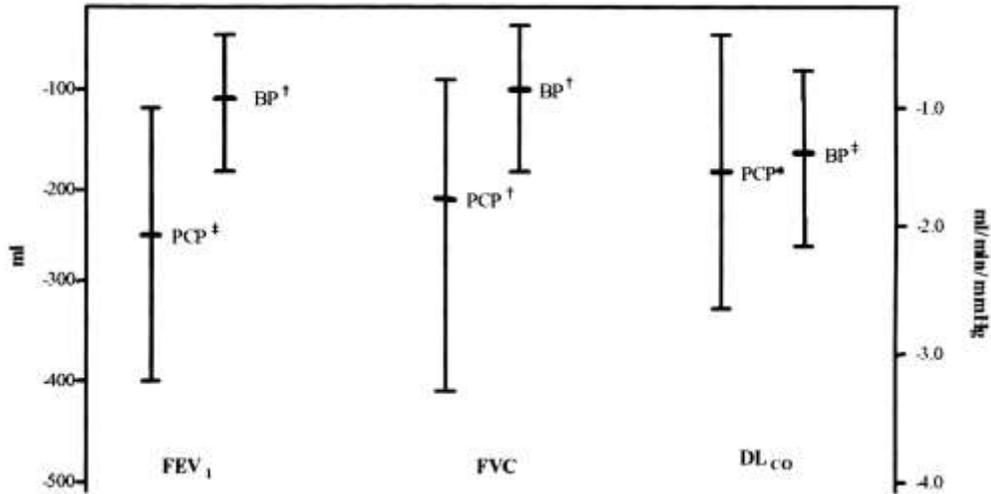
HIV D+/R+ lung transplant will pose unique challenges

- Effects on the lung that may not show up on
 - Pre-transplant laboratory testing
 - Imaging
 - Biopsies
- Hidden opportunistic infections
 - PJP (?mitigated by prophylaxis?)
 - *Mycobacterium avium* complex
 - Tuberculosis
 - Endemic fungi

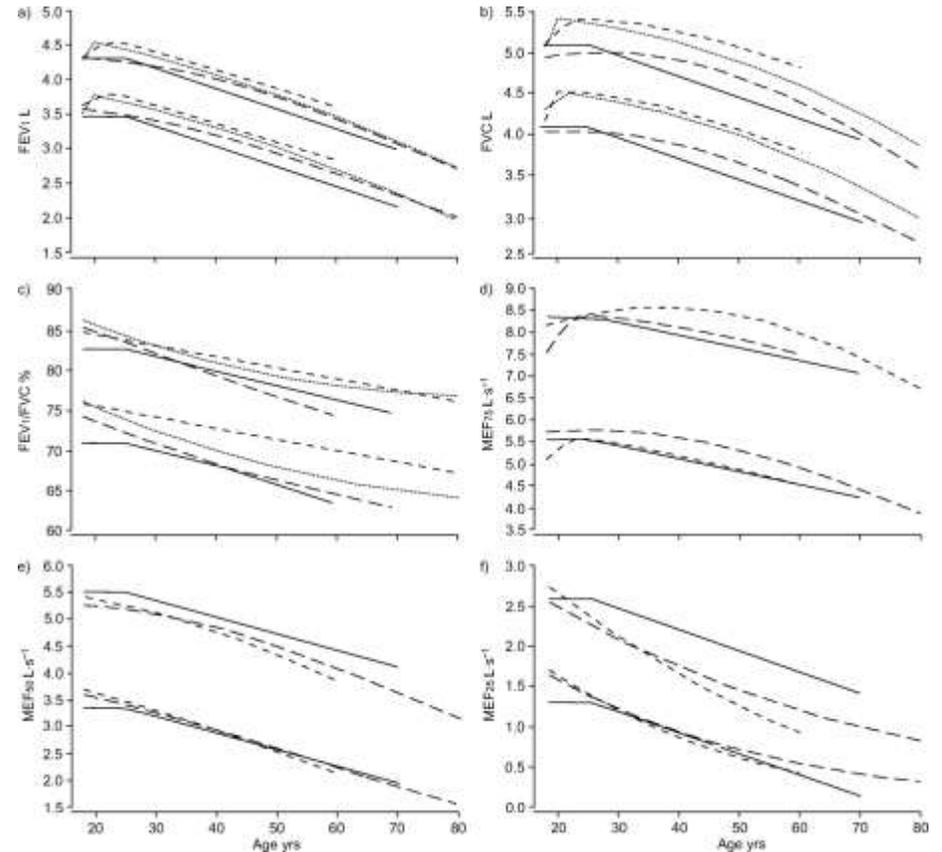
Evaluating the HIV D+ lung donor



Long-term effects of pneumonia



- FEV₁ decrease after PJP the equivalent of aging ~8 years
- Decreases did not resolve with time in this pre-HAART era study



Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):612-6.
European Respiratory Journal 2008; 31: 860-868.

People with HIV are more likely to smoke and more likely to experience medical complications from smoking

- High prevalence of smoking
- 2-5 fold higher rates of lung cancer; association persists after controlling for smoking rates (VACS study 1.5-1.7 IRR).
- Again cumulative time with low CD4+ lymphocyte count may be predictive

Clin Infect Dis. 2013 Mar;56(5):727-34.

Curr Opin HIV AIDS. 2017 Jan; 12(1): 31–38.

AIDS. 2012 May 15; 26(8): 1017–1025.



Nodules are common in smokers with HIV

Table 2 Baseline results of selected American low-dose computed tomography lung cancer screening trials and the IELCAP trial

Variables	NLST (28,29)	ELCAP (30)	IELCAP (6)	Mayo [†] (31)	PLuSS [†] (5,32)
Participants					
Received CT screening	26,309	1,000	31,567	1,520	3,642
Age, mean (SD) [‡] or median (IQR) [§]	NA	67 (NA) [§]	62 (NA) [§]	59 (NA) [‡]	59 (NA) [‡]
Pack years, mean (SD) [‡] or median (IQR) [§]	NA	45 (NA) [§]	30 (NA) [§]	45 (NA) [§]	47 [33–62] [§]
Nodule detection limit	≥4 mm	None reported [¶]	≥5 mm	None reported	None reported
Participants with lung cancer	270/26,309 (1.0%) ^{††}	27/1,000 (2.7%)	405/31,567 (1.3%)	31/1,520 (2.0%)	53/3,642(1.5%)
Participants with NCNs	7,041/26,309 (26.8%)	233/1,000 (23.3%)	4,186/31,567 (13.3%)	780/1,520 (51.3%)	1,477/3,642 (40.6%)

CD4 count and viral load are likely associated with chest CT findings

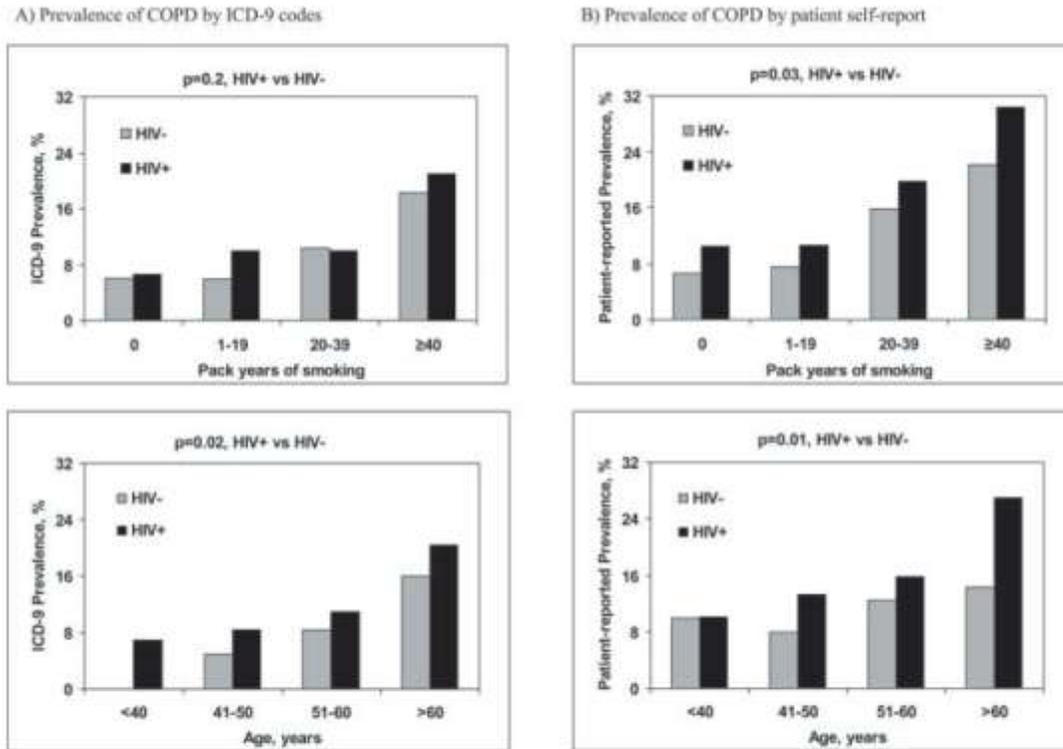
- EXHALE study (part of the VACS study):
 - noncalcified nodule ≥ 4 mm in 55% of patients with CD4+ lymphocyte count $< 200/\mu\text{L}$
 - 25% if CD4+ lymphocyte $200/\mu\text{L}$ or greater
- COCOMO study:
 - CD4⁺ T lymphocyte count under 500 cells/ μl and CD4⁺ T lymphocyte nadir less than 200 cells/ μl were each associated with increased odds of a positive image (OR) 2.32 (95% CI: 1.01–5.13, $P = 0.04$)
 - Previous history of PCP [OR 4.32 (95% CI: 1.34–11.9), $P = 0.01$] independently associated with abnormal CT chest

AIDS 2014, 28: 1007–1014.

AIDS 2017, 31: 1973-1977.



Accelerated COPD development in PLWH



- Younger age
- Lower pack-year history

Table 3—Predictors of COPD in HIV-Positive and HIV-Negative Subjects*

Predictors	COPD Diagnosis	
	ICD-9 Codes	Patient Self-Report
HIV status	1.47 (1.01–2.13)†	1.58 (1.14–2.19)†
Age, per 10 yr	1.57 (1.29–1.87)†	1.17 (1.00–1.37)
Black	0.77 (0.53–1.13)	0.63 (0.46–0.87)†
Hispanic	1.13 (0.67–1.90)	0.80 (0.50–1.27)
Smoking, per 10 pack-yr	1.12 (1.07–1.18)†	1.16 (1.11–1.22)†
IDU	1.44 (0.99–2.12)	1.56 (1.13–2.16)†
Alcohol abuse	2.24 (1.54–3.25)†	1.52 (1.09–2.12)†

*Values are given as the OR (95% CI).

†Significant at $p \leq 0.05$.

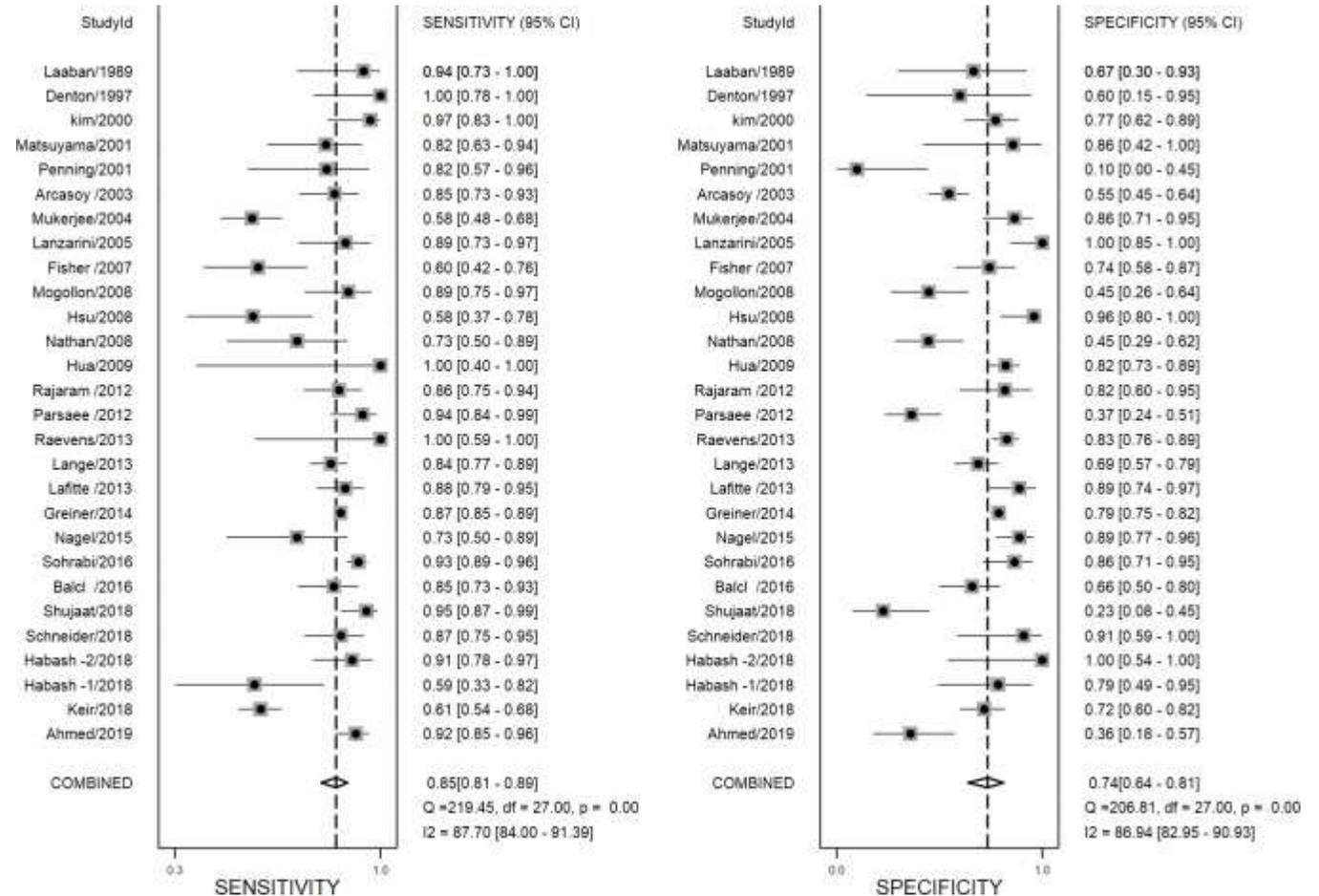
FIGURE 1. Prevalence of COPD among HIV-positive and HIV-negative subjects stratified by number of pack-years of smoking or age. *Left top and bottom, A:* the prevalence of COPD as diagnosed by ICD-9 codes. *Right top and bottom, B:* the prevalence of COPD as diagnosed by patient self-report. The p values are given for the likelihood of COPD in HIV-positive subjects vs HIV-negative subjects adjusted for either age or smoking group. HIV+ = HIV-positive; HIV- = HIV-negative.



Pulmonary hypertension and HIV

- Ten-fold higher prevalence in people with HIV
- Sensitivity of echocardiography for diagnosing pulmonary hypertension ~80%.

Lancet Healthy Longev. 2021 Jul;2(7):e389-e390.
BMJ Open. 2019 Dec 22;9(12):e033084.



- Traditional vs. extended criteria for the lung donor without HIV.

Table 1

Criteria used to assess donor lung suitability, defining a “standard lung donor”

<u>Traditional Criteria (Standard Donor)</u>	<u>Extended Criteria (Marginal Donors)</u>
Age ≤ 55 y	Age >70 y
Clear chest X-ray	Minor diffuse and moderate focal chest radiograph changes acceptable
$Pao_2 \geq 300$ on $Fio_2 = 1.0$ and positive end-expiratory pressure (PEEP) 5 cm H_2O	$Pao_2/Fio_2 < 300$ mm Hg on PEEP 5 cm H_2O
Tobacco history ≤ 20 pack yr	Tobacco history < 40 pack yr
Absence of chest trauma	Chest trauma not relevant if good pulmonary function
No history of primary pulmonary disease or active pulmonary infection	
No evidence of aspiration/sepsis	Aspiration/sepsis acceptable if good, stable/improving pulmonary function
Absence of pulmonary secretions at bronchoscopy	Purulent secretions not relevant if good, stable/improving pulmonary function
No evidence for human immunodeficiency virus, hepatitis B, hepatitis C, or any other relevant viral disease	
No history or evidence of malignant disease	
ABO compatibility	
Sputum Gram stains: absence of organisms	

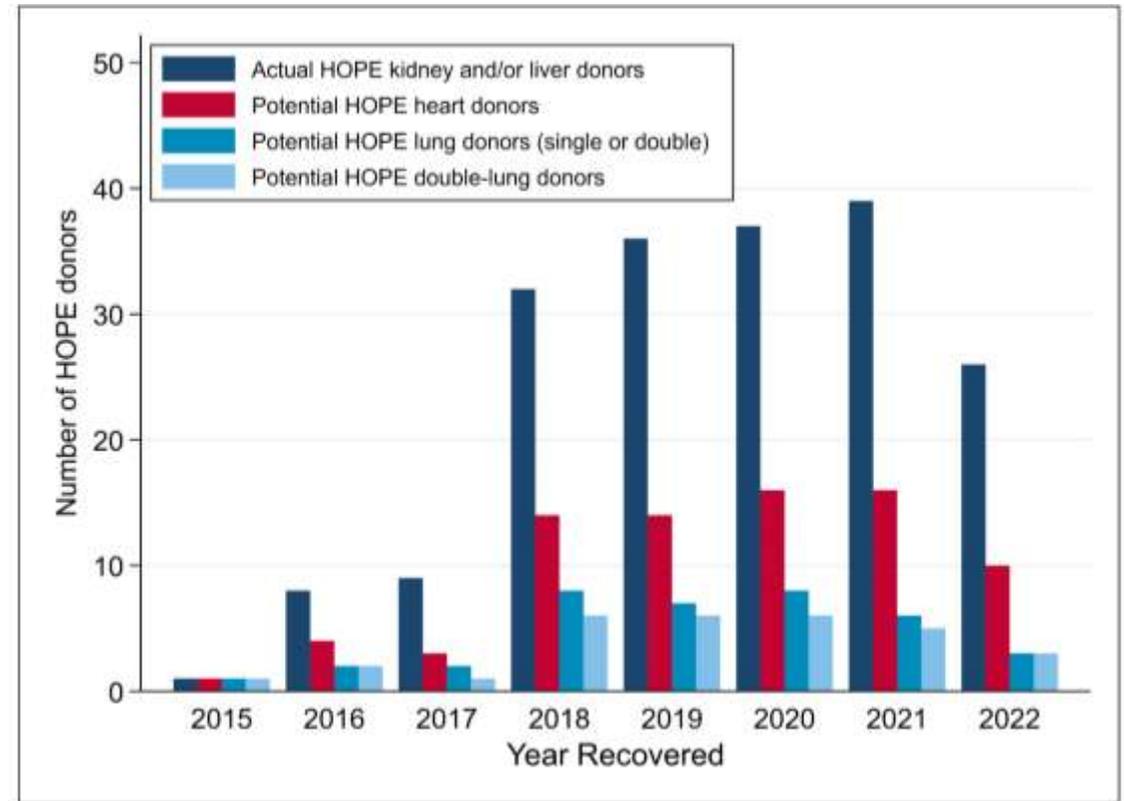


Questions for the future

- What is an acceptable treatment history for the HIV D+ lung donor?
- When should opportunistic infections exclude lung donation?
- What smoking history is acceptable?
- Single vs double?

The anticipated number of available thoracic HOPE donors will be less than demand

- I think these numbers are an upper bound on the actual number of available donors via the HOPE program
- False positive donors will be the low-hanging fruit



Acknowledgments

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Thank you!

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