

HIV and transplantation

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Disclosures

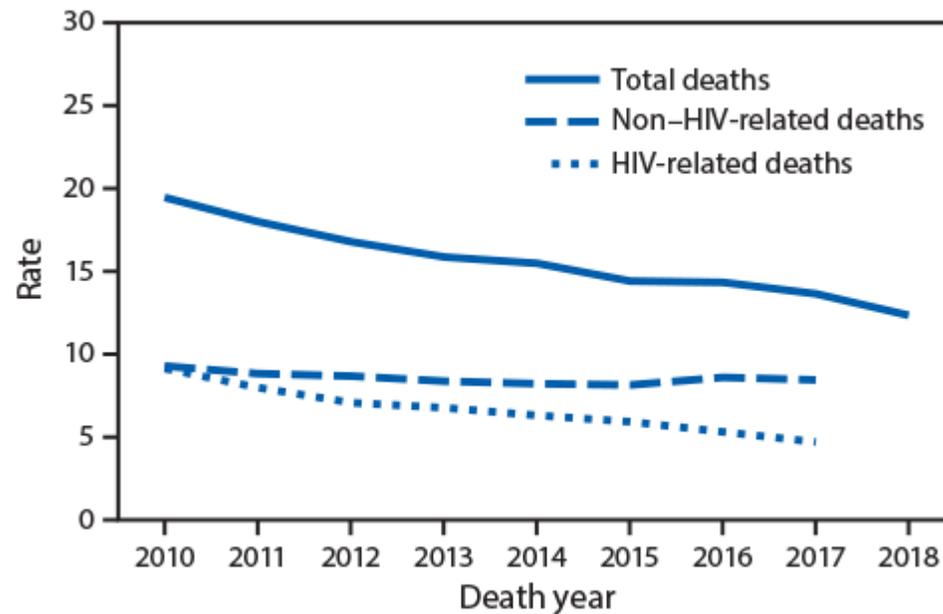
- Research funding from Merck to study pneumococcal vaccine response in LVAD recipients

Case #1

- A 60 year old women with remote history of kidney cancer requiring nephrectomy presents for evaluation for transplant after initiating peritoneal dialysis
- Her current regimen is rilpivirine and dolutegravir, but she has been on many prior regimens
- How should her case be evaluated?

Introduction

- Antiretrovirals have transformed HIV into a chronic disease
- In the modern era, the majority of people living with HIV die from non-HIV comorbidities



MMWR Morb Mortal Wkly Rep 2020;69:1717–1724.

HIV and end-organ disease

Kidney disease	<ul style="list-style-type: none">• Direct effects of HIV• Older antiretrovirals (TDF)	900 new dialysis patients/year
Liver disease	<ul style="list-style-type: none">• Hepatitis B/C• Alcohol• Older antiretrovirals	~15% of deaths in people with HIV
Cardiac disease	<ul style="list-style-type: none">• Direct effects of HIV• Inflammation→increased risk of myocardial infarction• Smoking• Abacavir	~2400 people with HIV with advanced heart failure
Lung disease	<ul style="list-style-type: none">• HIV-associated pulmonary hypertension• Smoking• Prior infection (pneumocystis)• Independent effect of HIV?	Unknown

J Heart Lung Transplant. 2014 Sep;33(9):924-30.
Clin J Am Soc Nephrol. 2017 Mar 7; 12(3): 467–475.
Arch Intern Med. 2006 Aug;166(15):1632-41.

HIV and end-organ disease

- People with HIV are *more* likely to die once they develop end organ disease
- They are *less* likely to be:
 - Referred to a transplant center by their providers
 - Listed for transplant once referred
 - Transplanted once listed

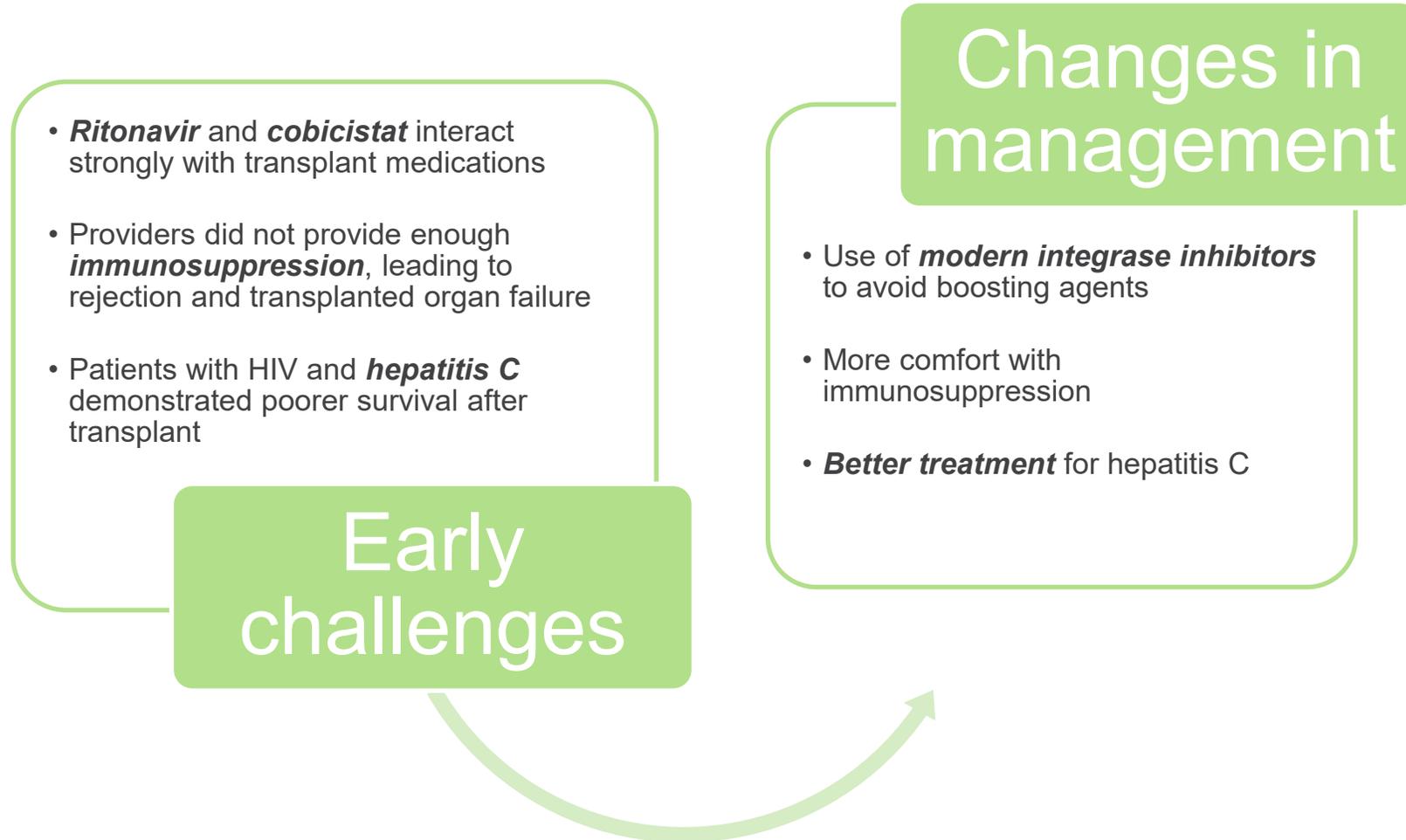
Early experience with HIV and transplant

- Studies in the early 2000s demonstrated that people living with HIV with suppressed viral loads could safely receive kidney and liver transplants under select conditions:
 - CD4 count 200+ cells/uL for kidney, 100+ for liver
 - Viral load under 75 copies/mL (except for “blips”). Note: this requirement can be waived under appropriate circumstances.
 - No history of opportunistic infection for which prophylaxis does not exist (e.g. PML)

Ann Surg. 2016 Mar;263(3):430-3.

N Engl J Med. 2010 Nov 18; 363(21): 2004–2014.

Early experience with HIV and transplant



Case #2

- A 40 year old woman initiated efavirenz-based antiretroviral therapy
- Two months later, she presented with jaundice and transaminitis, leading to her ARVs being stopped and hospitalization
- Nevertheless, she progressed to submassive hepatic necrosis with MELD 30+, and was admitted and referred to a liver transplant center
- How should she be evaluated?

Evaluation

- Patient should be on a stable regimen at least three months prior to transplant or in the case of a patient with liver failure who may not be able to tolerate ARVs the ability to obtain viral suppression post transplant
- Kidney patients should demonstrate viral suppression at least 6 months prior to transplant. Patients may have non sequential “viral blips”, which can be acceptable if less than 200 copies as long as repeat values are <40 copies.
- HIV/ID specialist should review regimen. Integrase regimen preferred.
- Previous opportunistic infection is not necessarily a contraindication.

Infection History	Comments
Pneumocystis jirovecii	no active disease, evidence of immune reconstitution
Candidiasis, esophageal or oral	no active disease, evidence of immune reconstitution
Herpes Simplex infection	No active disease, easy suppression with antivirals
Mycobacterial disease (tuberculosis, MAC)	Patients must have completed treatment prior to transplant evaluation, no evidence of disease
Cutaneous Kaposi sarcoma	No evidence of disease, evidence of resolution following immune reconstitution

Opportunistic Infection	Prophylaxis
Pneumocystis	Tmp/smx Alternates: atovaquone, dapsone
CMV	Valganciclovir
History of cryptococcus Successful treatment With immune reconstitution	Fluconazole
Mycobacterium avium complex with successful treatment and immune reconstitution	Azithromycin
Toxoplasmosis	TMP/SMX

Contraindications

- Active opportunistic infection
- History of CNS process such as PML, lymphoma
- Visceral Kaposi's Sarcoma or active malignancy (exception anal/cervical dysplasia)
- Inadequately treated fungal or mycobacterial process
- Multidrug resistant virus is less of an issue given newer and more potent agents

Case #2 (continued)

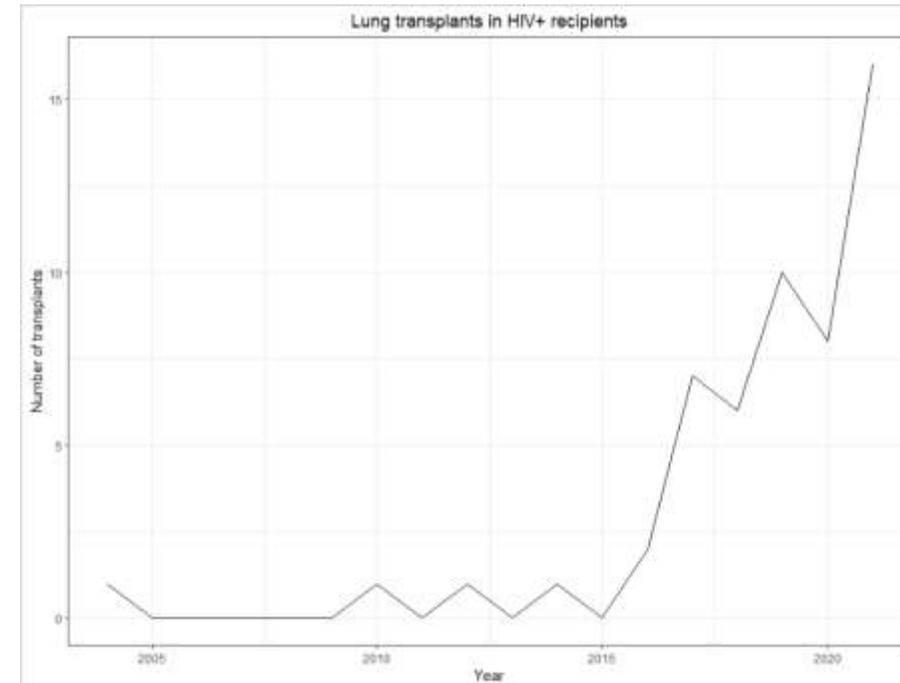
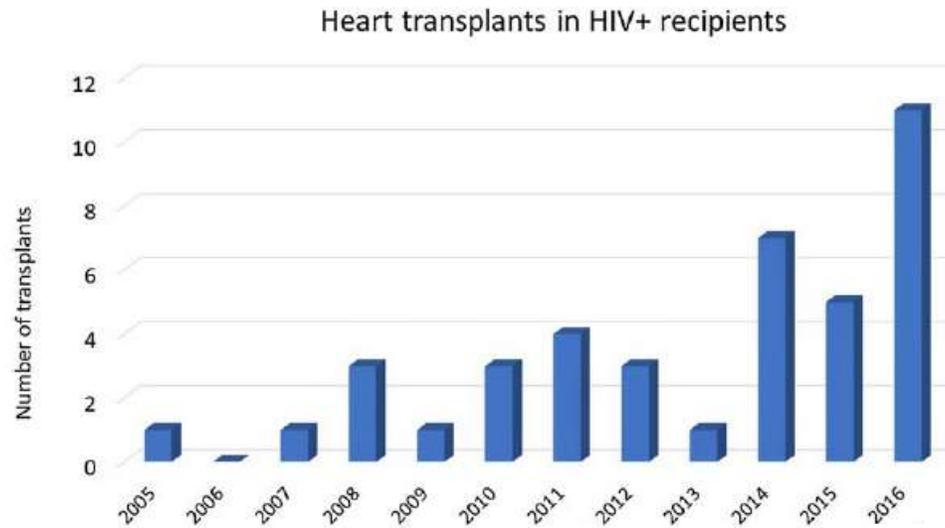
- ARVs held due to hepatorenal syndrome with pancytopenia
- Ultimately underwent liver transplant, but no renal recovery and listed for kidney transplant

Case #1 (continued)

- Listed for kidney transplant
- Develops heart failure while on the list.

HIV and thoracic transplant

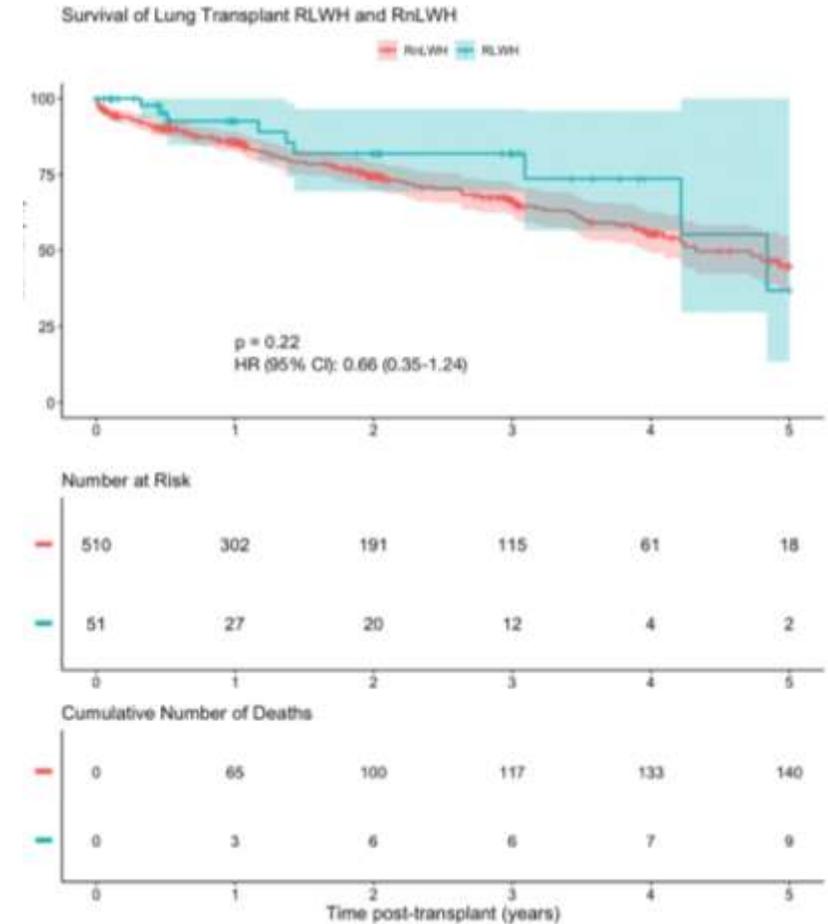
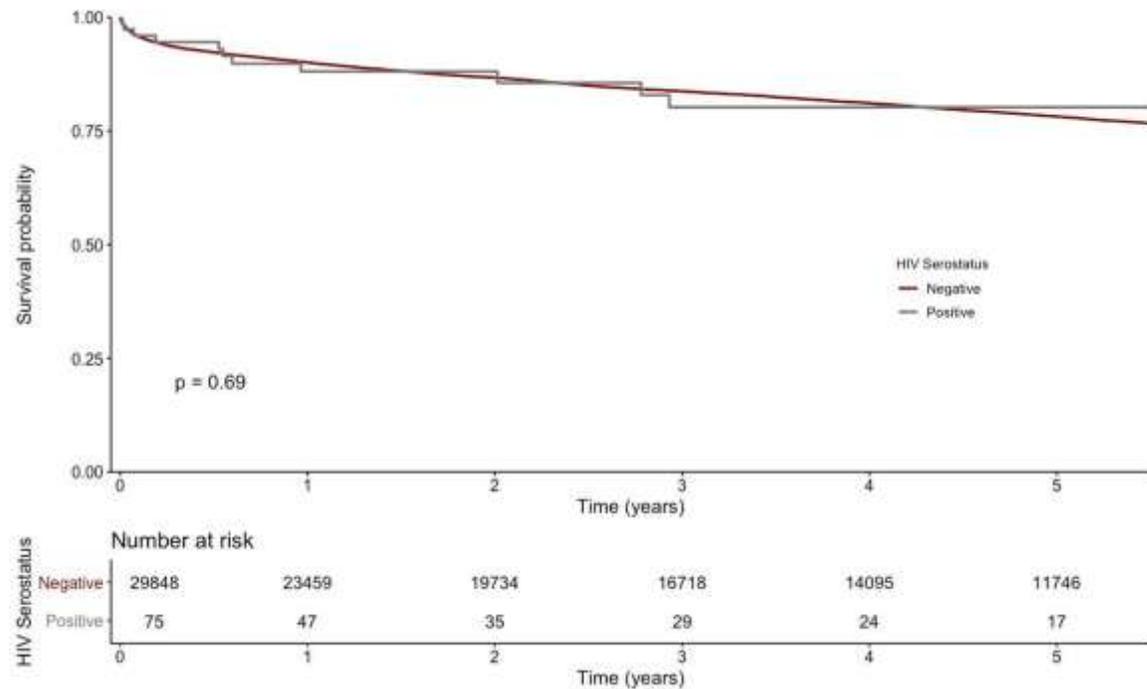
Until recently, *very* few centers were willing to offer heart or lung transplant to patients living with HIV



Am J Transplant. 2019 May;19(5):1529-1535.
Personal research (unpublished).

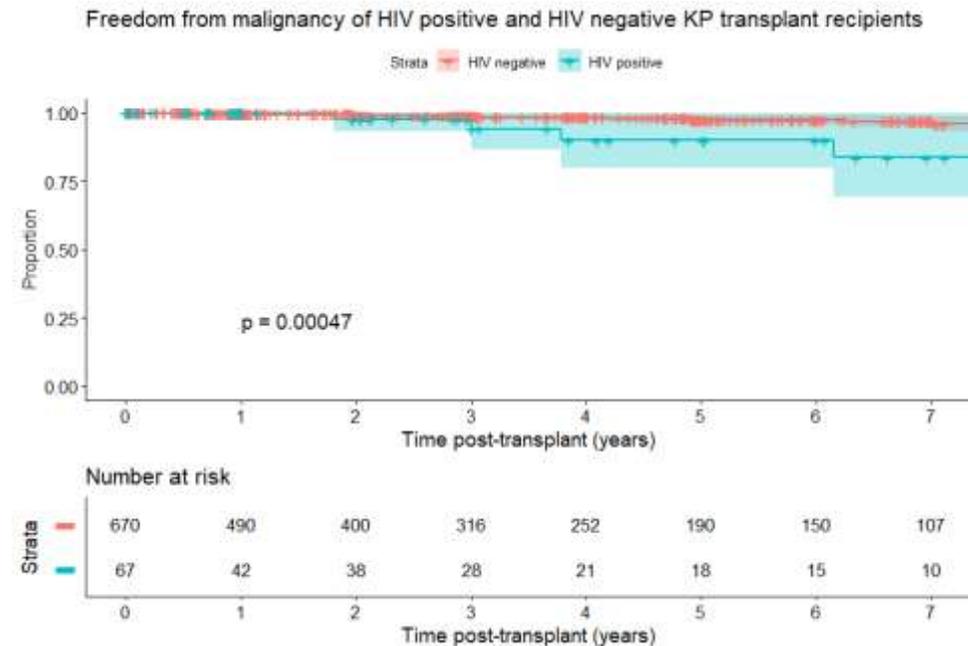
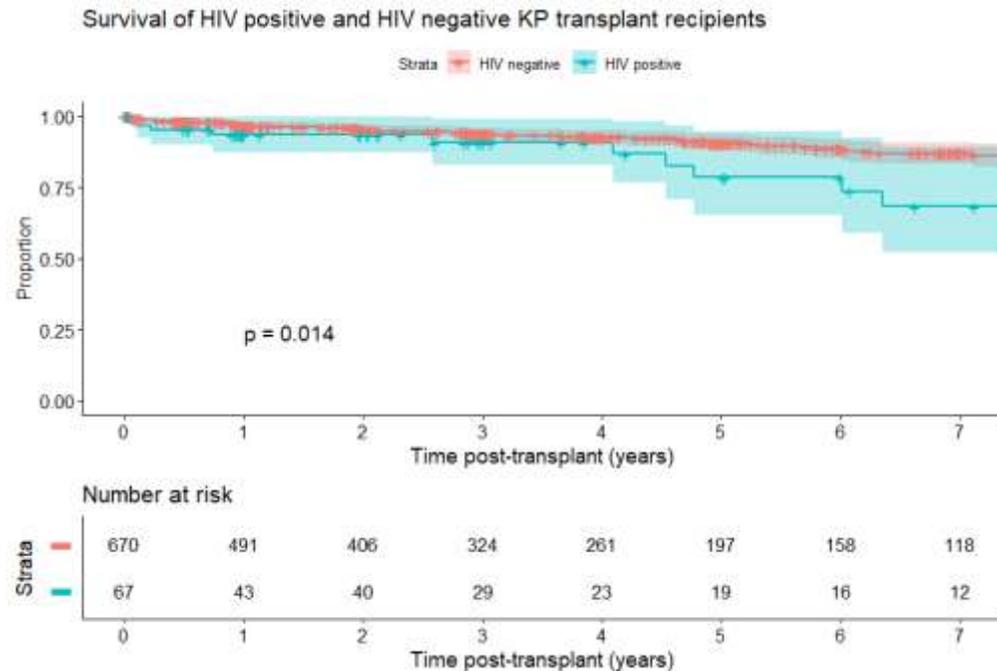
HIV and thoracic transplant

- Recent data has suggested that patients with HIV can safely receive heart and lung transplants.



Pancreas

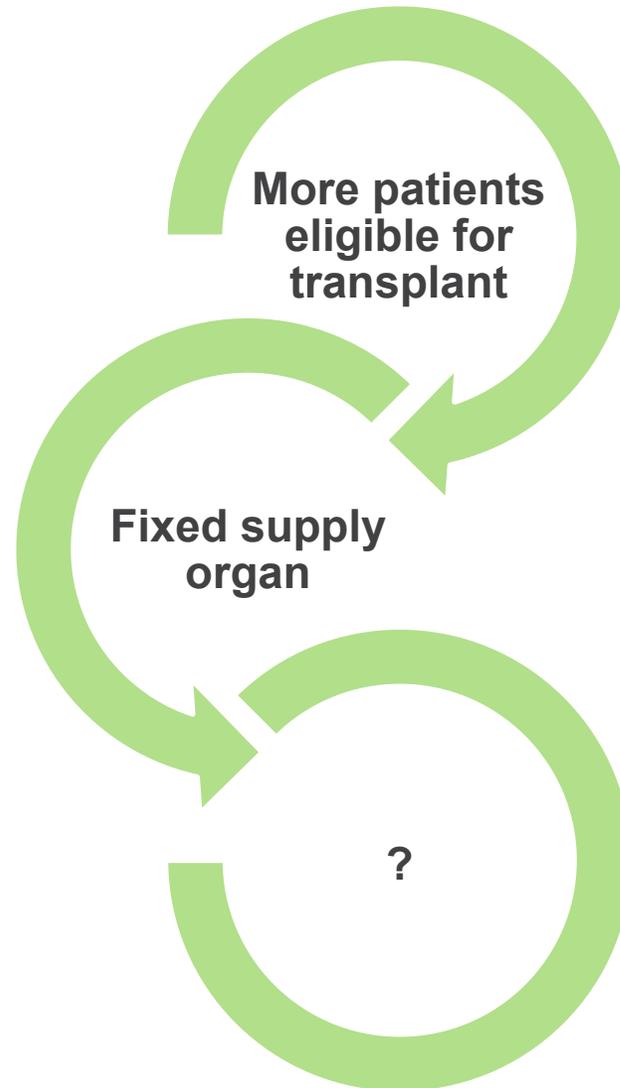
- My own research has shown that national outcomes in kidney-pancreas transplant in people with HIV are acceptable, with a late risk of malignancy



Case #1 continued

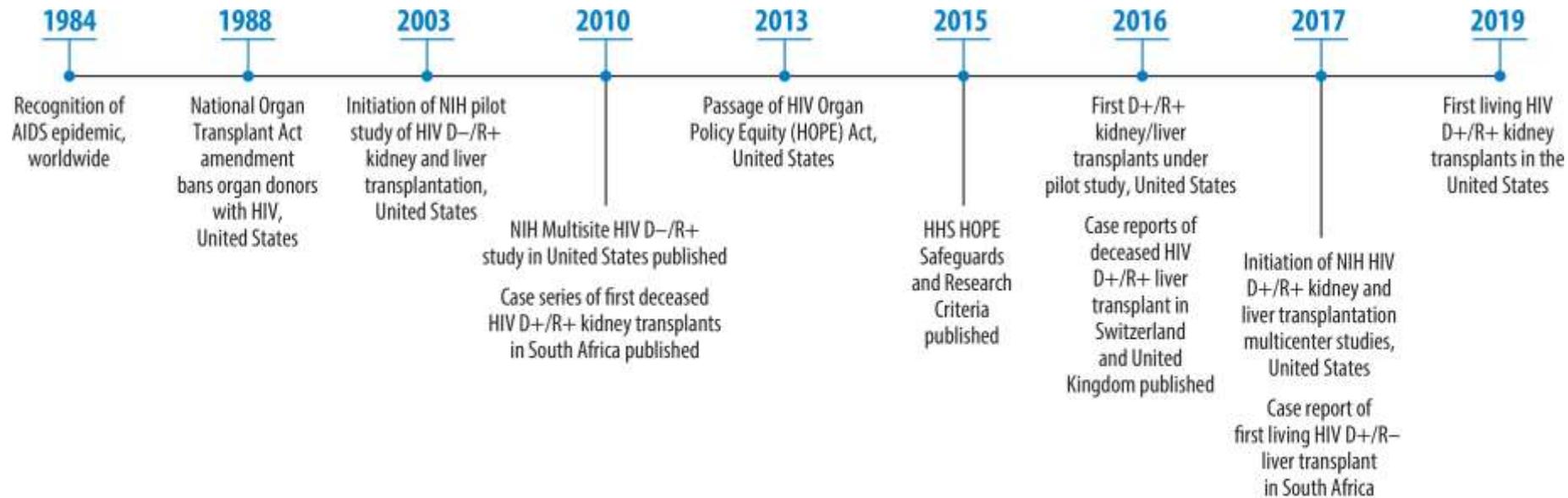
- The patient was listed for a heart transplant, but did not receive any offers
- How can we expand the donor pool?

Increasing the donor supply



Federal law

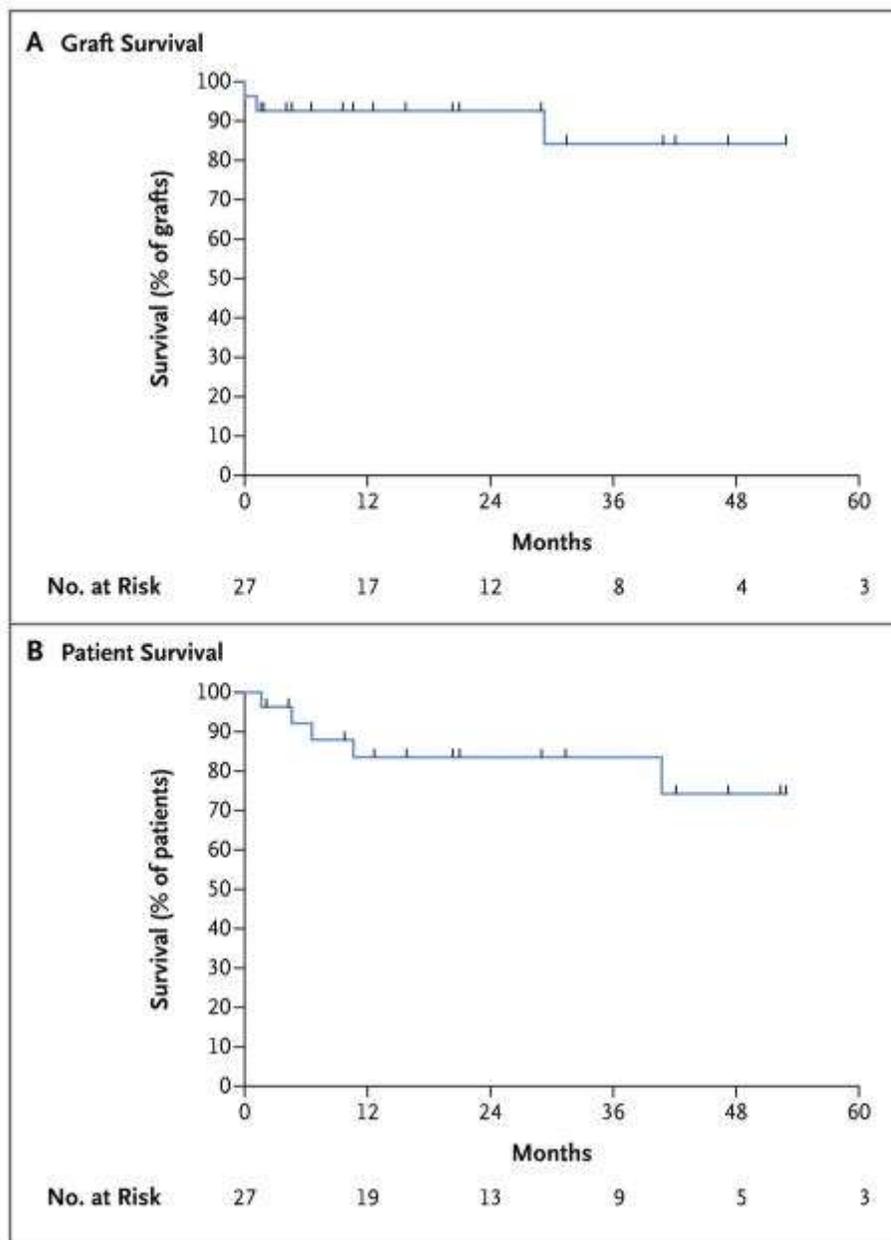
- Transplantation of organs from donors who test positive for HIV was banned by the National Organ Transplant Act amendment (NOTA) Act of 1988, which reflected the poor outcomes of transplant-associated HIV in an era without effective treatments for HIV



First HIV-to-HIV transplants

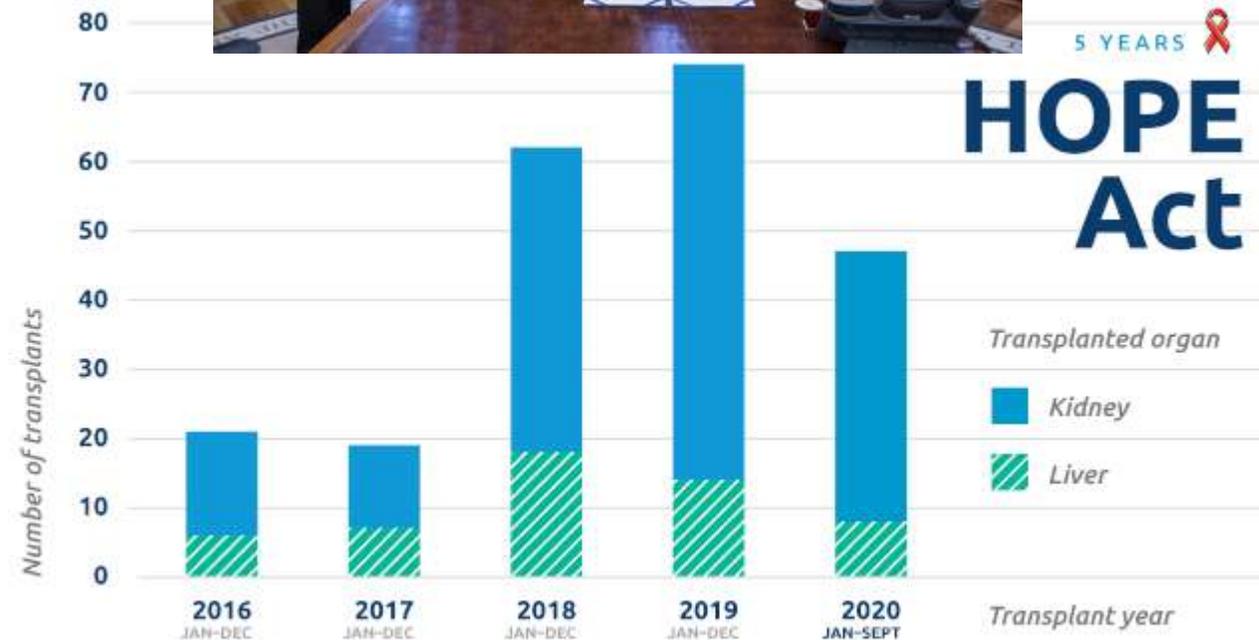
- The first study of HIV D+/R+ transplant was done in South Africa
 - Limited access to dialysis
 - High prevalence of HIV

N Engl J Med. 2010 Jun 17; 362(24): 2336–2337.
N Engl J Med. 2015 Feb 12; 372(7): 613–620.



The HIV Organ Policy Equity Act (the HOPE Act)

- Federal law signed 21 Nov 2013
- Permits transplantation of kidneys and livers from HIV+ donors (D+) into HIV+ recipients (R+) *under research protocols*
- On 7 Jun 2020 amended to include other organs
- Program must have organ-specific experience with 5 HIV D-/R+ to perform D+/R+



Based on OPTN data as of Nov. 13, 2020. Data subject to change based on future data submission or correction.

Why is HIV D+/R+ different? What were the concerns?

Resistance

Infection

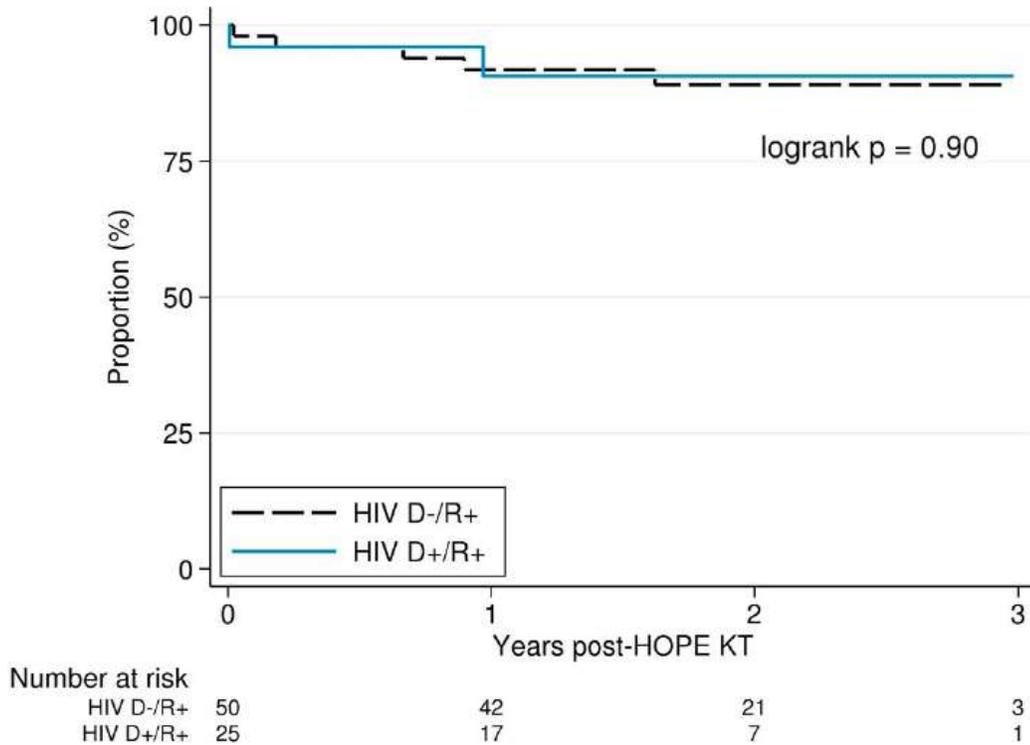
Malignancy
(especially
lymphoma)

Rejection

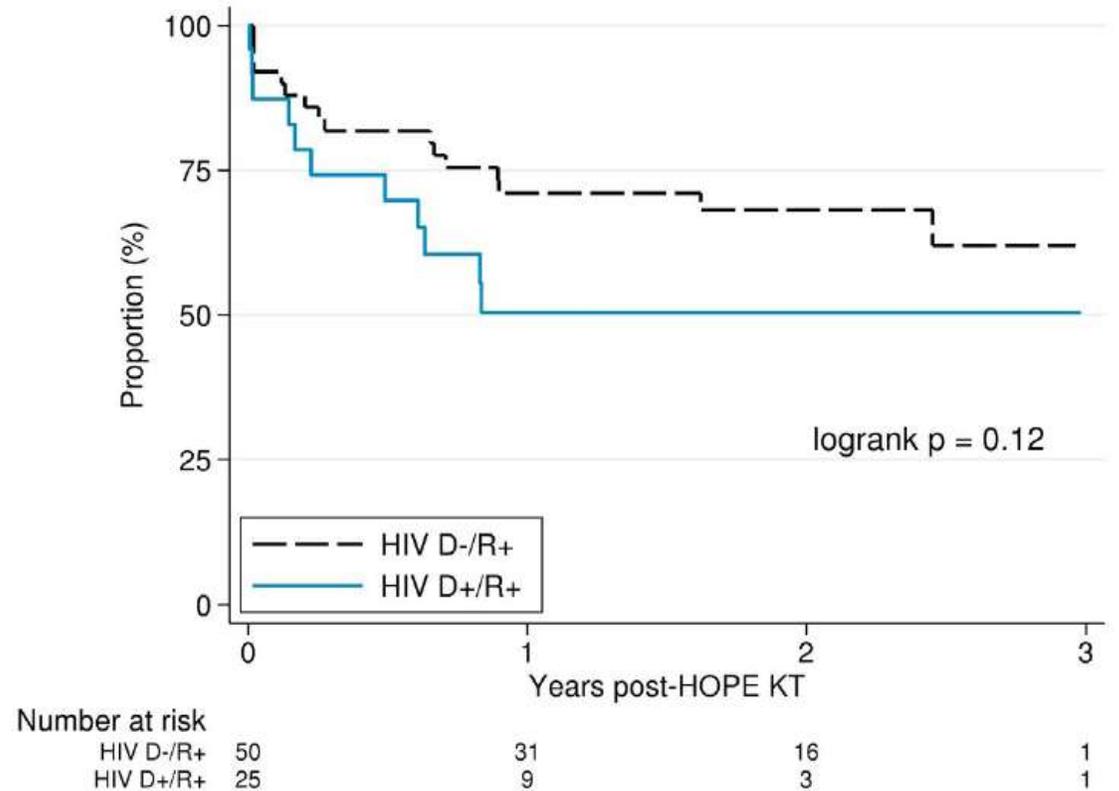
Of note, only rejection has been an issue in actual practice.

Outcomes in kidney transplant patients under the HOPE Act

A Graft survival by donor HIV status

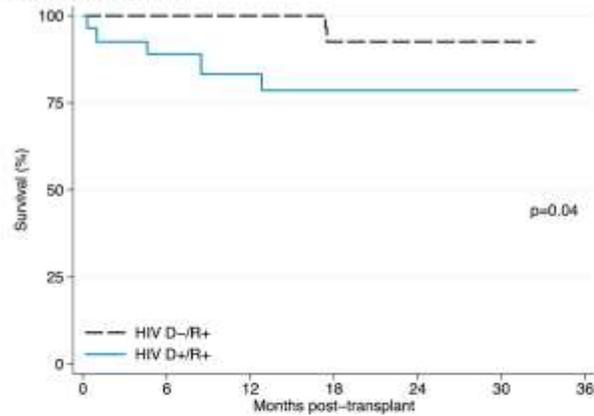


B Rejection-free survival by donor HIV status

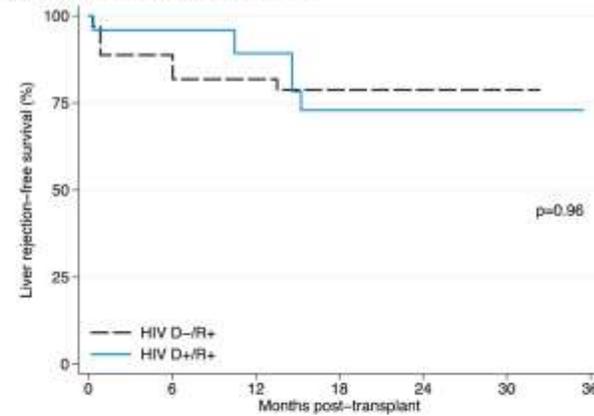


Outcomes in liver transplant patients under the HOPE Act

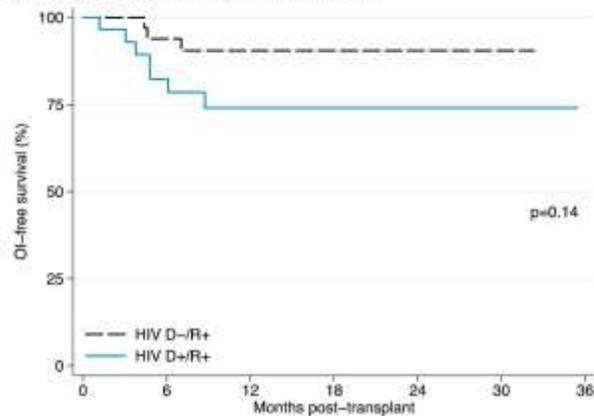
(A) Overall survival



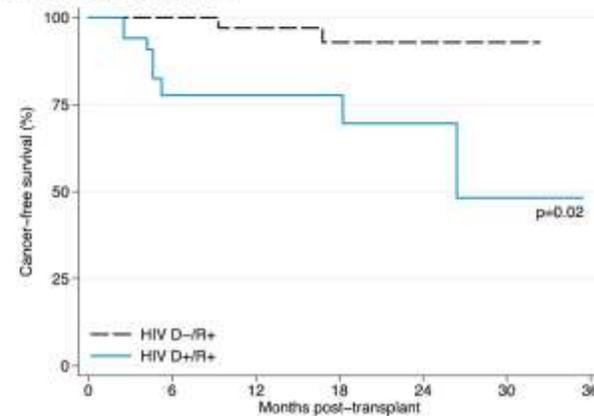
(B) Liver rejection-free survival



(C) Opportunistic infection-free survival



(D) Cancer-free survival



- So far, 24 HIV D+/R+ transplants done to date
- Survival numbers acceptable but liver may have more infections and cancer, which needs to be balanced against risk of dying on liver transplant list

So, as a practical matter, what needs to happen for an HIV-positive donor?

- Organ offer received
- ID contacted EARLY IN THE PROCESS
- ID to reach out to Hopkins (either via email or cell phone)
 - OPO is supposed to reach out to Hopkins, but frequently this does not happen
- Hopkins dedicated HOPE act coordinator can obtain pharmacy records and clinic notes (note, this typically has to happen during waking hours)
- Detailed review of all medical records and multidisciplinary discussion leading to decision to accept or reject
 - Much of this area is a completely evidence-free zone, so we frequently find ourselves hitting the “phone a friend” button



So, as a practical matter, what do we do when we get called about a potential HIV-seropositive donor?

Resistance

- Prior HIV genotypes
- Treatment history

Opportunistic infection

- CD4+ count
- Viral load
- Medical records

Malignancy

- Medical records

Case #3

- “We have a pre-OR offer from TX for an **HIV NAT positive** donor.
- 42 y/o M COD anoxia. O-Blood group. BMI 28.7. KDPI 40%. Cr. 1.8>>8. HA1C 5.8%. PHS high risk.
 - UTxo + amphetamines, cocaine
 - UA + protein, blood, WBC, bacteria
 - Bronch + GPC in pairs
- Serologies: EBV IgG, CMV, **HIV Ab** and **HIV NAT – positive**
- Per donor risk assessment interview:
 - Donor went to a medical facility 6 weeks ago for shingles.
 - Did not see family physician or specialist regularly.
 - Did not take any prescription medication regularly.

Case #3

Initial ID input:

- *On intake, listed as no known prior history of HIV.*

Sounds like either

- *noncompliant*
- *not taking*
- *antiretroviral naive is possible.*

Case #3

- I had worked with the TX DOH on several papers regarding HIV in Texas and knew people with access to the state database of known HIV positives:
 - Donor was NOT in the database of people with known HIV
 - Donor WAS in the database of people identified via contact tracing, but contact tracers had not been able to get him in for testing

Case #3

- Undiagnosed HIV in the Bronx is not highly prevalent
 - Our own internal data using blinded blood samples from the Montefiore ER in 2015 suggested that only **5%** of seropositive samples were from patients without an EMR history of HIV
- This is *absolutely not typical* of the experience in the rest of the country
 - In Houston, the proportion of seropositive patients in the county hospital ER without a prior HIV diagnosis 2009-2012 was **25%**

Am J Public Health. 2018 May;108(5):652-658.

J Acquir Immune Defic Syndr. 2015 May 1; 69(0 1): S8–15.

Donor characteristics	HIV D+ (N = 15)	HIV FP (N = 14)	HIV D- (N = 28)
Age (Med [IQR])	30 (23, 33)	24 (20, 41)	29.5 (25, 37)
Female, no. (%)	4 (27%)	4 (29%)	11 (39%)
Race, no. (%)			
White	4 (27%)	7 (50%)	14 (50%)
Black	9 (60%)	5 (36%)	10 (36%)
Asian	0%	0 (0%)	1 (4%)
Other	2 (13%)	2 (14%)	3 (9%)
Ethnicity, no. (%)			
Hispanic	1 (7%)	2 (14%)	2 (7%)
Body mass index (Med [IQR])	23 (22, 26)	26 (20, 34)	26 (22, 30)
Brain death donor, no. (%)	15 (100%)	11 (79%)	28 (100%)
Increased infectious risk, no. (%)	12 (80%)	2 (14%)	16 (57%)
Kidney donor profile index	30 (20, 39)	30 (21, 58)	36 (29, 54)
Mechanism of death, no. (%)			
Anoxia	8 (53%)	1 (7%)	16 (57%)
Cerebrovascular/stroke	3 (20%)	5 (36%)	2 (7%)
Head trauma	4 (27%)	7 (50%)	10 (36%)
Other	0 (0%)	1 (7%)	0 (0%)
Hepatitis C RNA positive, no. (%)	0 (0%)	1 (7%) ^a	8 (29%)
HIV Ab positive, no. (%)	15 (100%)	12 (86%)	0 (0%)
HIV NAT positive, no. (%)	10 (67%)	2 (14%)	0 (0%)
CD4 count, median (IQR)	300 (142, 479)	ND	ND
New diagnosis of HIV, no. (%)	5 (33%)	N/A	N/A
On ART, no. (%)	9 (60%)	N/A	N/A
HIV RNA < 400 copies/mL	5 (56%)	N/A	N/A
Not on ART, no. (%)	6 (40%)	N/A	N/A
HIV RNA, median	183 326	N/A	N/A

Abbreviations: ART, antiretroviral therapy; NAT, nucleic acid test.

^aReactive nondiscriminated Procleix Ultrio in donor with negative HCV Ab, likely false positive.

Donors of with HIV are frequently undiagnosed and not on medications

This is fine! Outcomes when the donors are carefully evaluated have been acceptable with no transmissions of any infection or resistant virus

Case #3

- A pt story may be telling as to why a careful evaluation is needed:
 - A 24 year old Afro-Latino male presented to my clinic to establish care in January 2014
 - Febrile 103, clearly dragging foot, so sent immediately to the ER
 - CT head with brain mass-> progressed to full hemiparalysis->brain biopsy demonstrated CNS lymphoma
 - High dose steroids->profuse diarrhea->CMV VL of 1.6 million and presumptive diagnosis of CMV colitis
 - Multiple skin lesions->diagnosis of Kaposi's sarcoma
 - Continued fevers->blood cultures positive for MAC
 - HIV virus quickly responded to meds (VL undetectable within weeks) with no improvement in CD4 count (10->20) and no response to therapy of CNS lymphoma
 - Ultimately died of neutropenic fever/septic shock

Case #3

- In this case, the only concerning element was the history of shingles. Pt had been found unresponsive on the kitchen floor after complaining of choking while cooking breakfast—not a mechanism c/w untreated opportunistic infection.
- In this case, decision made that organ acceptable from an HIV perspective
- However, did not proceed to transplant due to poor organ quality on biopsy (donor had developed AKI with Cr 8)

Case #4

58 kidney donor (UNOS ID AHJH145, match 1281351) in the NYC area. Had PEA/arrest in the setting of ?PNA and cocaine use. HIV x 35 years with non-adherence. 2 HIV notes in DonorNet so far. DCD donor

11/2019:

VL 757, CD4 17

TAF, AZT, atazanavir/ritonavir (so a protease inhibitor)

9/24/2020:

VL 51, CD4 373

Biktarvy, atazanavir/ritonavir

Genotype according to the 9/2020 HIV note:

- K65R
- K103N
- M184V
- L100I
- 15V

Case #4

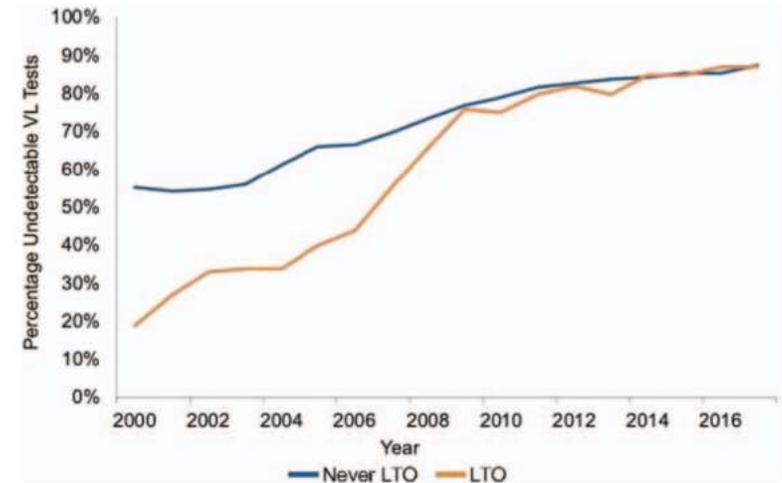
Potential recipient was doing well (both from HIV and HD perspective) on TDF+rilpivirine+Tivicay. High recipient PRA.

Points made:

- Can likely suppress virus with a 4-drug regimen that doesn't interact with tacrolimus and is non-nephrotoxic (Doravirine+Tivicay+lamivudine+TAF)
- Worst case scenario would involve having to switch to a PI to achieve virologic suppression, with risk to the graft due to drug-drug interactions. Likelihood of needing to do so is under 10% but is non-zero.
- If recipient is highly sensitized and has a low likelihood of getting other offers in the future, we can likely make this work from an HIV perspective given that dialysis itself has known risks to survival
- If the kidney is of high quality, even the worst case scenario (PI +tacrolimus) would probably be tolerated, but would be a huge pain to manage and would have increased risk of rejection
- If the kidney's marginal quality to begin with, this gives another reason to say no

Case #4

- The rate of prevalent resistance in ARV-naïve patients in the modern era is negligible and fewer than 1% of all patients with HIV in the modern era meet criteria for having limited treatment options (LTO).
- Pts with LTO in recent years have the same outcomes as pts with susceptible virus
- In fact, many clinics don't even check resistance genotypes before starting ARVs anymore (*same-day initiation*).



AIDS. 2020 Nov 15;34(14):2051-2059.

Case #4

Ultimate decision: kidney quality was too marginal to bother, but could have accepted if kidney of higher quality

Case #5

- 47 yo female with bronchial alveolar proteinosis diagnosed about 2.5 weeks ago and placed on prednisone.
- Developed acute shortness of breath and arrested on the way to the hospital.
- HIV Ab and NAT positive and it seems to be a new diagnosis.
- DRAI was obtained from husband and there is no known history of HIV or provider listed
- There is also a background history of 2 weeks of 10 lb weight loss and diarrhea, which has been attributed to her recent hospital stay.



Case #5

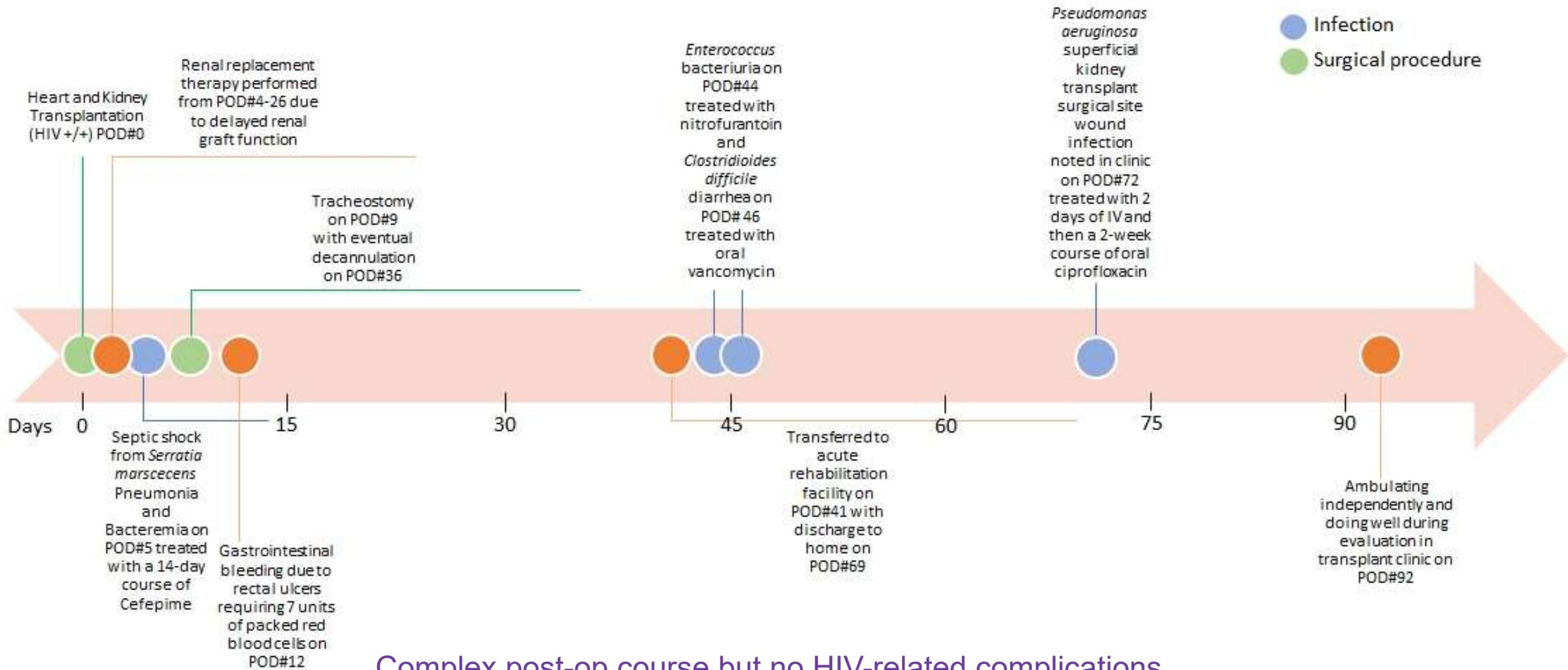
- Concern was that PAP diagnosis was secondary to undiagnosed PJP
- PJP wouldn't affect kidneys, and recipient gets PJP proph anyway, but it's illegal to accept a donor organ with any opportunistic infection and would take Congress changing the law for this to change
- Had 2 wedge biopsies of the lung -> stains and cultures neg for fungus, PJP, AFB, bacteria.
- Ultimately declined by all centers (with some regrets)

Case #1 continued

- Listed for HIV D+/R+ OHT/kidney
- Offer from 30-year-old donor within 7 days
- Cause of death MVA
- HIV AB+, NAAT negative
- Unknown regimen

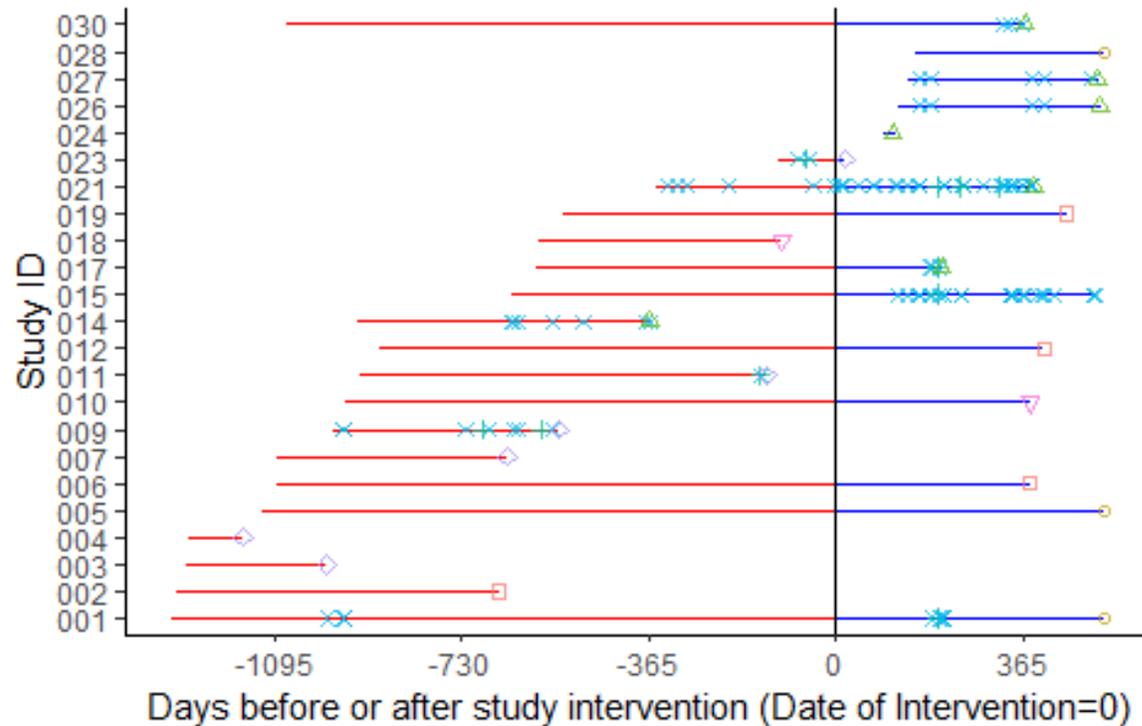
- Can we accept this organ?

HIV D+/R+ Cardiac/kidney Transplant: Post Transplant Course



Complex post-op course but no HIV-related complications
 Normal renal and cardiac function 1.5 years post-transplant
J Heart Lung Transplant, online 24 Nov 2022

Benefits of receiving an organ from a donor with HIV



△ HIV offer accepted and transplanted × HIV offer declined
+ HIV offer accepted, but not transplanted ◇ Non-HIV offer accepted and transplanted

- Our own internal data demonstrate that kidney patients were transplanted much faster once we started more aggressively accepting HOPE offers

IDWeek 2022.

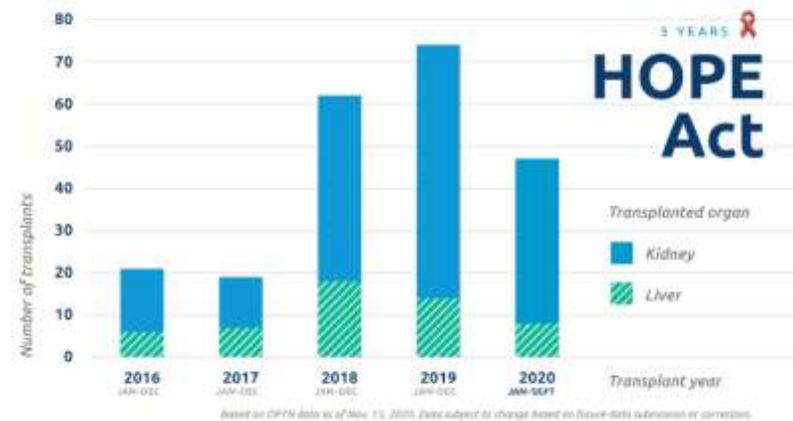
HOPE Act

Despite the successes, volumes to date have been less than anticipated

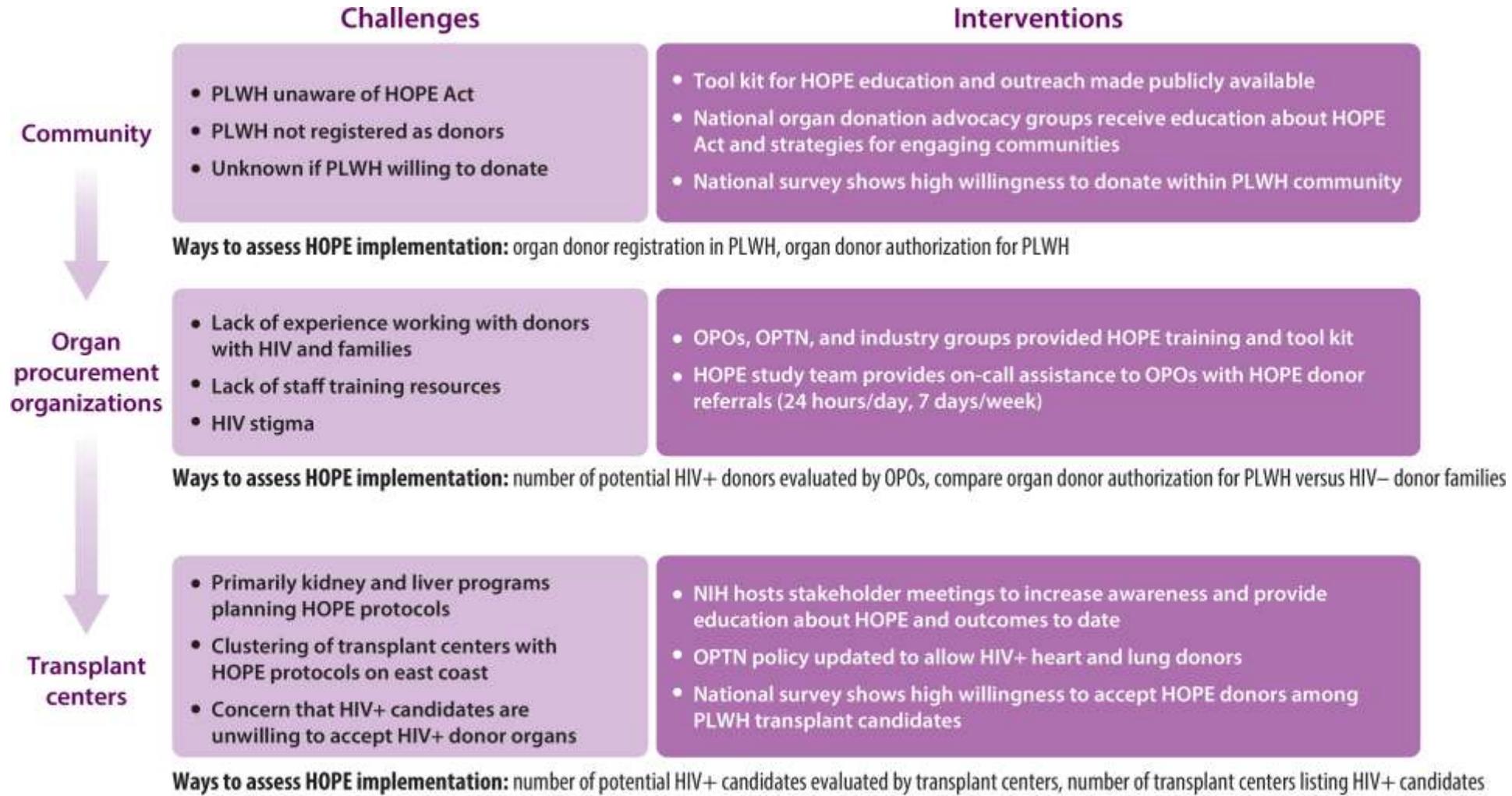
Anticipated volume:

500-600
transplants/year

Actual volume:



Many barriers exist to HIV D+/R+ transplant



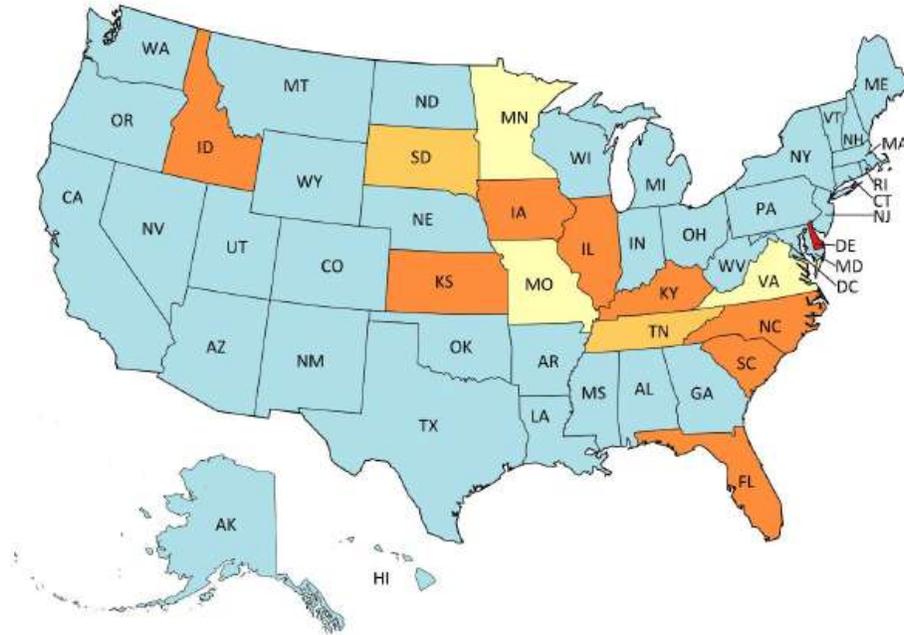
Referral patterns

- There is no organized system to funnel patients with HIV and advanced organ failure to centers experienced with their care
- It's up to patients (and their providers) to navigate the system, find an appropriate transplant center, and navigate the transplant cascade of care



Legal barriers

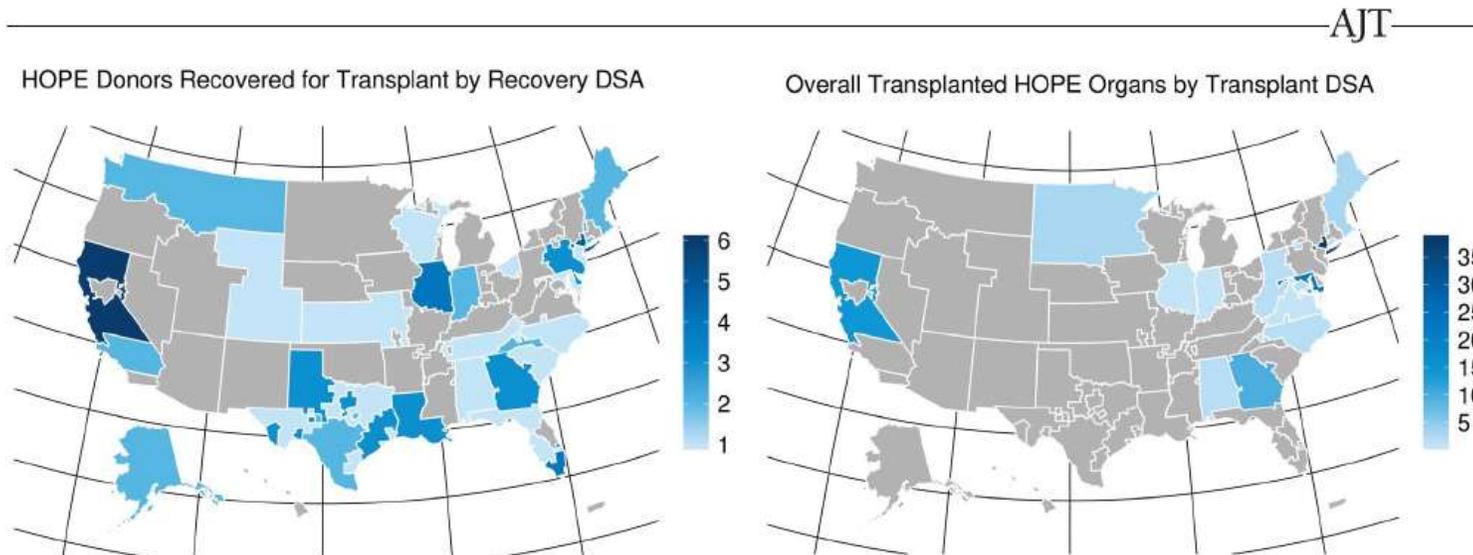
Figure 1:



Type of legal Prohibition	States	Applies to OPOs and transplant center?	Applies to deceased or living donors?	Interpretation
<p>■ Law prohibits transfer or use of organs from HIV+ individuals</p>	Delaware	Yes	Living and Deceased	<ul style="list-style-type: none"> • HIV+ to-HIV+ donation and transplantation is prohibited • Revision to state law required in order to facilitate HOPE Act protocols
<p>■ Law prohibits HIV+ individuals from donating organs.</p> <p>■ Law prohibits HIV+ individuals from donating but permissible with consent</p>	Florida Idaho Illinois Iowa Kansas Kentucky North Carolina South Carolina Tennessee Virginia West Virginia <i>Permissible with consent:</i> South Dakota Tennessee	No	Living	<ul style="list-style-type: none"> • "Individuals" is interpreted as a living person • The state cannot prosecute a decedent. • Participation in deceased donor HOPE Act research protocols should not be impacted • Living HIV+ donors are implicated and revision to these state laws is necessary to enable HIV+ living donor transplantation. • For 2 states living donation is nonetheless permissible with living consent
<p>■ Law allows for HIV+ organ donation for "medical research."</p>	Minnesota Missouri US VI Virginia	No	Living and Deceased	<ul style="list-style-type: none"> • HIV+ to-HIV+ transplants should be permissible in these states as they are currently limited to research protocols • If HIV+ to-HIV+ transplantation becomes standard of care, it will be prohibited in these states
<p>■ Laws don't directly implicate organ donation</p>				

Volume requirements

- Center must have collective experience with at least five recipients of the same organ who are HIV D-/R+ in the previous four years



Availability of HOPE act centers nationally



Map Legend	
+	HOPE Approved Transplant Center(s)

Are patients with HIV willing to accept HIV positive organs?

- Most pts willing to accept:
 - HIV+ living donor organs (87%)
 - HIV+ deceased donor organs (84%)
 - Increased infectious risk donor organs (70%)
- Thirty percent of patients expressed concerned about HIV superinfection and transmitted resistance, but even a majority (71%) of these pts would accept an HIV offer
- Other concerns that led them to decline enrollment:
 - HIV D+/R+ transplantation was safe (45% vs. 77%, $P = 0.02$),
 - HIV D+ organs would work similar to HIV D- organs (55% vs. 77%, $P = 0.04$)
 - Would receive an infection other than HIV from an HIV D+ organ (64% vs. 13%, $P < 0.01$).

J Acquir Immune Defic Syndr. 2020 Sep 1;85(1):88-92.

False positive HIV tests

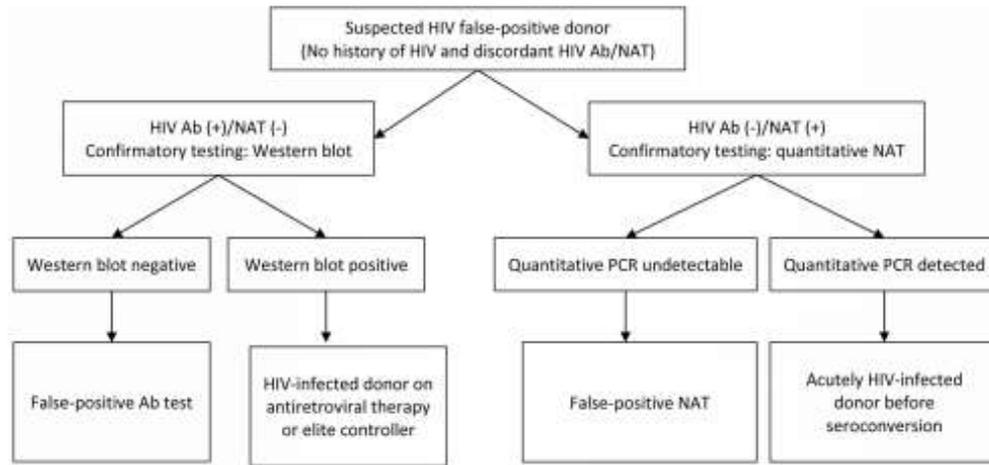


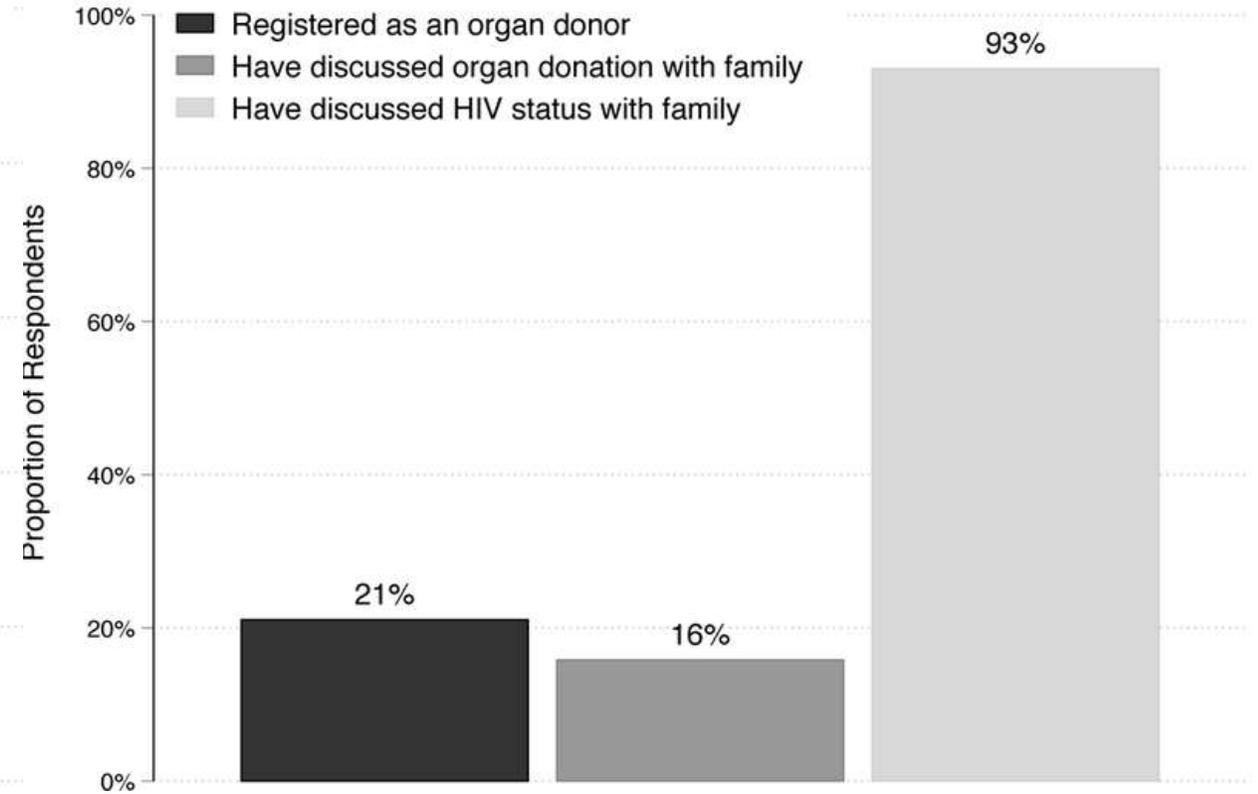
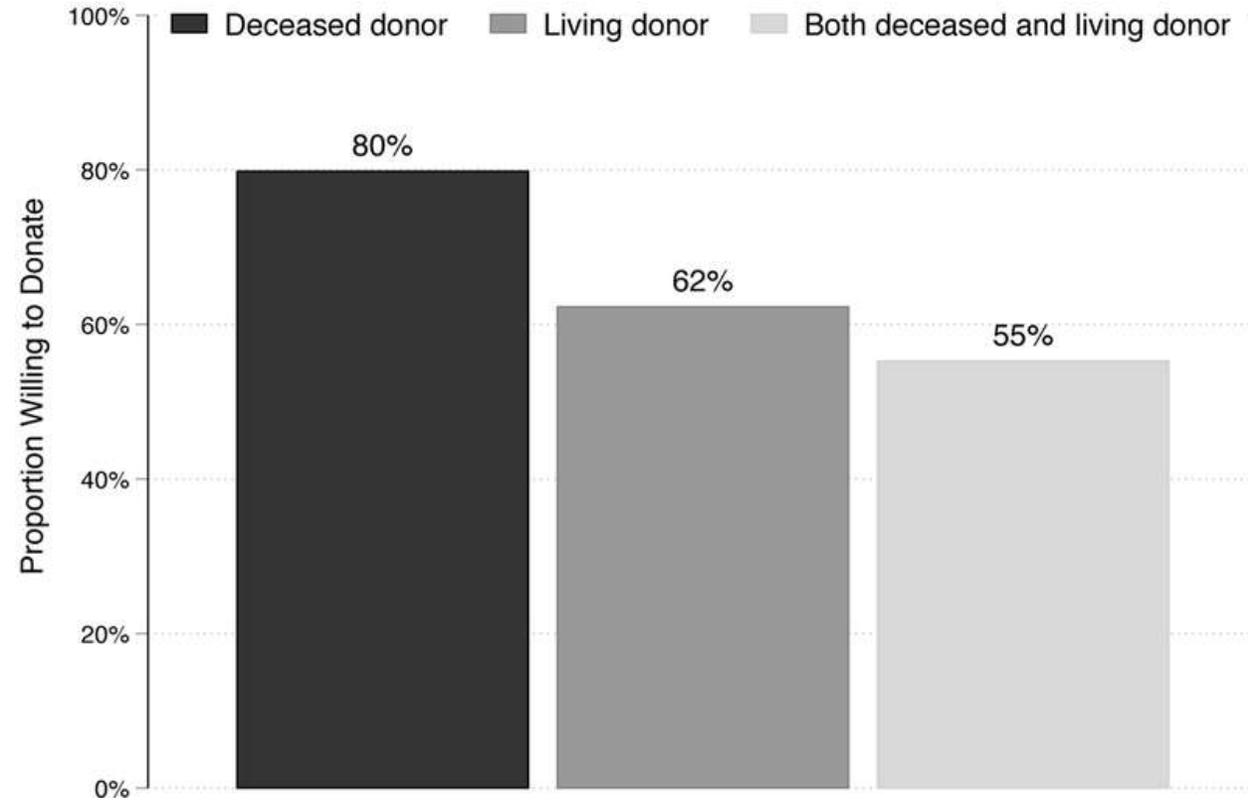
Figure 1. Suspected False-positive Donor Algorithm

Potential explanations for discordant HIV Ab and NAT testing in a potential donor with no prior history of HIV per the medical record or family history. In cases of a reactive Ab test (left), a Western blot or HIV Ag/Ab combination assay would be the preferred next test. If the Western blot is negative, this confirms result was a false-positive. If the Western blot is positive, the donor could be HIV-infected and taking effective antiretroviral therapy or have an effective immune response (i.e. elite controller). In cases of a nonreactive Ab test and a positive qualitative NAT (right), a quantitative viral PCR would be the preferred next test. If the quantitative PCR is undetectable, this confirms the qualitative NAT was a false-positive. If the quantitative PCR is positive this indicates the donor was recently HIV-infected and has not yet

Typically, organs from potential donors with suspected false positive HIV testing were discarded, but the HOPE act means that these organs can now be used.

These donors have reflected ~1/3 of organs transplanted under the HOPE Act.

Are people with HIV willing to sign up for organ donation?



Encouraging organ donation in primary care

I CAN'T REGISTER AS AN ORGAN DONOR WITHOUT SHARING MY HIV STATUS.

You never have to share your HIV status when registering to save lives as an organ donor...just say "YES"! Everyone can register. Everyone can save lives.



PEOPLE LIVING WITH HIV CANNOT RECEIVE ORGAN TRANSPLANTS.

Research shows that people living with HIV wait longer to receive a life-saving organ transplant. But YOU can change that. Living with HIV? Register as an organ donor. Be a hero to someone waiting.




CELEBRATE WORLD AIDS DAY... BY REGISTERING AS AN ORGAN DONOR!

Living with HIV? You can register as an organ donor! The HOPE Act of 2013 made HIV-HIV transplants legal in the U.S.

DON'T LET HIV STOP YOU FROM BEING A HERO... REGISTER TODAY AT REGISTERME.ORG!



DEAR TEAM HOPE, I'M LIVING WITH HIV. HOW CAN I REGISTER AS AN ORGAN DONOR?

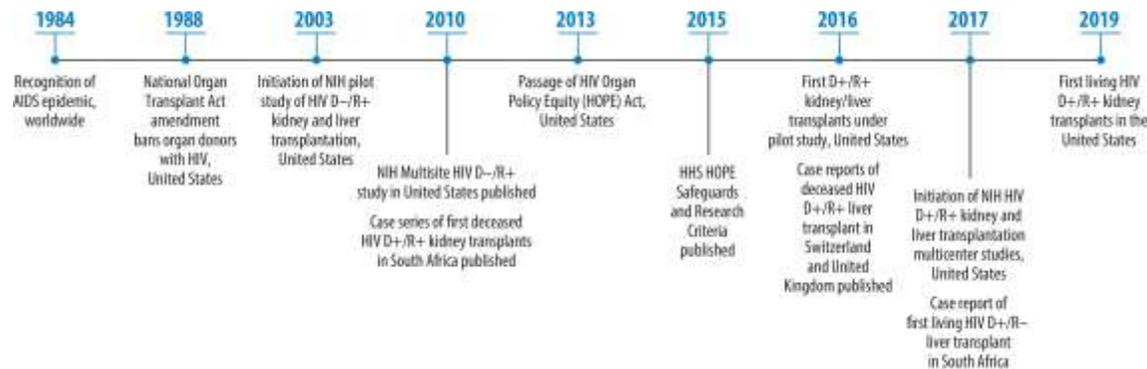
Great question! Registering to be an organ donor is the same for everyone, HIV+ or HIV-. Take your pick from options 1, 2, or 3. Remember, you are **not** required to disclose your status to register:

- ONLINE AT REGISTERME.ORG
- AT YOUR LOCAL DMV WHEN YOU GET YOUR DRIVERS LICENSE
- ON YOUR IPHONE IN THE HEALTH APP



What does the future hold?

- Kidney and liver transplant no longer to be considered experimental → more centers to offer
- Other organs will require that HOPE transplants will continue to be done under research protocols *with removal of the volume requirement*
 - More centers to offer heart transplant
 - HOPE lung approved at Montefiore; HIV pancreas pending
- Further research into how to minimize rejection rates
 - Montefiore in talks to be a funded center for this!



Thank you!

Montefiore



Albert Einstein College of Medicine

