Transplantation of HCV-Infected Organs into Uninfected Recipients

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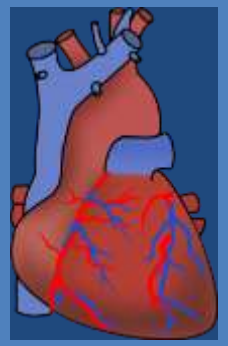


DISCLOSURES

- I have received consulting fees from Merck
- I will be discussing off-label use of an FDA-approved drug (Grazoprevir/Elbasvir)
- This study is supported by an investigator-initiated grant from Merck, the makers of the medication used for the study. The University of Pennsylvania will receive money from Merck over the course of this study.
- I will be discussing use of laboratory-derived test for testing of HCV genotype

Should organs from deceased donors infected be transplanted into recipients without HCV?

A. No, this should never be done.

B. Yes, but only in a research protocol.

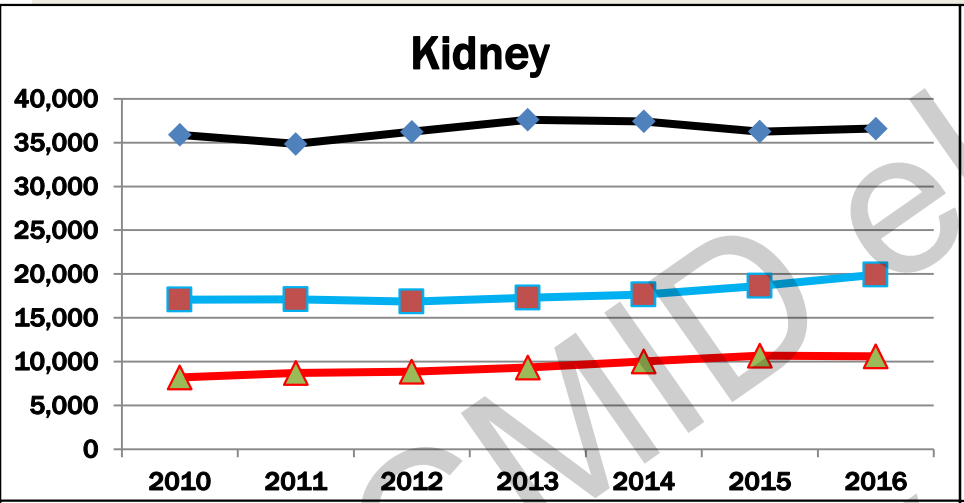
C. Yes, this should be offered to all patients as the ability to cure Hepatitis C is so high.

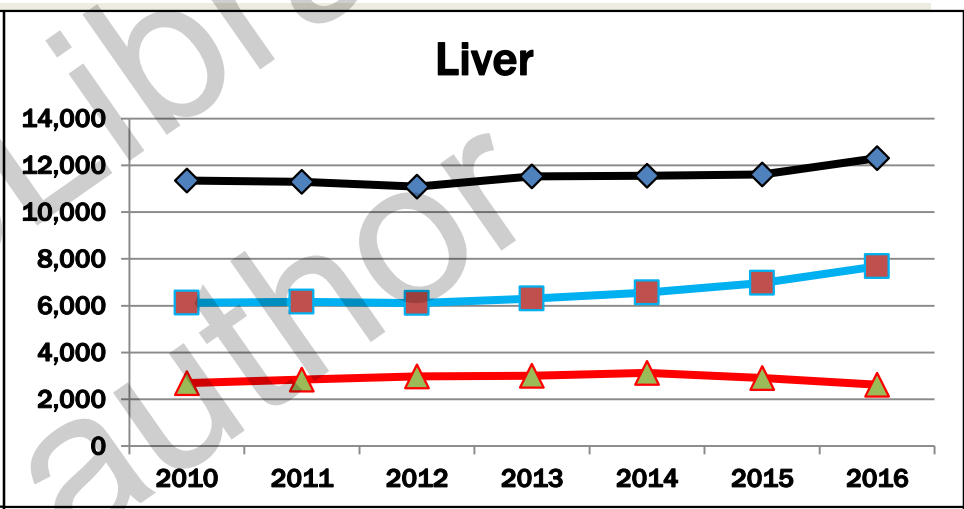
INTERPRETING HCV SEROLOGIES IN THE ORGAN DONOR

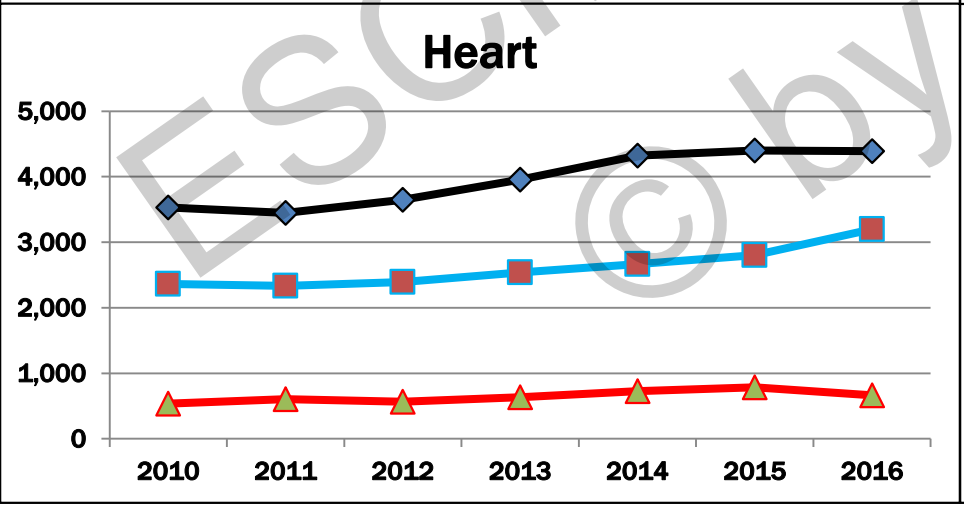
- In the US, since 2014, all deceased donors have
  - HBV, HCV, HIV serologies
  - HBV, HCV, HIV nucleic acid
- HCV antibody: Prior exposure to virus
- HCV Nucleic Acid Test (NAT): Active virus in the blood
- Ab-/NAT-: Never exposed or window period
- Ab+/NAT-:
  - False (+) Ab
  - Active infection with low-level virus (acute or chronic)
  - On-treatment with viral suppression
  - Prior infection with spontaneous clearance
  - Prior infection with treatment
    - Latter two thought to pose no risk of transmission aside from window period
    - Differs from Hepatitis B Core Ab+ which represents cleared infection but few viral particles still hiding out in the liver
- NAT+: Active infection

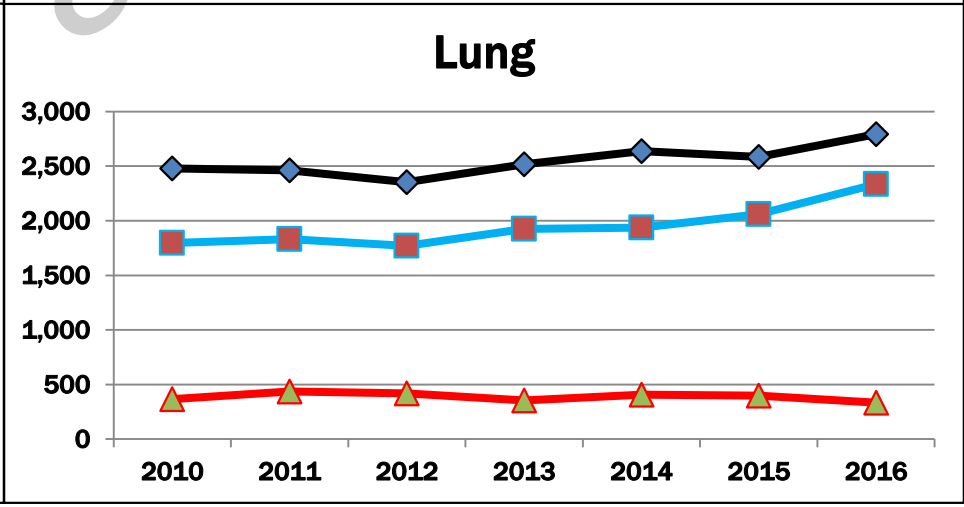
SCOPE OF THE ORGAN SHORTAGE IN THE UNITED STATES

Added to waitlist Transplanted Died/too sick

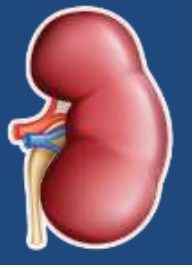


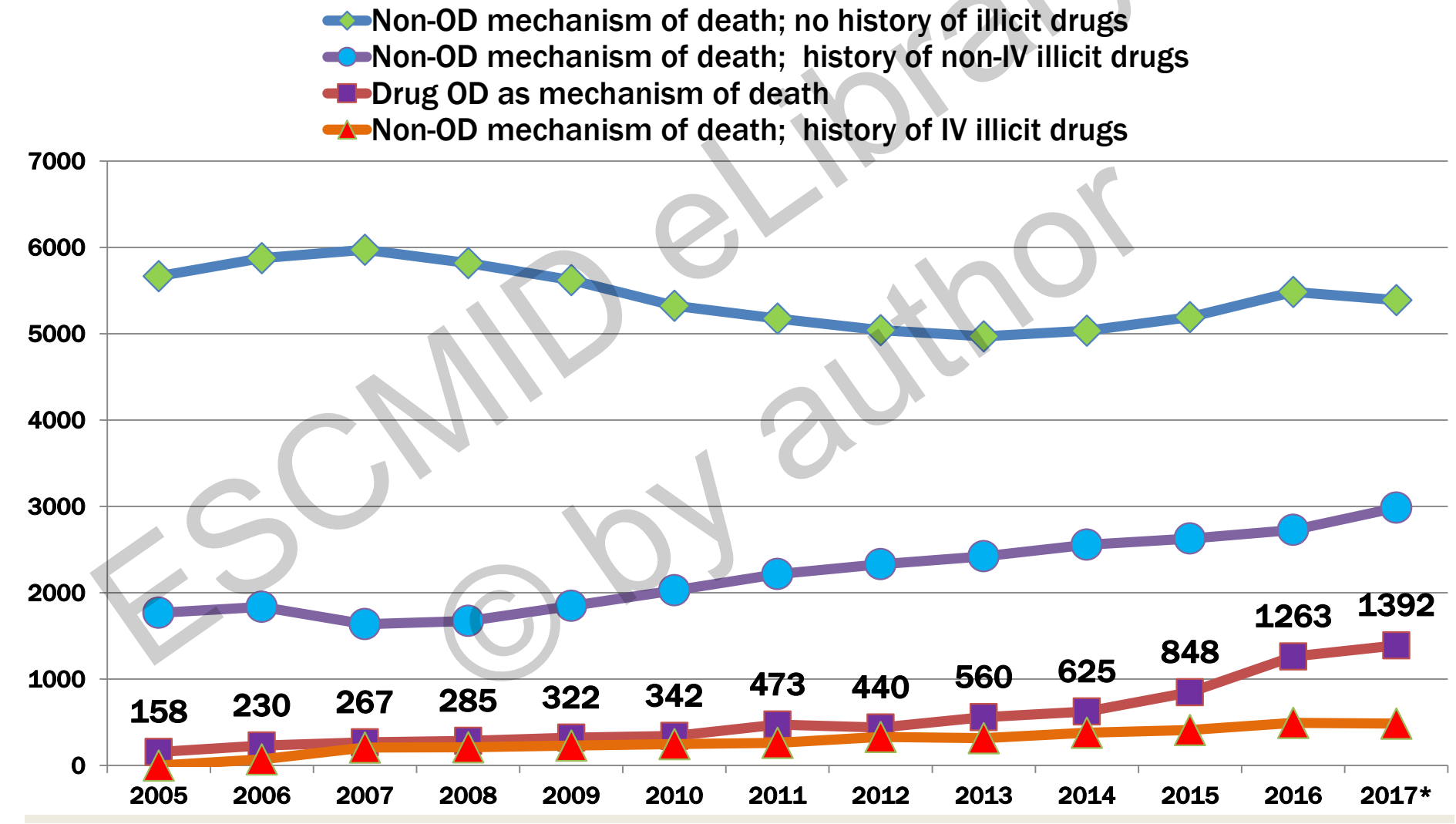




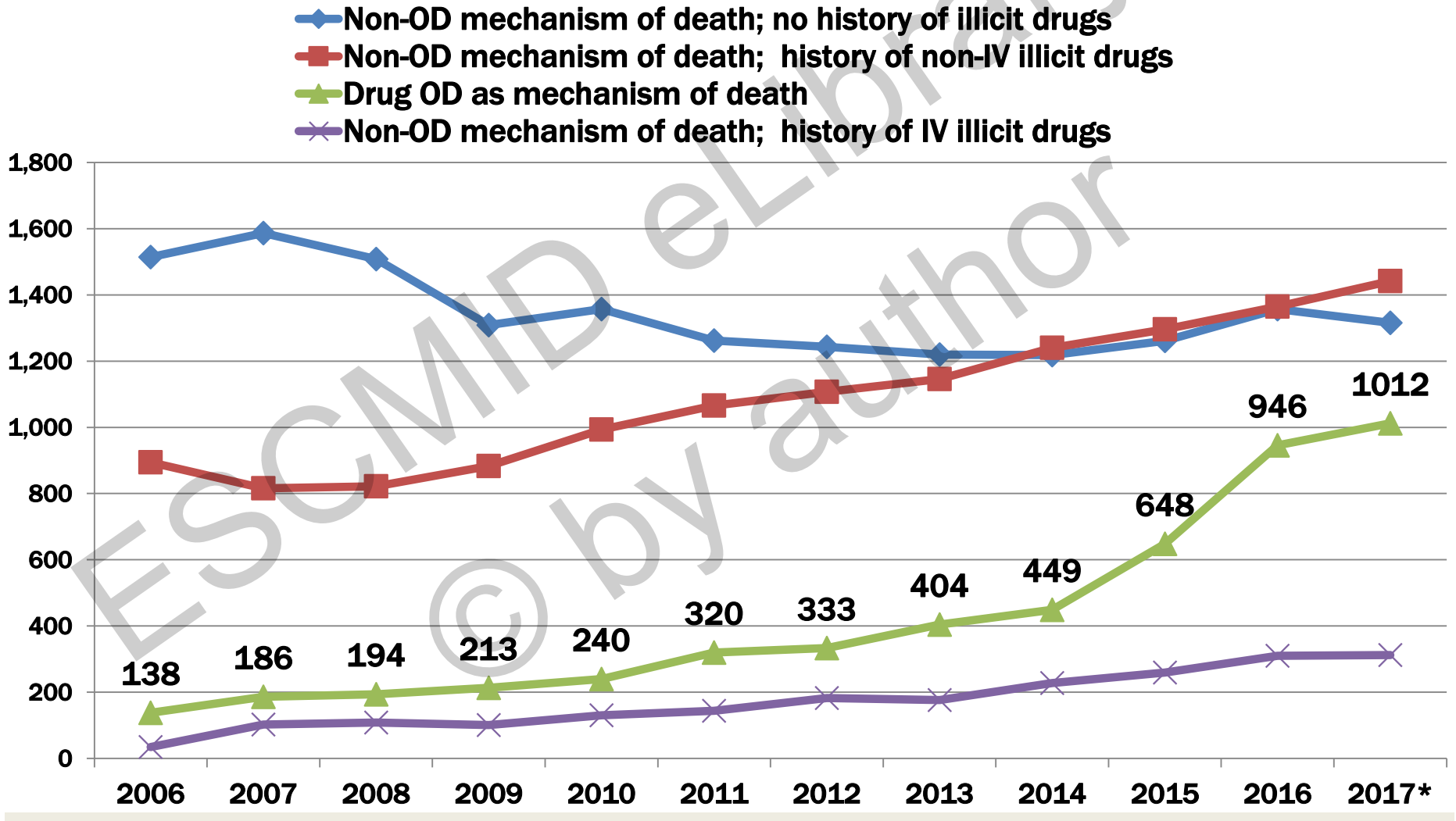


UNFORTUNATE REASON WHY I AM HERE GIVING THIS TALK: OPIOID EPIDEMIC

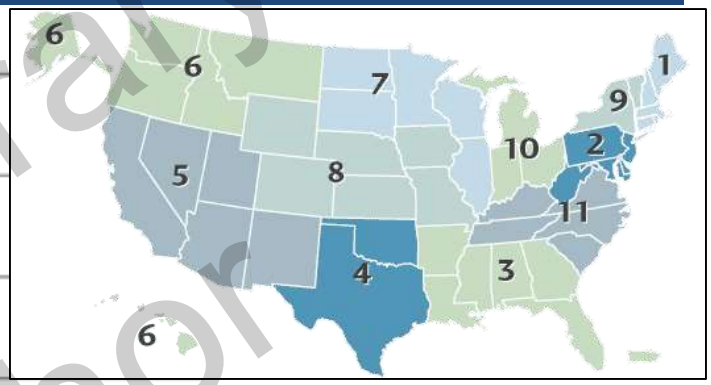


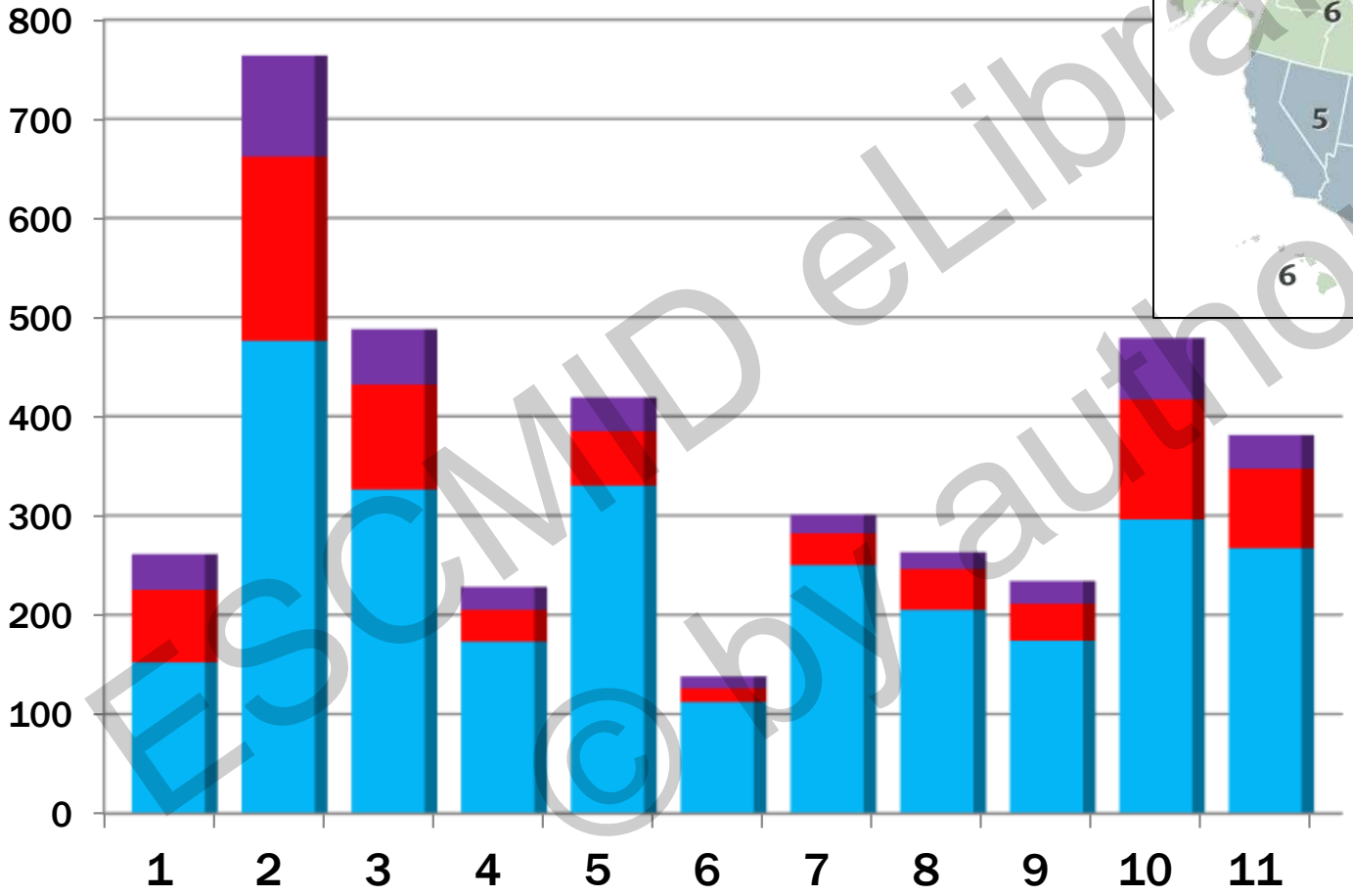


IMPACT OF OPIOID EPIDEMIC ON DECEASED DONATION AMONG "IDEAL" AGE DONORS (18-39)

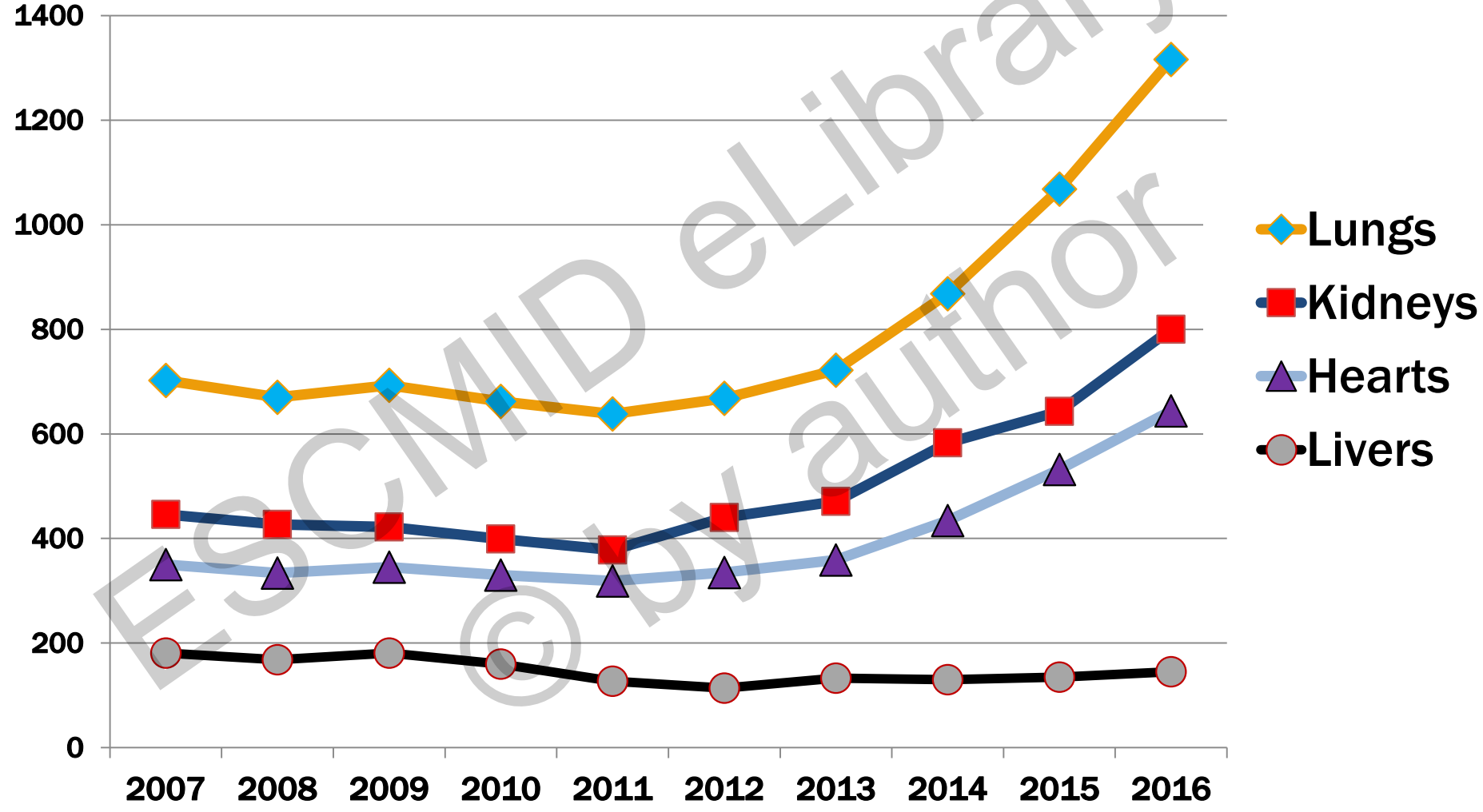


GEOGRAPHIC DIFFERENCES IN HCV AMONG DECEASED DONORS WITH A DRUG OVERDOSE OR IVDU IN 2016





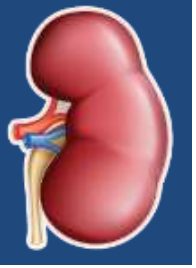
ORGAN DISCARDS FROM "HCV-POSITIVE" DECEASED DONORS IN THE US



WHY WE ARE UNDERESTIMATING THE SUPPLY OF POTENTIAL HCV+ DONORS

- "Donor" defined by UNOS as a patient whose organs are recovered with the intent to transplant
- Who is excluded by this definition
  - Potential donors without authorization for donation
  - Potential donation after circulatory determination of death (DCDD) donors not considered for donation
    - Common in HCV (livers not used)
  - 'Single-organ' donors who are not considered
  - Donors never referred for donation or considered
    - Potentially more common with HCV+ donors as lower utilization

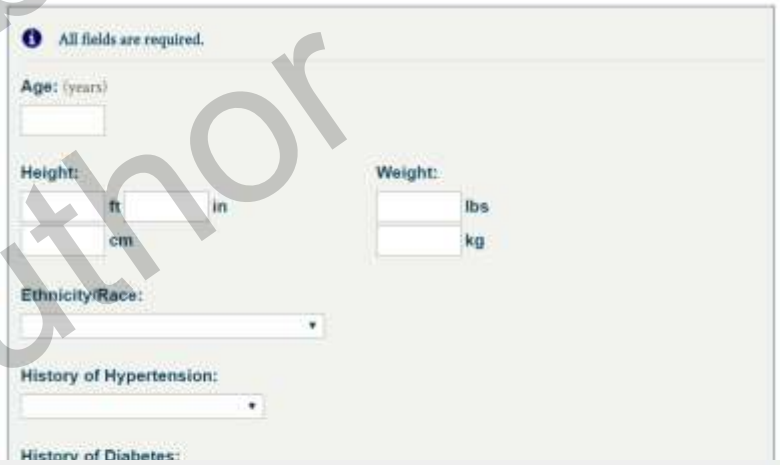
WHY ARE KIDNEYS FROM HCV+ DONORS DISCARDED SO FREQUENTLY

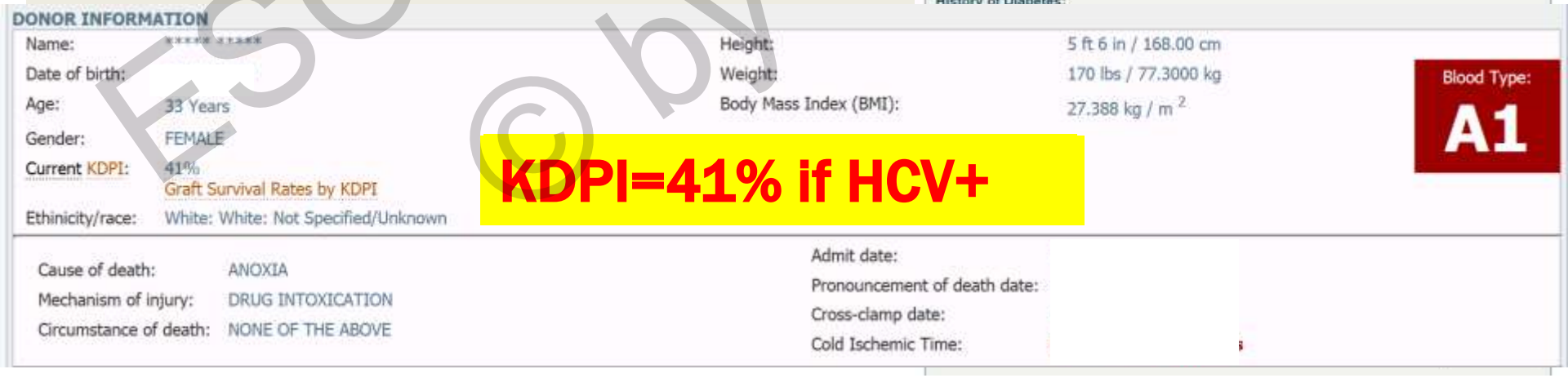


- Small number of HCV+ patients on waiting list
- HCV+ patients (or specific centers) don't want to receive (or use) kidneys from HCV+ donors
  - According to OPTN/UNOS data as of 1/30/16
    - 1.8% of patients on kidney waitlist opt in for kidneys from HCV+ donors
    - Estimated 5% of waitlisted patients on dialysis have HCV
- Risk of other infections
  - PHS-increased risk (HBV, HCV, HIV)
  - Frequently have current or active IV drug use or other behaviors
- Thought of being lower quality

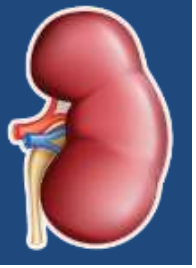
WHY ARE KIDNEYS FROM HCV+ DONORS DISCARDED SO FREQUENTLY

- Limitations of KDPI
- 10 donor factors to measure risk of graft failure
- Low c-statistic (0.6-0.65)
- Doesn't differentiate donor vs recipient factors (i.e., HCV)
- Do kidneys from HCV+ donors have worse outcomes because of kidney quality or patients receiving them





INTENTIONAL HCV TRANSMISSION IN RENAL TRANSPLANT RECIPIENTS-UW

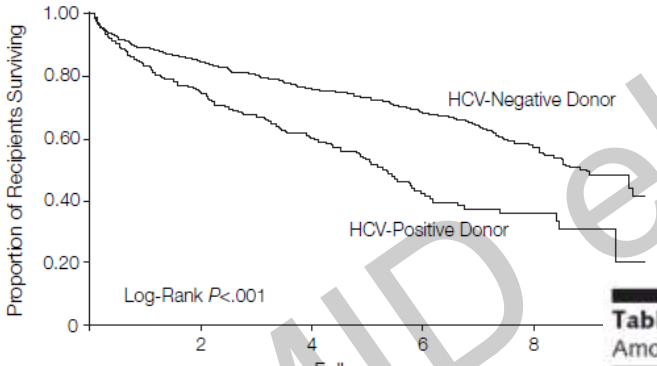


- University of Wisconsin, 1991-1996
- HCV- patients "**considered to have a poor life expectancy**"
- 118 D+/R-
  - Survival
    - 10-year survival 22.6%
    - Median survival 5.3 years
    - 52 (50%) died with a functioning graft
  - 93 deaths
    - 22 (24%) cardiac
    - 15 (16%) chronic allograft nephropathy
    - **4 (4%) developed "liver failure"**
      - Essentially no HCV treatments available
- Appeared to be poor-recipient quality rather than HCV driving worse outcomes

Singh N, et al. Clin Transplant 2012; 26: 684-693

OUTCOMES OF HEART TRANSPLANTS USING AN HCV+ DONOR

Figure 3. Kaplan-Meier Estimates of Survival According to Donor HCV Status for the Propensity-Matched Cohort (Imputed Data Set 1)



No. at Risk

HCV-Negative Donor	1044	776	537	326	157
HCV-Positive Donor	261	179	117	53	20

Table 5. Cox Proportional Hazards Analyses of Donor HCV Positivity and Mortality Among Propensity-Matched Patients

Model	Hazard Ratio (95% Confidence Interval)	
	Entire Cohort (n = 1305)*	Patients With Complete Data (n = 730)†
Unadjusted	2.10 (1.60-2.75)	2.46 (1.81-3.33)
Adjusted for recipient HCV status	2.08 (1.55-2.78)	2.34 (1.72-3.18)
Stratified by recipient HCV status		
Negative	2.13 (1.59-2.85)	2.31 (1.67-3.19)
Positive	1.48 (0.44-4.99)	2.76 (0.74-10.4)
P Value, test for interaction	>.10 in all 5 data sets	.80
Adjusted for recipient age	2.11 (1.60-2.79)	2.42 (1.77-3.30)
Stratified by recipient age, y		
18-39	1.75 (0.70-4.40)	1.21 (0.37-3.98)
40-59	2.23 (1.42-3.52)	3.64 (2.22-5.97)
≥60	2.07 (1.32-3.27)	1.82 (1.09-3.04)
P Value, test for interaction	>.10 in all 5 data sets	.09

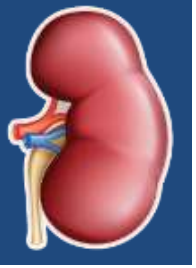
Abbreviations: HCV, hepatitis C virus.
*Using the method of multiple imputation. Five imputed data sets combined to produce an overall estimate with confidence intervals incorporating uncertainty attributable to missing data and sampling variation.
†Patients with missing data on any variables (eg, recipient HCV status, variables used in the propensity score) were excluded.

Gasink L, at al. JAMA 2006; 296(15): 1843-1850

KEY CONSIDERATIONS IN HCV TREATMENT OF HCV-NEGATIVE PATIENTS TRANSPLANTED WITH AN HCV-INFECTED ORGAN

- Acute kidney injury/chronic kidney disease
  - Sofosbuvir (eGFR<30mL/min)
  - Zepatier + Mavyret FDA-approved
- Immunosuppressant
  - Cyclosporine: drug levels increase >15-fold
- Costs and insurance approval (US)
- Amiodarone + Sofosbuvir interaction
- Inability to take PO's (transplant recipients)

KEY LIMITATIONS OF HISTORICAL DATA OF TRANSPLANTING HCV-INFECTED ORGANS INTO HCV-NEGATIVE PATIENTS



- Recipient selection
  - 'Higher-risk' organs used in high-risk recipients
    - Older
    - More medical co-morbidities
- Limited ability to treat HCV
  - IFN and side effects
  - IFN and cytopenia
  - IFN and increased risk of rejection

WHAT DON'T WE KNOW YET (OR DON'T KNOW ENOUGH ABOUT YET)?

- How is HCV transmitted in non-hepatic transplantation?
- Will all patients contract HCV?
- Are there risks of liver injury from acute HCV post-transplant?
- Will HCV therapies work as well?
- Will patients be willing to accept an organ from a donor infected with HCV?

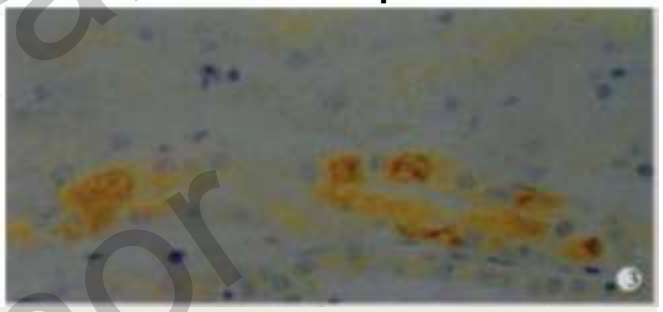
ARE THERE EXTRAHEPATIC RESERVOIRS OF HCV?

- Autopsy study of 9 HCV patients
  - Tested 38 distinct extrahepatic sites (9 kidneys)

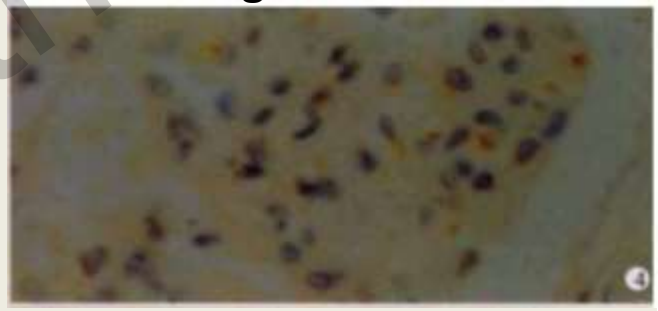
Table 1 Results of HCV RNA and HCV antigens detection in extrahepatic organs and livers

Tissue	Cases	HCV RNA (+)		HCV antigens (+)		
		RT-PCR	ISH	NS3	NS5	CP10
Kidney	9	7	4*	3	6	5	4
Heart	9	5	3*	2	5	4	4
Pancreas	9	5	3*	2	6	6	5
Intestine	5	3/4	1/4*	1	3	2	0
Adrenal gland	2			1	1	1	0
Spleen	2			0	0	0	0
Lymph node	1			1	1	1	1
Gallbladder	1			1	1	0	1
Liver	9	9	7*	9	8	7	7

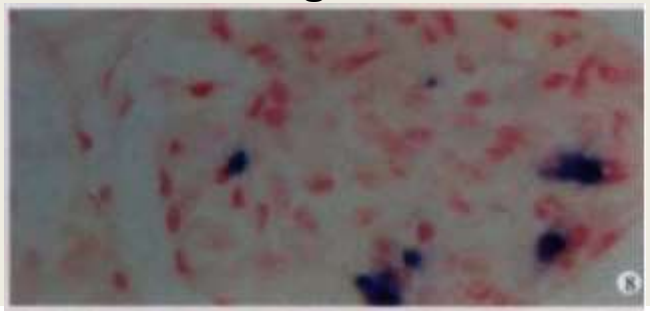
HCV NS5 in tubular epithelial cells



HCV NS5 in glomerulus



HCV RNA in the glomerulus



Yan FM, et al. World J Gastroenterology 2000; 6(6): 805-11

ARE THERE EXTRAHEPATIC RESERVOIRS OF HCV?

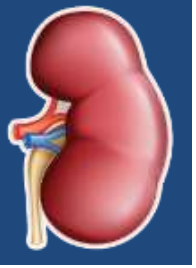


TABLE 1. Prevalence of HCV RNA Detected by PCR in the Serum and the PBMC of Patients With Acute PTHC in Comparison With That of Patients With Chronic HCV Infection

Disease Phase	Incubation Period	Acute Phase	Chronic Phase
No. of specimens*	29	82	48
Serum	17 (59%)†	67 (82%)†	41 (85%)†
PBMC	0 (0%)‡	0 (0%)‡	12 (25%)‡

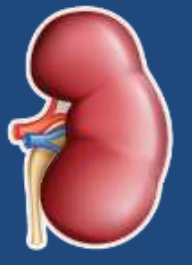
* The specimens from 11 patients with acute PTHC were obtained during the incubation period and the acute phase. The specimens from 48 patients with chronic HCV infection were obtained during the chronic phase.

eral blood

- Acute post-transfusion HCV (n=11) and chronic HCV (n=48)

1-Castillo I, et al. Gut 2005; 54: 682-685; 2-Chang TT, et al. Hepatology 1996: 23(5): 977-81

WHEN SHOULD PATIENTS START HCV TREATMENT



- Prophylactic
  - Before infection occurs
  - When organ offer accepted, on call to OR, in OR
- Pre-emptive
  - When infection first detected
  - When to check
  - What defines an infection

PROPHYLACTIC TREATMENT

- Pros:
  - Could potentially prevent infection
  - Have near steady state when virus at lowest level
  - Could prevent replication in other tissues (i.e., PBMCs)
  - Could potentially shorten therapy[1]
- Cons
  - Never confirm if infection occurs
  - Currently no data on NG tube administration
    - Delayed treatment and/or treatment interruption
  - Real-world applicability
    - Insurance authorization ahead of time infeasible—requires confirmation of infection
    - Having available drug—not stocked on formulary

1-Levitsky J, et al, NEJM 2016

1-Levitsky J, et al. NEJM 2016; 375 (21): 2106-2108

PRE-EMPTIVE TREATMENT

- Pros:
  - Can confirm infection occurs
  - Ensures sufficient samples for additional testing (depends on therapy)
  - Treat when patient clinically stable and taking POs
  - If using Sof-based regimen->ensure stable renal function
  - More real-world as would never have drug available pre-infection
- Cons
  - Theoretical risk of severe acute HCV
  - Determining optimal timing and defining infection
    - Is one positive viral load sufficient
    - What time point to check

WHAT IS THINKER TRIAL?

- Pilot trial of transplanting kidneys from HCV-positive deceased donors into HCV-negative patients
- Key considerations
  - Recipients ages 40-65
  - ≤548 days of waiting time
  - No major contraindications to liver transplantation
  - Genotype 1 donors (use of Grazoprevir)
  - Pre-emptive treatment of HCV using Zepatier
  - Treatment per FDA package level
  - Real-time genpotyping of deceased donors

Transplanting
Hepatitis C Kidneys
Into
Negative
Kidn**E**y
Recipients

CT.gov: NCT02743897

IN-DEPTH MULTI-STAGE INFORMED CONSENT PROCESS

Research coordinator reviews list of potential study subjects (EMR query)

Potential study subjects reviewed by PI to confirm eligibility

Transplant nephrologist approves patient for study

Patient called on phone by PI

Patient attends educational session

≥24 hour waiting period before informed consent can be signed

THINKER ENROLLMENT

Enrollment

Assessed for eligibility (n=297)
Meeting blood type, age and wait-list time priority criteria

Excluded (n= 231)
- Not yet on Dialysis (n= 100)
- Previous/Multi-organ Transplant (n= 59)
- Contraindication for Liver Transplant (n= 25)
- Under weight requirement (n= 10)
- HIV/HCV/HBV (n= 10)
- Living Donor (n= 9)
- Became ineligible for a transplant (n= 5)
- Recurrence Risk (n= 7)
- High PRA (n= 4)
- Substance Abuse (n= 2)

Preliminarily eligible and invited to educational session (n=66)

Declined to participate (n=34)

Attended Educational Session (n=32)

Declined to participate (n= 2)
Screen fail (n= 4)
- *Due to liver evaluation (n=3)*
- *Due to FSGS (n=1)*

Allocation

Activated for HCV+ kidneys on Waitlist (n=26)

Transplanted (n= 20)

Awaiting Transplant (n=6)

Follow-Up

Lost to follow-up (n= 0)

Analysis

Analysed (n= 20)

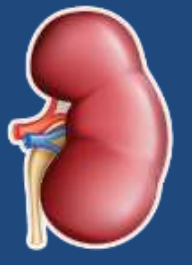
WHY PATIENTS DECLINED TO ATTEND EDUCATION SESSION

- Concerns about HCV
  - Didn't want an additional medical problem
  - Social stigmas and/or know someone with HCV
- Concerns about research
  - Don't want to participate in experimental
- Outside pressures
  - Social support
  - Nephrologist or other physicians

DONOR CHARACTERISTICS

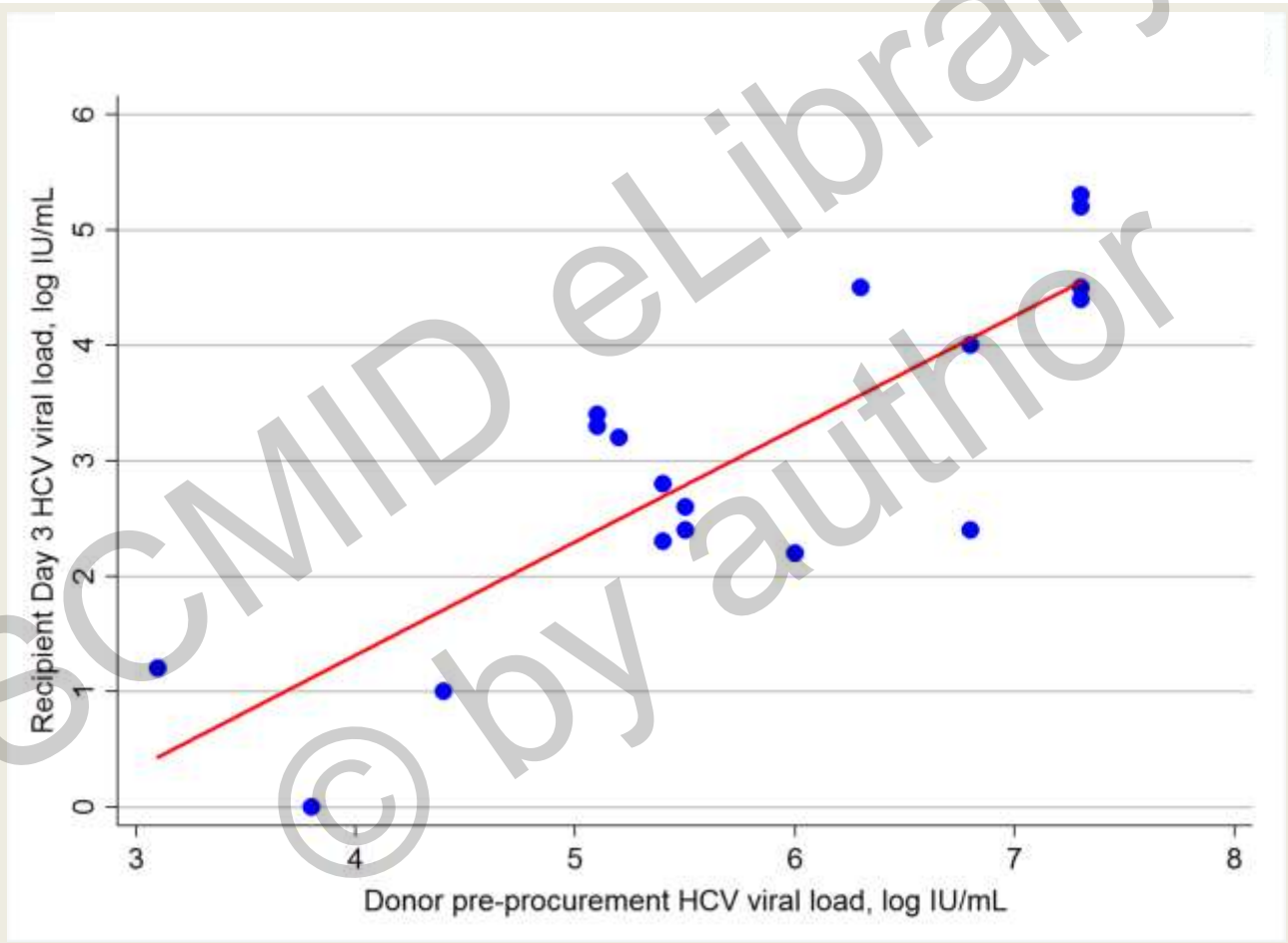
Race	Gender	OPTN Region	Age	Mechanism of death	Terminal creatinine, mg/dL	KDPI
White	Male	10	46	Cardiovascular	0.5	48%
White	Female	3	28	Drug intoxication	0.5	32%
White	Male	2	31	Drug intoxication	1.4	46%
White	Female	2	45	Intracranial hemorrhage/stroke	1	73%
White	Male	10	46	Cardiovascular	0.5	48%
White	Female	3	28	Drug intoxication	0.5	32%
White	Female	11	53	Intracranial hemorrhage/stroke	0.55	70%
White	Male	2	29	Drug intoxication	0.79	35%
White	Male	2	30	Drug intoxication	1.4	58%
White	Male	2	25	Drug intoxication	0.71	23%
White	Male	2	32	Drug intoxication	0.6	37%
White	Female	2	26	Drug intoxication	1.82	49%
White	Female	2	26	Drug intoxication	1.82	49%
White	Male	2	37	Drug intoxication	1.5	63%
White	Female	2	23	Drug intoxication	1.16	33%
White	Female	2	23	Drug intoxication	1.16	33%
White	Male	1	33	Cardiovascular	1.39	45%
White	Male	2	37	Drug intoxication	1.5	63%
Hispanic	Female	11	23	Drug intoxication	0.66	29%
White	Male	2	22	Asphyxiation	1.06	41%

EARLY POST-TRANSPLANT HCV VIRAL LOADS OF THINKER RECIPIENTS



Donor HCV viral load, log IU/mL	Recipient HCV viral load, log, IU/mL							
	POD 1	POD 2	POD #3 (Rx start date)	POD 4	POD 5	POD 7 ± 1	POD 14 ± 3	POD 21 ± 3
5.1	1.7	1.84	2.95	2.74	1.54	–	0	0
5.1	1.41	2.35	3.02	2.97	2.29	–	0	0
N/A	1.0	1.85	2.58	–	–	1.59	0	0
N/A	1.56	3.01	3.29	–	–	1.46	–	0
7.3	3.31	3.71	3.86	–	2.56	1.94	0	0
3.1*	0	0	0	0	0	0	0	0
3.8	0	0	1.36	–	1.81	–	–	0
5.5	–	1.83	2.58	–	1.0	0	0	0
5.5	–	1.76	2.73	1.84	–	1.0	0	0
5.4	–	1.1	1.29	1.81	1.08	0	0	0
5.4	–	1.76	2.24	1.32	1.42	1.0	0	0
6.0	–	1.0	1.28	1.1	–	0	0	0

CORRELATION BETWEEN DONOR AND RECIPIENT HCV RNA

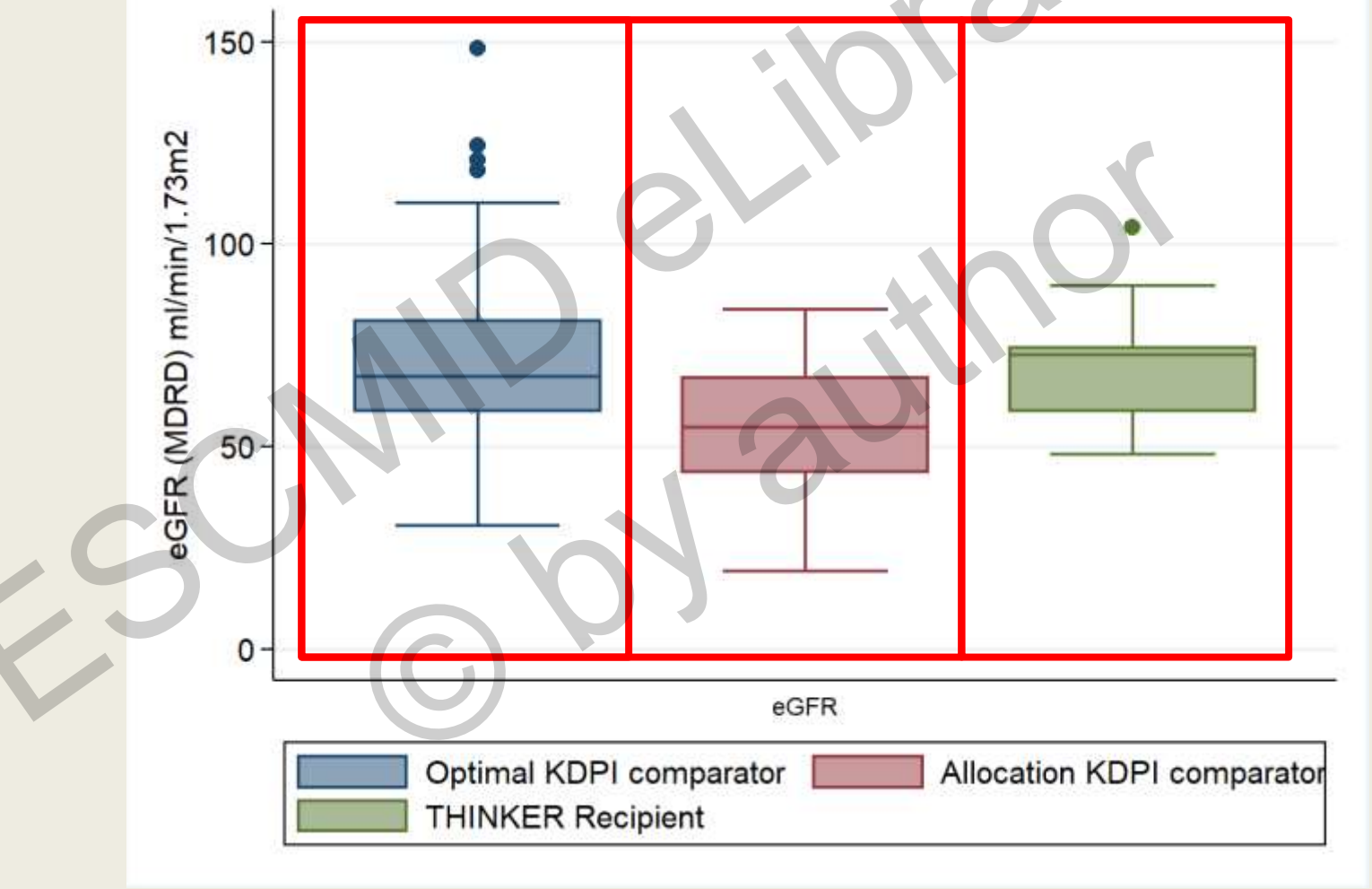


- Multi-level mixed-effects linear regression
  - Beta coefficient: 0.95 (95% CI: 0.60-1.31; p<0.001)

HCV CURE DATA

- SVR-12: 20 patients
- SVR-24: 10 patients

RENAL FUNCTION AT 12 MONTHS



PUBLISHED DATA IN MANUSCRIPT FORM

- EXPANDER study (Johns Hopkins)
  - 10 HCV+ to HCV- transplants
  - 'Prophylactic' therapy on call to OR
  - 5/10 detectable on POD 1 (2 not quantifiable)
  - 10/10 cured
- Vanderbilt University ('standard-of-care')
  - 9 HCV NAT+ to HCV- heart transplant
  - 8/9 cured (1 died of PE during post-transplant week 7)
  - Treatment started ≈1 month post-transplant
- University of Alberta (research protocol)
  - 5 HCV NAT+ to HCV- lung transplants
  - 5/5 cured

1-Durand C, et al. Annals of Internal Medicine 2018; 2-Schlendorf KH, et al. J Heart Lung Transplant 2018; Abdelbasit A, Am J Respir Crit Care Med 2018

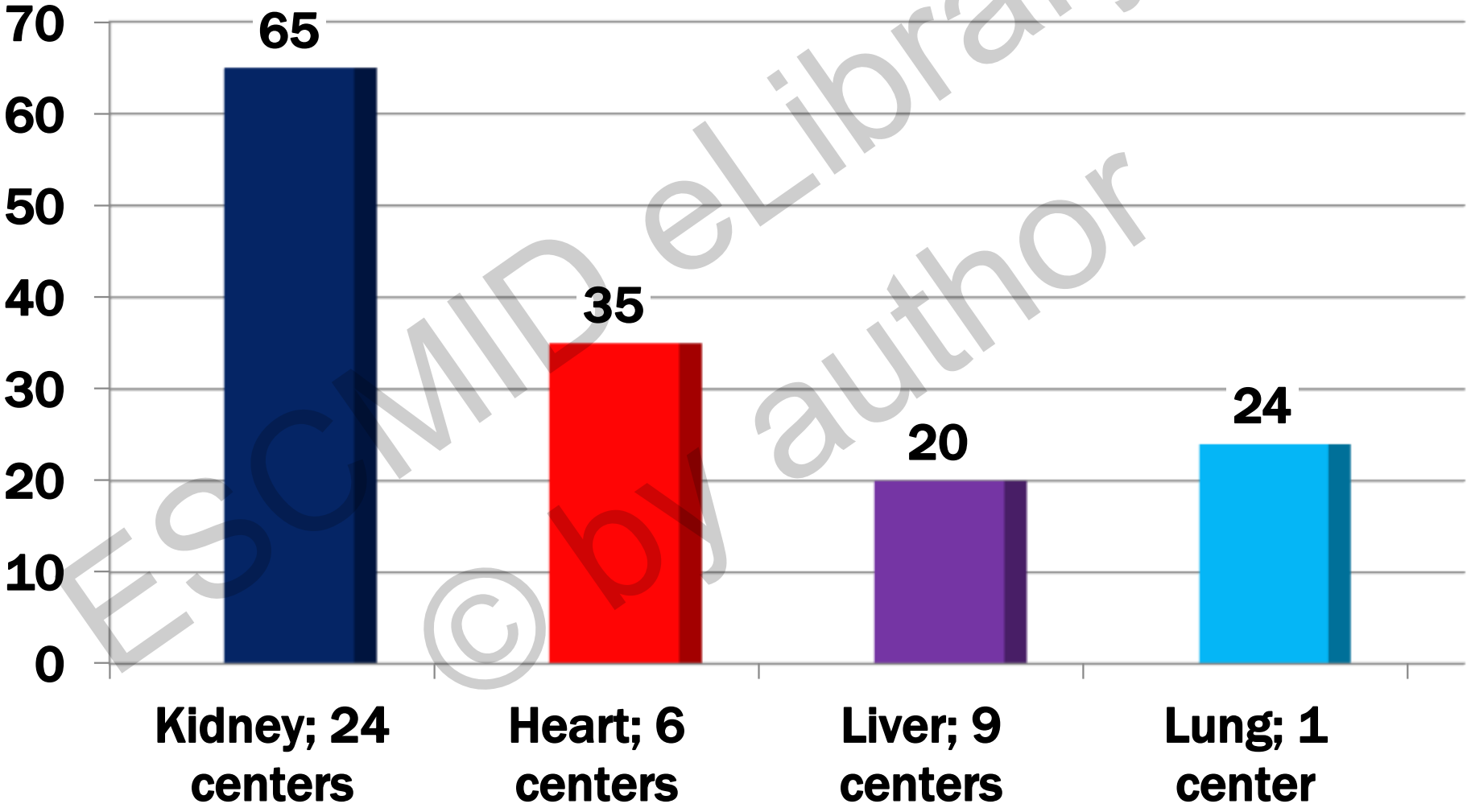
DATA PRESENTED AT ISHLT

- Vanderbilt: 31 OHTs from HCV NAT+ donors to HCV- patients
  - 17 completed therapy: 14 with SVR-12, 3 awaiting SVR-12
  - 5 ongoing therapy
  - 6 not yet initiated
  - 3 unable to be initiated or completed
    - 1 death at week 7 due to PE
    - 2 deaths at 2 weeks due to multi-organ failure
- UCSD: 6 OHTs from HCV NAT+ donors into HCV- recipients
  - No SVR-12 data available
- Brigham and Women's Hospital
  - Lung transplants: 24 HCV NAT+ to HCV-
  - Heart transplants: 7 HCV NAT+ to HCV-
  - Sofosbuvir/Velpatasvir for 4-6 weeks
  - SVR-12 in first 20 patients

WHAT IS CURRENT HCV+ TO HCV- TRANSPLANT LANDSCAPE IN THE US

- Some centers offering this as “standard of care”
  - No IRB approval except for data collection
  - Plan to apply to insurance company for approval
    - Some health systems agree to pay if insurance declines
- Variable information provided to patients
  - “<1% risk that HCV will not be cured after the first medication course, and in rare instances, HCV may not be cured after subsequent therapy”
  - “Your medical insurance will be responsible for the cost of all tests and services”
    - Does not state that insurance may decline to pay

WHAT IS CURRENT LANDSCAPE OF TRANSPLANTING HCV-INFECTED ORGANS INTO HCV-NEGATIVE PATIENTS IN THE US



WHAT ARE NEXT STEPS IN HCV+ TO HCV- TRANSPLANTS?

- Need to demonstrate safety and efficacy in larger number of patients to make it considered standard of care
  - What is N?
- Utilize pan-genotypic drugs
- Increase time between transplant and initiating therapy?
  - What is real-world
    - Would insurance pre-approve?
    - Is it safe to wait for 2-4 weeks post-transplant?

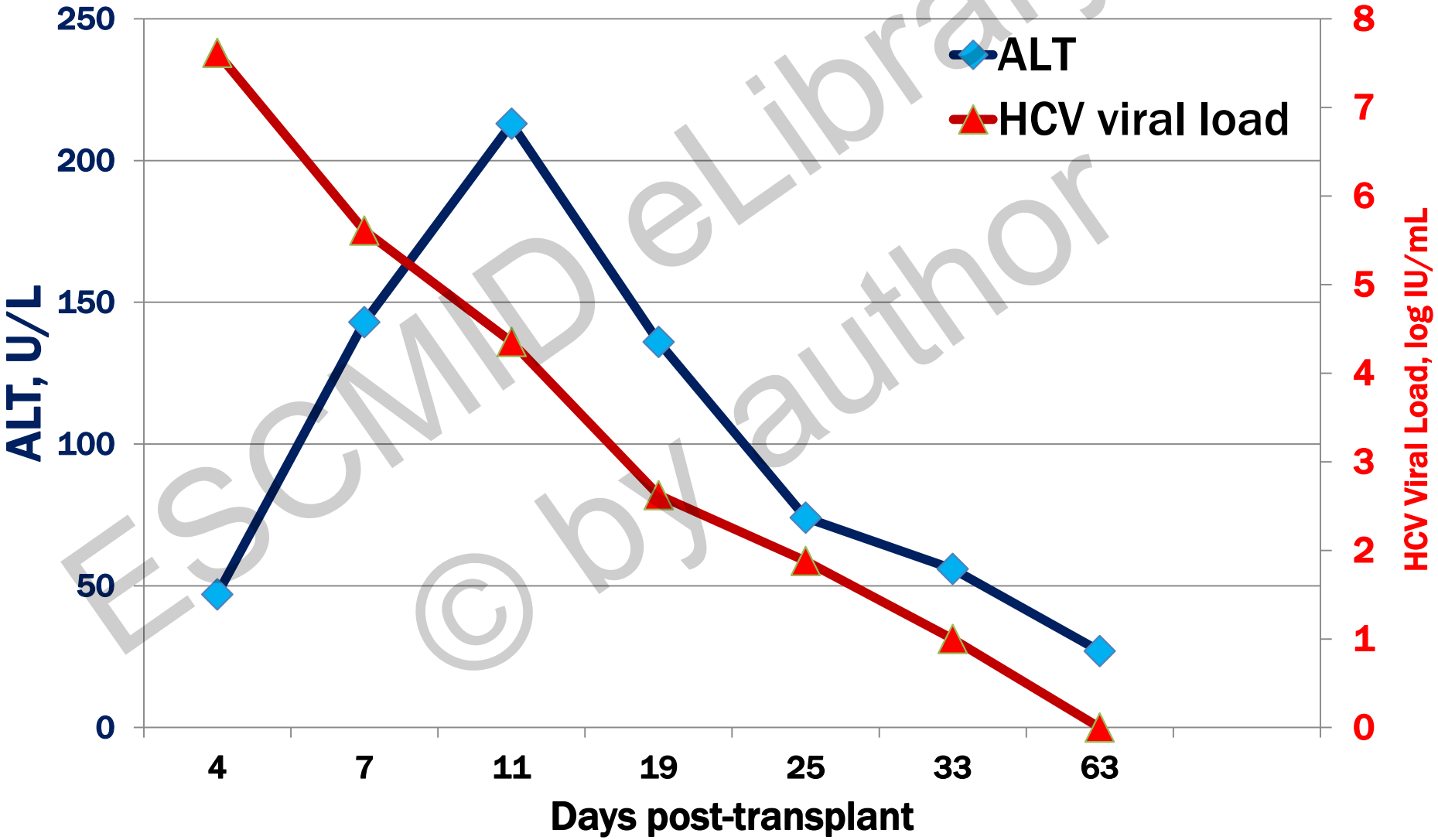
WHAT ARE NEXT STEPS IN HCV+ TO HCV- TRANSPLANTS?

- Expand donor and recipient criteria
  - Donor
    - Upper age limit
    - Elevated KDPI
    - Other Medical co-morbidities
      - Can HCV be viewed like any other risk factor in a deceased donor?
  - Recipient:
    - Pre-transplant liver assessment
    - Non-OLT candidates
    - Older and/or more dialysis time

WHY I STILL THINK EXPERIMENTAL PROCEDURE

- Cannot 100% guarantee payment of drug (US phenomenon)
- Unknown cure rates
  - 20/20 does not mean 100% cure rates
- Acute immune-mediated risks
  - DSA
  - Rejection
- Public trust/stigmas of HCV
- Unknown kidney quality (data on HCV+ kidneys essentially restricted to HCV+ recipients)
- Potential implications of delaying therapy in real-world setting
- Need to decide if liver disease (Fibroscan) screening needed
  - Implications if performed

IS THERE A RISK IN DELAYING HCV TREATMENT OUTSIDE OF RESEARCH PROTOCOLS: CAUTIONARY TALE



Should organs from deceased donors infected be transplanted into recipients without HCV?

A. No, this should never be done.

B. Yes, but only in a research protocol.

C. Yes, this should be offered to all patients as the ability to cure Hepatitis C is so high.

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