Abdominal Transplantation: Innovations and Emerging Trends

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Starzl Transplant Institute
University of Pittsburgh Medical Center



Objectives for Today

- Learn every aspect of liver, pancreas and kidney organ transplantation
- Learn to how to perform the actual surgery
- Learn to how to speak Sanskrit

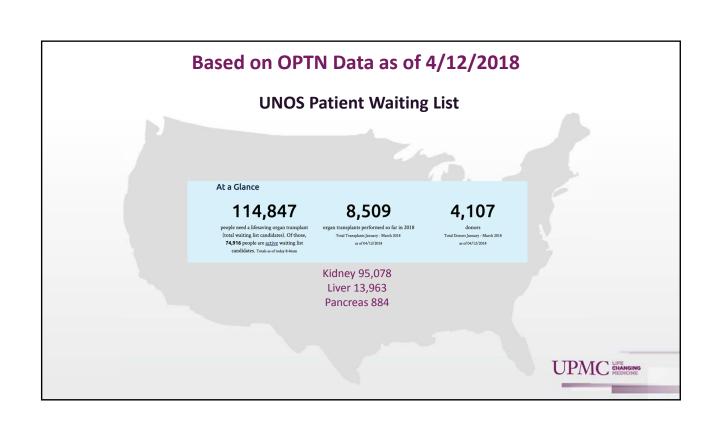


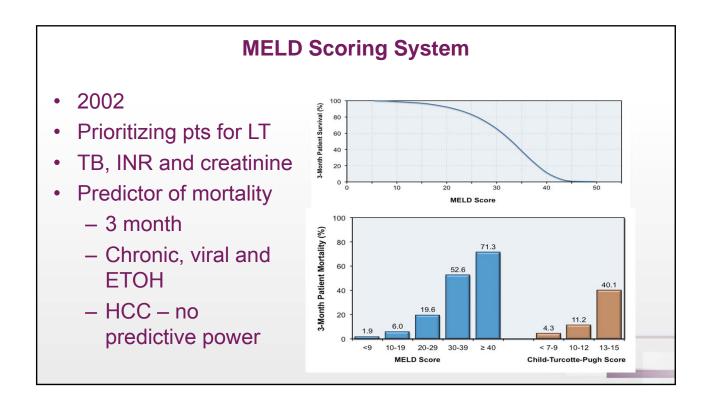
Top 10 List - 2018 Emerging Topics in Transplantation

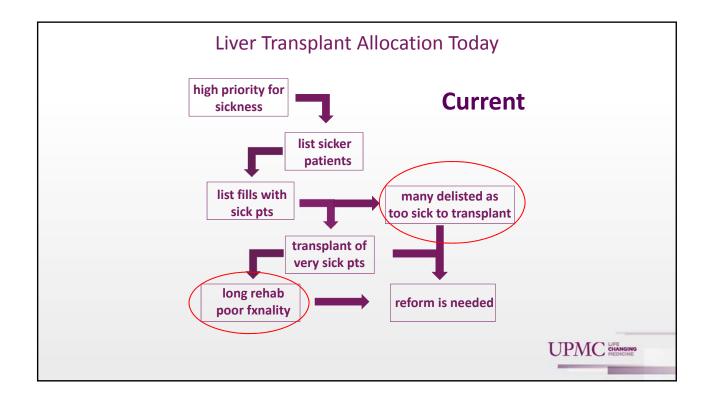
- Organ Distribution
- Liver Non-DSA Allocation
- HCV+ transplantation
- The Artificial Kidney
- Machine Pump Perfusion
- Xenotransplantation
- Increasing Live Donation
- Hope Trial

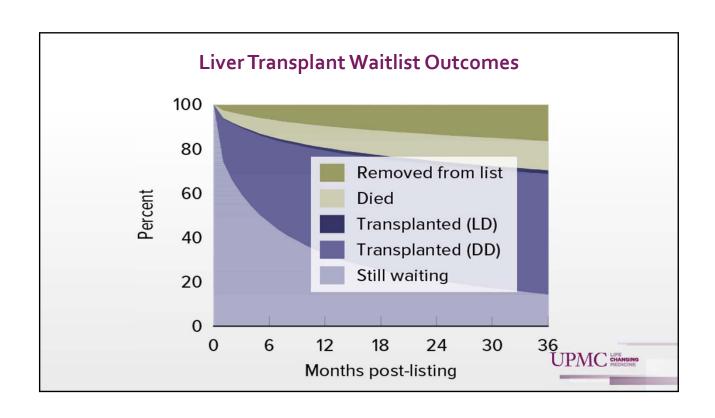




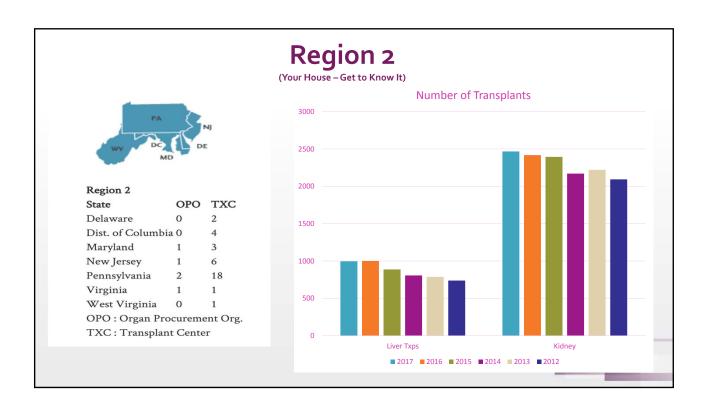


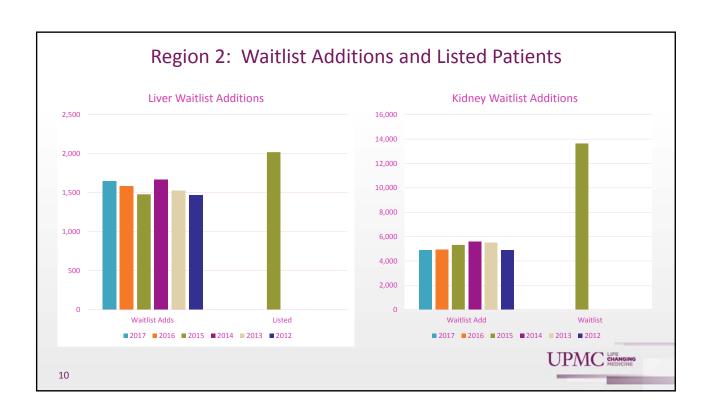


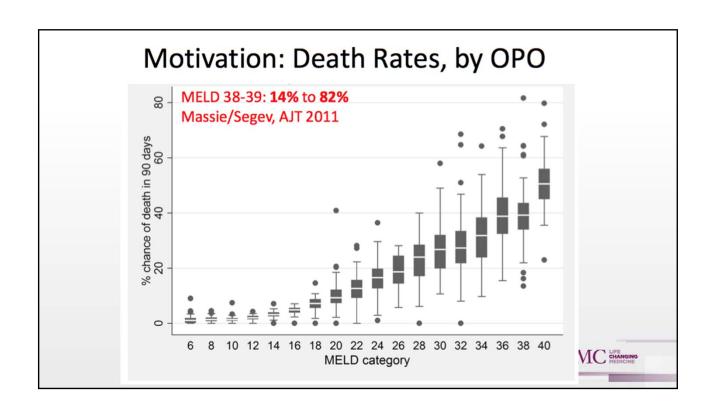


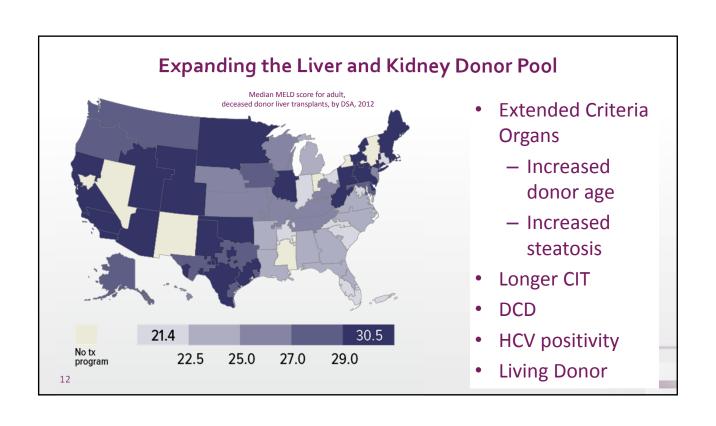






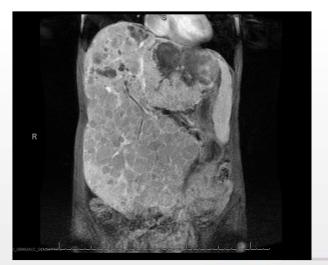




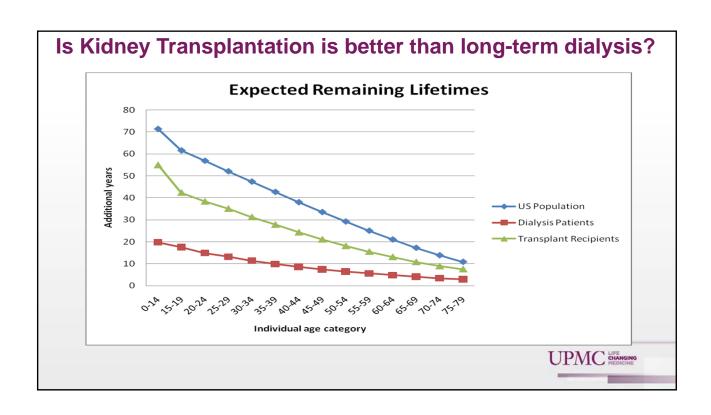


Rationale for Liver Transplantation

- Treats lesion and disease
 - Most HCC multifocal
 - Oncologically margins
- Treats underlying disease
 - Cirrhosis
 - Restores portal pressure
 - Restores hepatic function



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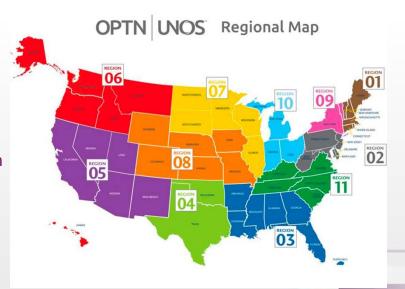
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OPO LI M	ELD/PELD = 37	- Adult and Pediatric Age 0-	17							
Region	al LI MELD/	PELD = 37 - Adult and	Pediatric Age 0-17							
							or Weight (lbs)			
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OPO LI M	ELD/PELD = 36	- Adult and Pediatric Age 0-	17							
		PELD = 36 - Adult and								
							or Weight (lbs)			
Seq#	Center	Name	SSN	Age	LI seg	Min	Max	Score	Other Organs	
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OPO LI M	ELD/PELD = 35	- Adult and Pediatric Age 0-	17							
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							or Weight (lbs)			
Seq#	Center	Name	SSN	Age	LI seg	Min	Max	Score	Other Organs	
6	****.***	***, ***	********	61	Y	40	440	31.0000		
7	****	***, ***	*******	50	Y	40	440	29.0000		
8	****.***	***, ***	***.**.***	67	Y	40	440	28.0000		
9	****.***	***, ***	***.**.***	49	Y	40	440	28.0000		
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13	****.***	*** ***	***,**,***	53	Y	40	440	25,0000		
		*** ***	***,**,***	37	Y	40	440	24.0000		

Dept of Health and Human Services (DHHS) The Final Rule

- Issued in Mar 2000
 - Replaced local and regional organ allocation
 - Gave DHHS not medical community control of the organ allocation
 - Lawsuits by UW, Oregan Health Sciences and State of NJ
- Amended OPTN Final Rule
 - "organs should be distributed over as broad a geographic area as feasible" and considers the urgency of a recipient patient's need for an organ transplantation
 - policies "shall not be based on the candidate's place of residence or place of listing, except to the extent required"

Liver Distribution Now and in the Future

- Directive from the HHS Secretary
 - Liver and Intestine
 Committee no DSA
 and Region
 - Proposal
 - No DSA and region in liver allocation
 - Allocate 150m, 250m and 500m from donor hospital



Proposal – Available for Public Comment 10/8/2018

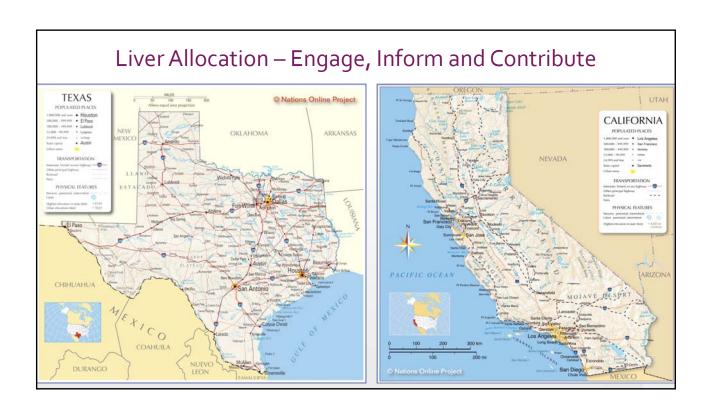
Table 3: Allocation of Livers from Non-DCD Deceased Donors at Least 18 Years Old and Less than 70 Years Old

Classification	Candidates that are within this proximity of the donor hospital:	And are:
1	500nm	Adult or pediatric status 1A
2	500nm	Pediatric status 1B
3	250nm	MELD or PELD of at least [35/32]
4	150nm	MELD or PELD of at least 15
5	250nm	MELD or PELD of at least 15
6	500nm	MELD or PELD of at least 15
7	National	Adult or Pediatric Status 1A
8	National	Pediatric Status 1B
9	National	MELD or PELD of at least 15
10	150nm	MELD or PELD less than 15
11	250nm	MELD or PELD less than 15
12	National	MELD or PELD less than 15

Proposal – Available for Public Comment 10/8/2018

Table 4: Overview of the SRTR Modeling Report

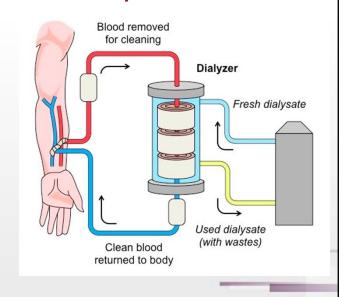
Scenario	Variance in Median Allocation MELD/PELD at Transplant	Transplant Count	Median Transport Time (hours)	Median Transport Distance (miles)	Percent of Organs Flown
Current	9.97	6651	1.7	88.5	50.7
2017 Board Approved	7.41	6643	1.7	100.4	54.4
Acuity 250+500	4.33	6594	1.9	183.5	71.4
Acuity 300+600	4.07	6583	2	211.3	74
Broader 2- Circle MELD 35	6.74	6620	1.8	107.7	58.4
Broader 2- Circle MELD 32	6.54	6616	1.8	117.1	60.8



Artificial Kidneys

Downside of Center HD

- -NEJM 2010 Home vs Center
 - Better QOL
 - HTN/anemia
- -High Cost of ESRD
 - -\$72,000/yr
- -1972 40% Home, 2009 <5%
- -Significant Pt Burden
 - -6hrs 3x/wk
- Facility waste and cost

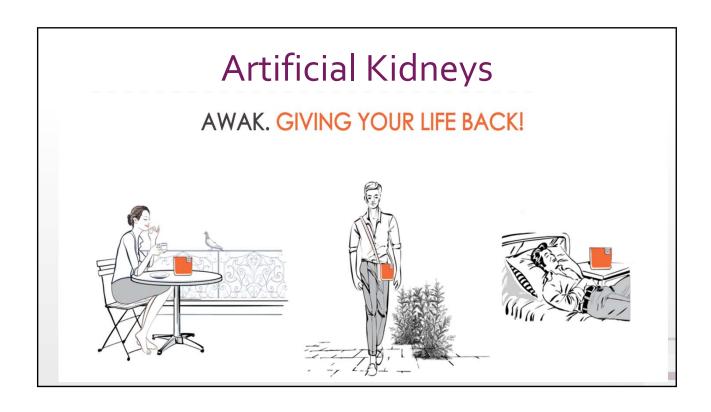


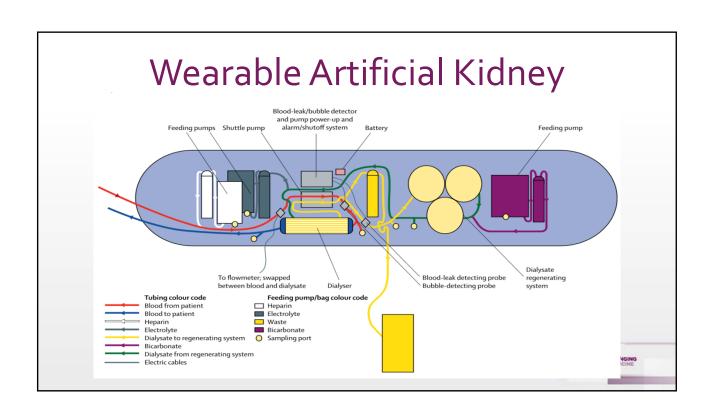
Artificial Kidneys

Barriers to Portability

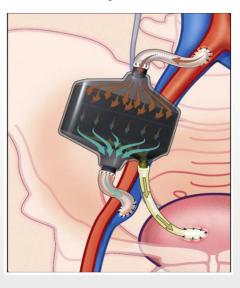
- -Package Size
 - -HD filter is large
- -Power
 - -Energy intensive
- -Water
 - -140L of dialysate

AWAK GIVING YOUR LIFE BACK! • <2 kg, ultra-portable, APD on-the-go • Bedside | Ambulatory | Wearable • Only 2L PD solution required per day • Single 6-8 hr therapy provides 12-16 L of total dialysate flow • Alarms for patient safety • Designed for simplicity and convenience Less than 2 kg





Implantable Artificial Kidney



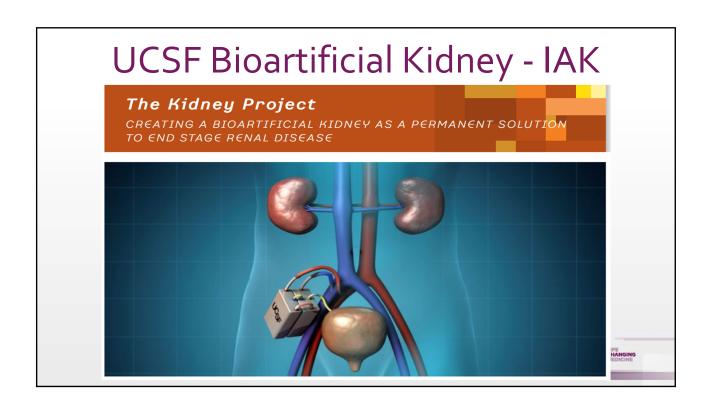
Challenges

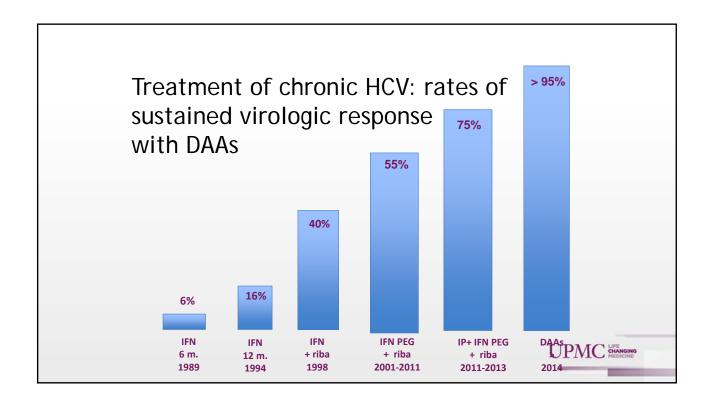
- Thrombus free operation for years
- Initial surgery for implantation
- Additional surgeries for complications
- Cost and reimbursement

Implantable Artificial Kidney

	AWAK	WAK	IAK
Weight	<2 kg	<5 kg	~500 g
Power requirements	Battery operated	Battery operated	None, uses cardiovascular pressure and chemical energy of cellular metabolism
Fluid requirements	~2 L dialysate/treatment	6 L dialysate/treatment	No dialysate, patients drink an electrolyte-rich fluid to keep up with losses
Stage of development	Trials in human	FDA clinical trials	Animal models
Strengths	Bloodless, easily portable, high clearances	Portable, low UF rate, electrolyte balance seen in clinical use	Low burden to patient, minimal waste generation
Limitations	Frequent exchange of cartridges (every 7 h)	Clotting and bleeding issues	May require repeated invasive procedures



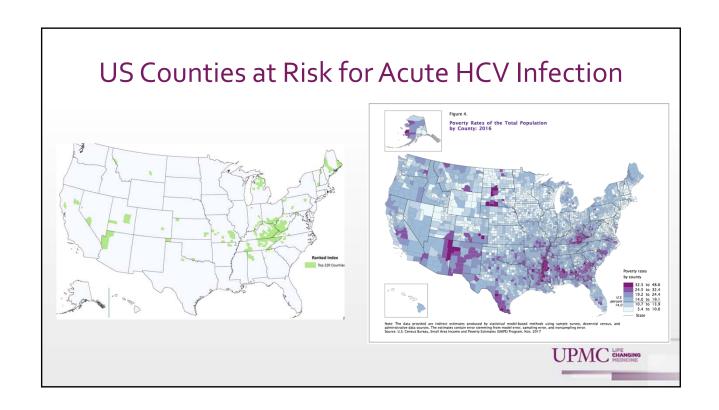


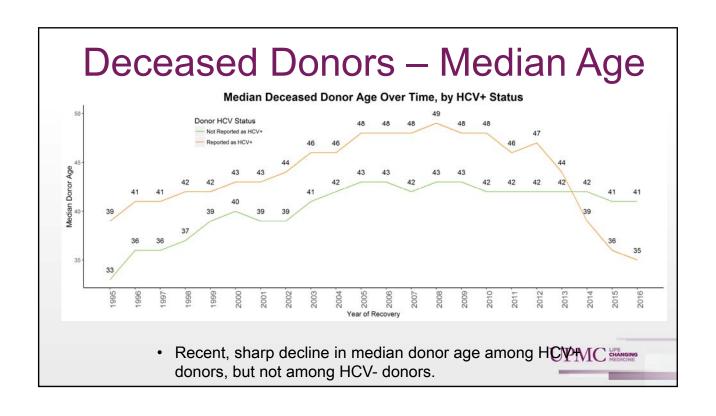


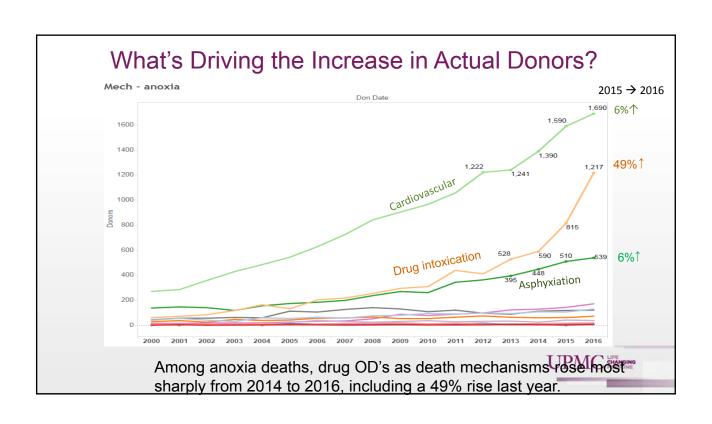
The Changing Demographic of US HCV Infection

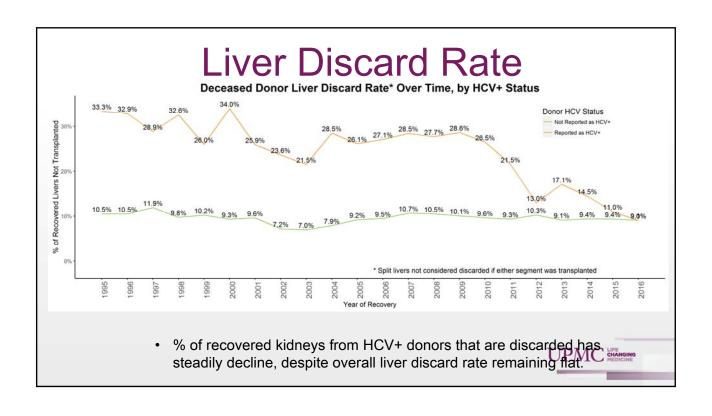
- Prior to 2010
 - AA account for 25% of chronic HCV in the US
 - American Indians and Alaskans with highest rate of new infection
- Since 2010
 - Greatest increase young, nonminority with history of opioid use
 - Age 18 to 29yrs
 - Equal male and female
 - Non-urban
 - KY, TN, VA, WV

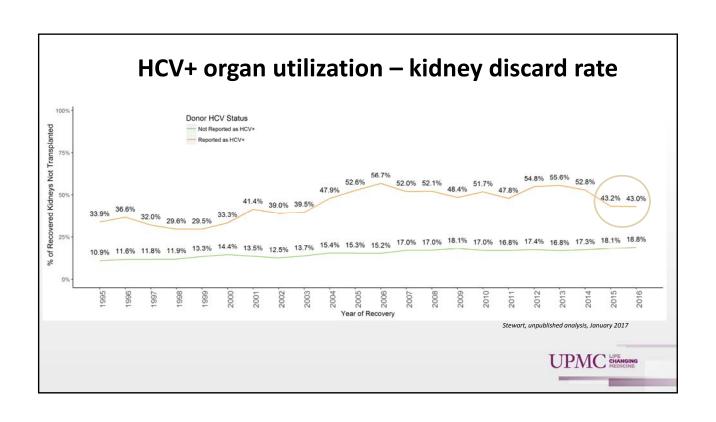












Renal Transplant and HCV+ Organs

- HCV among US ESRD in 6-10%
- US Centers Routinely use Donor HCV+ to Recipient HCV+
- Any Center in the US Protocol
 - HCV Genotype
 - Excellent Graft/Pt outcomes
 - Current Wait time
 - 6 weeks
 - Fast-tracked if HCV+

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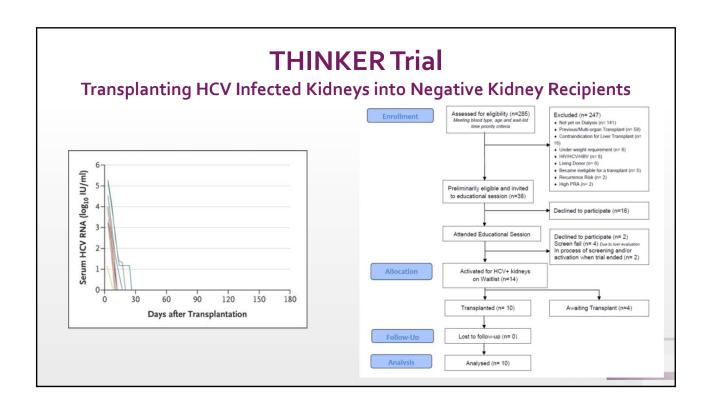
THINKER Trial

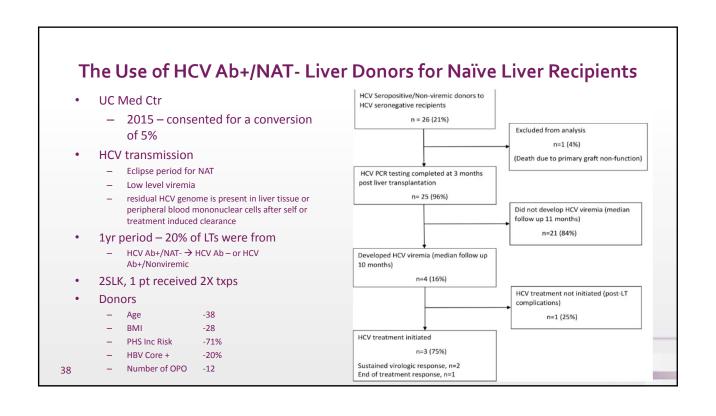
Transplanting HCV Infected Kidneys into Negative Kidney Recipients

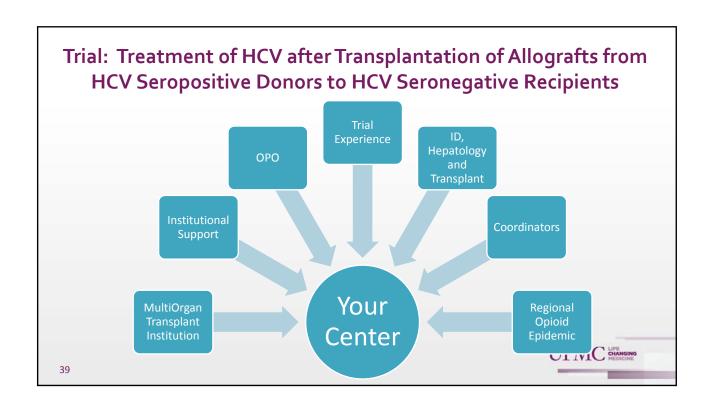
able S1: Inclusion and Exclusion Criteria for the THINKER Trial*

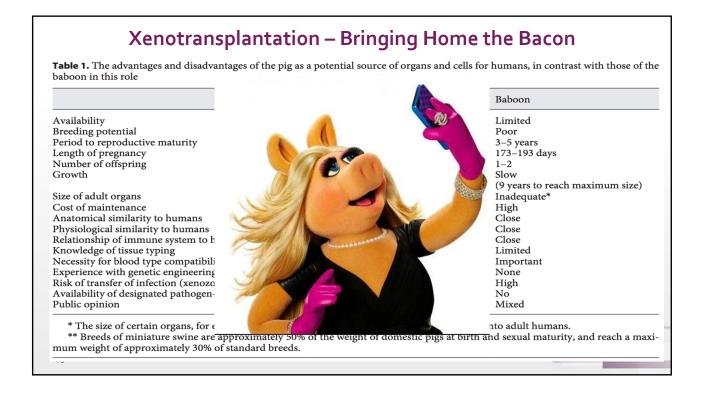
Inclusion Criteria	Exclusion Criteria					
On chronic hemodialysis or peritoneal dialysis	Hepatocellular carcinoma					
 Listed for an isolated kidney transplant with ≤548 days of accrued transplant waiting time and/or ≤548 days of dialysis time 	Patients with primary focal segmental glomerulosclerosis (FSGS), FSGS recurring after previous transplant, or disease process with increased risk of causing early graft failure					
No available living kidney donor	HIV positive					
Blood group A, B, or O	HCV RNA positive (can be isolated HCV antibody positive provided the subject has no history of previously treated HCV)					
Between 40-65 years of age	Hepatitis B surface antigen positive					
Have a panel reactive antibody level ≤97%	Any chronic liver disease (excluding non-alcoholic fatty liver disease (NAFLD) with abnormal liver enzymes					
 Obtained agreement for participation from the patient's treating transplant nephrologist 	Persistently elevated liver transaminases					
No evident contraindication to liver transplantation	Blood group AB (due to short expected waiting time on the kidney transplant waiting list)					
 Able to travel to the University of Pennsylvania for routine post-transplant and study visits 	 Significant hepatic fibrosis on screening elastograph (≥F2 fibrosis) 					
Women agreed to use birth control in accordance with Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) following transplant	 Known allergy or intolerance to tacrolimus that would require post-transplant administration of cyclosporine 					
 Men and women must agree to use at least one barrier method to prevent any secretion exchange 	Pregnant or nursing (lactating) women					
No active illicit substance abuse	Waitlisted for a multi-organ transplant (e.g., pancreas-kidney)					
Weigh at least 50kg	Cardiomyopathy (e.g., left-ventricular heart failure, pulmonary hypertension) that would preclude liver transplantation					
Able to provide informed consent						

- Safety and efficacy
- HCV Geno 1/Viremic → HCV neg pts
 - No NS5A resistance
- All treated with elbasivir-grazoprevir (Zepatier)
- ClinicalTrials.gov number, NCT02743897
- Physician led 3 step consent process
- Median waittime 58d
- KDPI 42%
- All with detectable HCV RNA/OFC BANGING









Xenotransplantation – Barriers to Success



- Ab-Dependent Complement-Mediated Rejection
 - humans develop Ab to certain carbohydrate (glycan) antigens galactoseα1,3-galactose (Gal)
 - 2003 Gal Knockout Pig
- T Cell Mediate Ab and Cellular Response
 - Cya and FK block signal 1
 - anti-CD154mAb, anti-CD40mAb (that block signal 2), successfully prevented a T cell response
 - Genetic engineering

Xenotransplantation – Barriers to Success

- Coagulation Dysregulation between Pigs and Primates
 - molecular incompatibilities between the pig and primate coagulation-anticoagulation systems
 - Thrombotic microangiopathy
- Inflammatory Response
 - prolonged and persistent inflammatory response to even a small pig xenograft, for example,
 - ⁴² an artery patch,

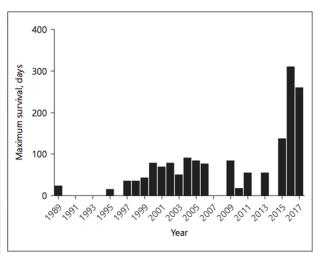


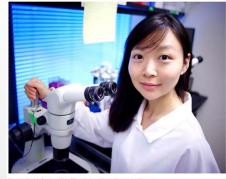
Fig. 1. Maximal pig kidney graft survival in a nonhuman primate by year. Maximum survival has increased from 22 days in 1989, to 90 days in 2004, and to >300 days in 2016.

Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9

Science 22 Sep 2017

Taking the PERVs out of Pigs

- Porcine Endogenous Retrovirus
- inactivated PERVs in porcine primary cell line and generated PERV-inactivated pigs via somatic cell nuclear transfer
- Huge



Egenesis chief scientific officer Luhan Yang Courtesy eGenesis

 Egenesis, a startup that raised \$38 million in March, just successfully used the gene-editing tool CRISPR to knock out a key virus in piglets.

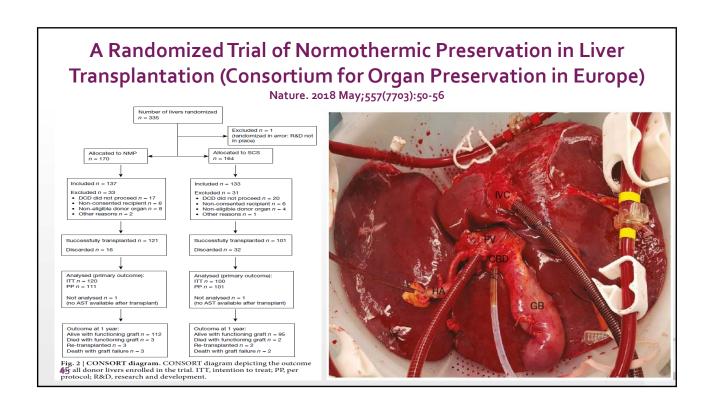
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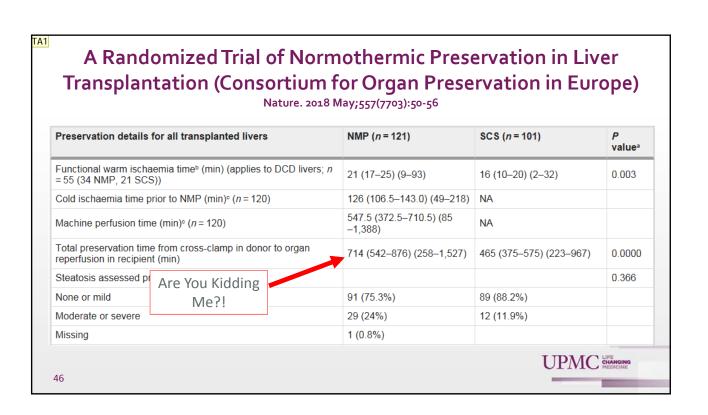
Machine Perfusion for Liver Transplantation

- ECD Characteristics
 - Advanced donor age
 - Extended cold time
 - Steatotic grafts
 - DCD variance and complications
- Pump perfusion history
 - 1970 Starzl hypothermia and hyperbaric oxygenation
 - Logistics, financial
- Dynamic Ex Situ Graft Perfusion
 - Preservation
 - reconditioning



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TA1 Tevar, Amit, 10/16/2018

	Nature 2018			
	1401010. 2010	May;557(7703):50-56		
	NMP (n = 121) ^a	SCS (n = 101) ^a	Effect (95% CI) ^b	P value
Peak AST				
ITT°				
Adjusted	488.1 (408.9–582.8)	964.9 (794.5–1,172.0)	0.5 (0.4–0.7)	0.0000
Unadjusted	484.5 (406.4–577.6)	973.7 (795.2–1,192.3)	0.5 (0.4-0.6)	0.0000
Test for interaction by donor type				0.012
Subgroup analysis by donor type				
DBD	526.2 (427.3-647.9)	880.2 (708.5–1,093.5)	40.2% (19.3–55.7%)	0.0009
DCD	389.7 (278.0-546.4)	1,458.1 (944.7–2,250.5)	73.3% (53.7–84.6%)	0.0000
PP analysis	498.6 (1.118–599.4)	982.9 (810.4–1,192.2)	0.5 (0.4–0.7)	0.0000
Secondary outcomes				
Discard rates ^d	16 (11.7%)	32 (24.1%)	-12.4% (-21.4 to -3.3%)	0.008
Primary non-functione	1 (0.8%)	Are You Kiddin	G.	NA
Post-reperfusion syndrome	15 (12.4%)	31).6% (-31.6 to -9.6%)	0.0002
Post-reperfusion lactatef	3.6 (2.6-4.2)	4 Me?!		0.018
Early allograft dysfunction	12 (10.1%)	29 (29.9%)	0.263 (0.126-0.550)	0.0002

What is Next for Liver Machine Perfusion?

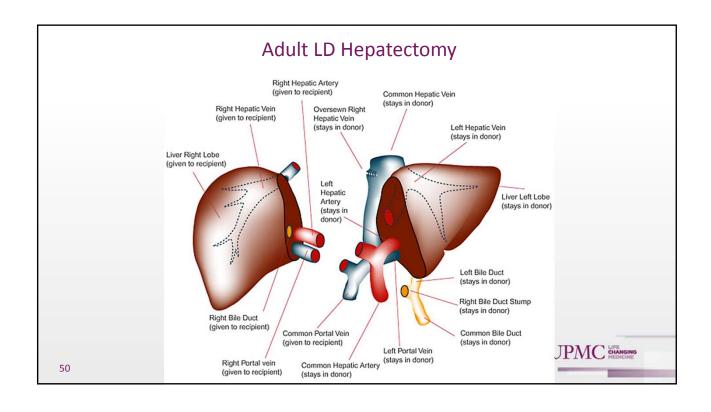
- 13 active ongoing and/or recruiting trials (US and Europe)
 - Preservation
 - Use of discards/DCD/ECD
- Wealth of data coming to a journal near you
- Benefits
 - Improved allograft function
 - Shorter LOS
 - PNF, EAD, pt/graft survival

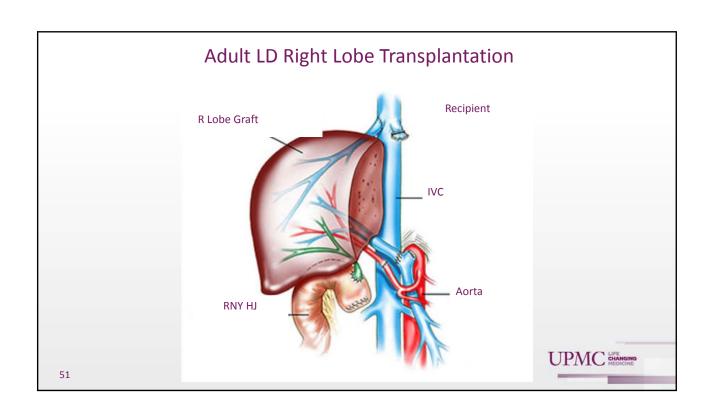


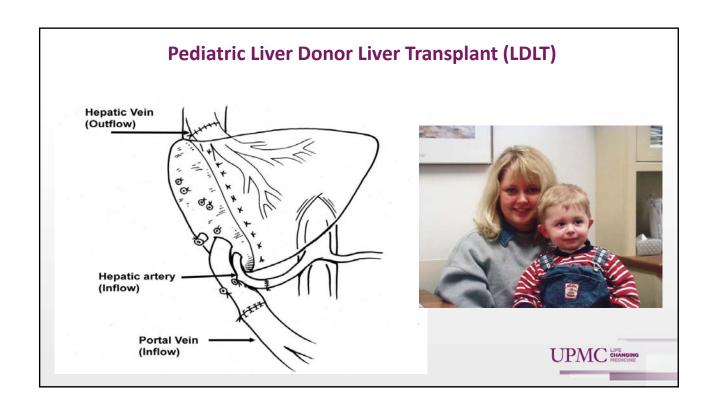
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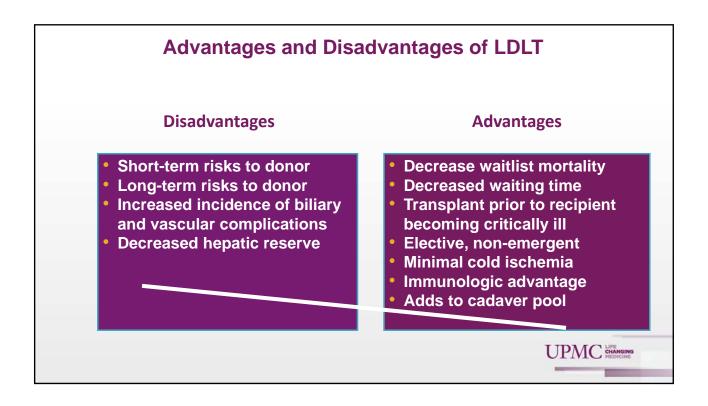
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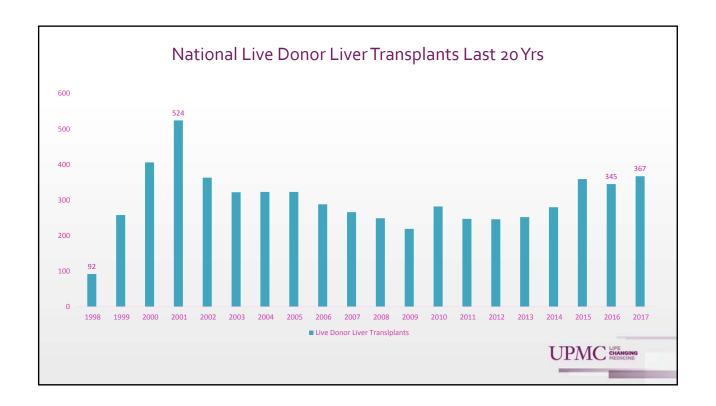










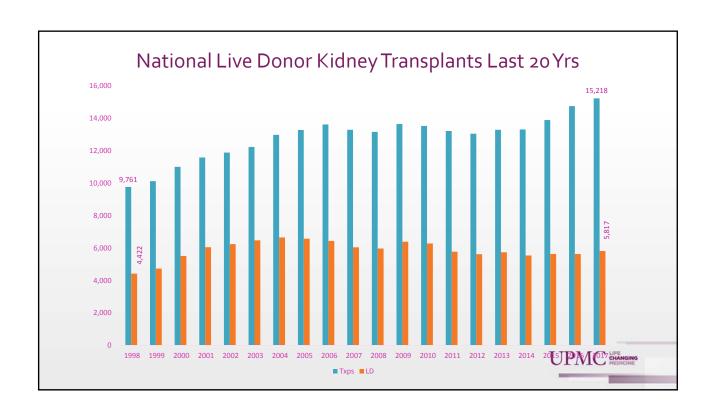


WHY HAVE THE NUMBER OF LDLTs REMAINED SO LOW?

- Numerous regulations with significant consequences:
 - -UNOS, CMS, state
- Donor complications/deaths that have been highly publicized
- Risk burden seems to rest on shoulder of small number of individuals
- Not all members of the "team" are equally supportive
- Recipients and Donors are misinformed

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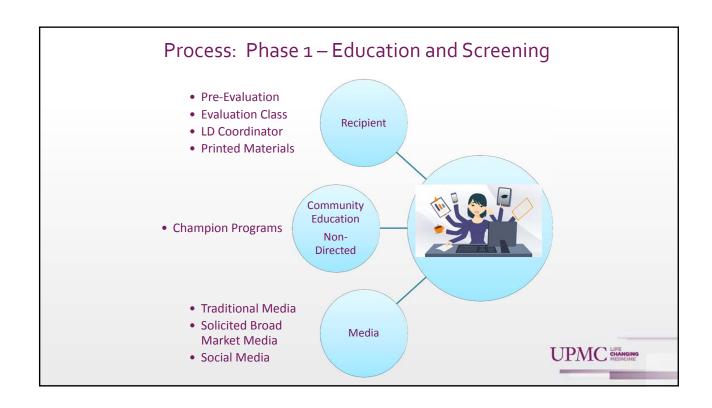


Who Can Be a Living Donor?

- Sibling
- Spouse
- Parents
- Other Relatives
- Co-Worker

- Friend
- Church/Temple Member
- Neighbor
- Non-compatible donor
- Republican or Democrat
- Must be willing to donate
- We will evaluate and screen for suitability











HIV-to-HIV Solid Organ Transplantation

Ghady Haidar, MD Assistant Professor of Medicine University of Pittsburgh Medical Center



Background

- 50% of deaths among patients who are well controlled on ART in North America and Europe
 - $\ \, \underline{\text{\textbf{Not due to AIDS}}}$ and opportunistic infections
 - Due to
 - Non-AIDS-defining cancers
 - CV and respiratory diseases
 - End-stage liver disease
 - End-stage renal disease

Maartens, Lancet 2014 PPMC CHANGING GIII, CID 2010 Smith, Lancet 2014 Bickel, HIV Medicine 2013

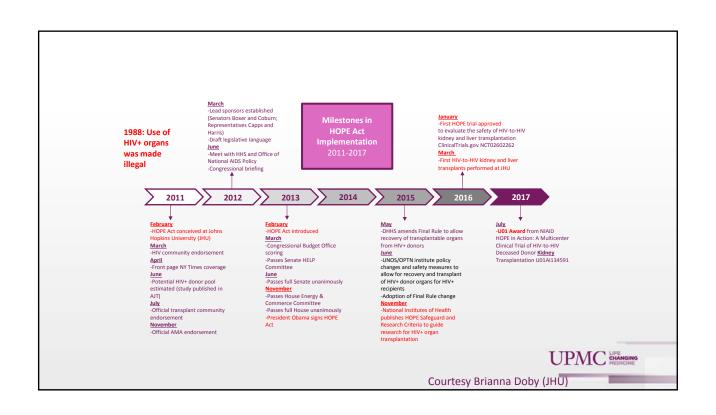
Using HIV+ deceased donors

- Expands donor pool by <u>360-600 patients</u> annually in the USA
- Wait times for HIV+ patients will decrease (KTx)
 - > 7 years to < 1 year</p>
- Benefits African Americans the most
- Benefits ALL transplant candidates

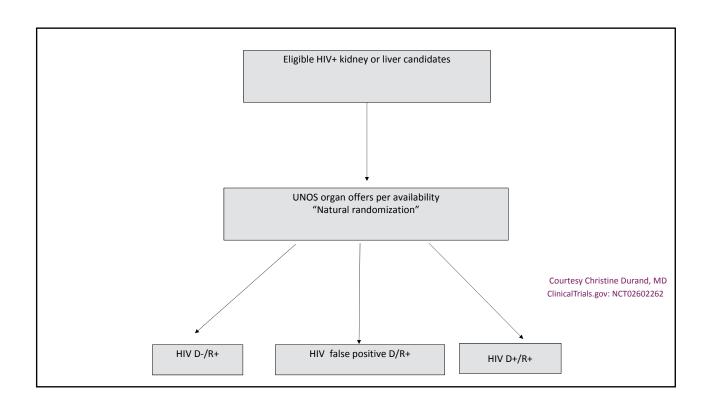


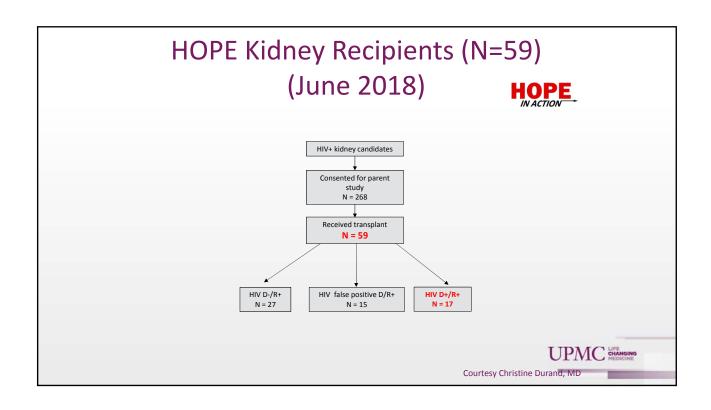


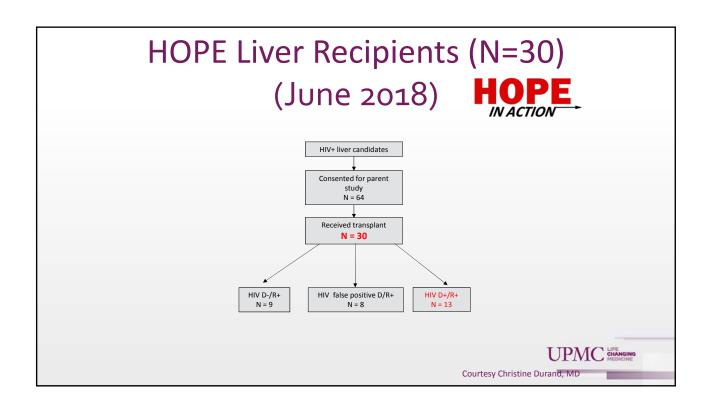
HIV +/+ SOT in South Africa ORIGINAL ARTICLE HIV-Positive—to—HIV-Positive Kidney Transplantation — Results at 3 to 5 Years Elmi Muller, M.B., Ch.B., M.Med., Zunaid Barday, M.B., Ch.B., Marc Mendelson, M.D., Ph.D., and Delawir Kahn, M.B., Ch.B., Ch.M. 27 patients (4 + 23) VL < 50 copies/mL on standard ART NRTI + NNRTI (59%) NRTI + PI/r (41%) No INSTI's in South Africa Median CD4: 288 (IQR: 236-511) 11% HBV+, none with HCV



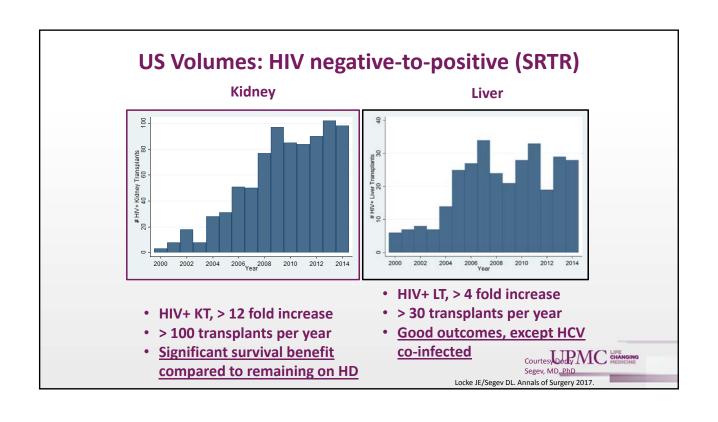












Patient/graft survival (NEJM 2010)

Patient survival

- 1-year: 94.6%

- 3-year: 88.2%

Graft survival

- 1-year: 90.4%

- 3-year: 73.7%

History of US Organ Distribution

- Uniform Anatomical Gift Act in 1968
 - US Congress effort to national organ policy
- National Organ Transplant Act (NOTA) in 1984
 - OPTN
- Division of DHHS → HRSA → UNOS to maintain the OPTN
- UNOS organized the country in 11 regions MC