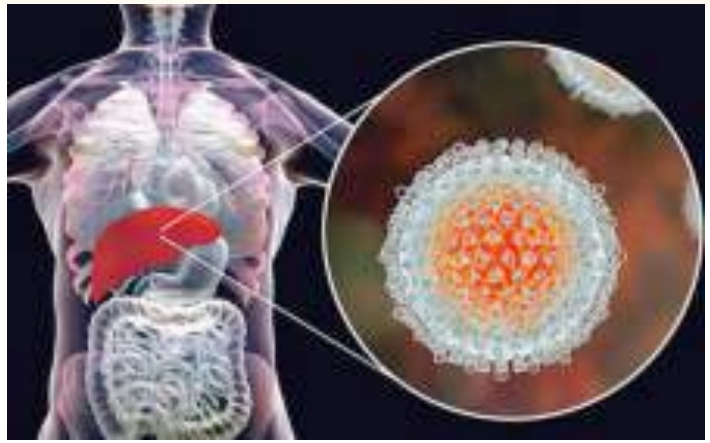
# TRANSPLANT
WEBINAR SERIES



# C-ing the Future: Medical, Ethical, and Financial Considerations of Hepatitis C Transplants

November 21, 2019| 3-4pm ET

Speakers: David Goldberg, MD, MSCE

The Alliance

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# WEBINAR SPEAKERS

Moderator:

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Professor of Surgery
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Miami, FL

# C-ing the Future: Medical, Ethical, and Financial Considerations of Hepatitis C Transplants

David Goldberg, MD, MSCE
Associate Professor Of Medicine
University of Miami Miller School of Medicine

# Disclosures

- Will be discussing research funded by investigator-initiated grants paid to the University of Pennsylvania (Co-PI; Merck, Abbvie)
- Received research funding from investigator-initiated grant paid to the University of Pennsylvania to evaluate HCV screening rates (PI; Gilead)
- Funding for multi-center THINKER-NEXT trial funded by NIH U34 grant (Co-PI; U34DK120091)
- I will be discussing use of laboratory-derived test for testing of HCV genotype

# Outline

- Basics of HCV and serology
- Timeline of HCV testing in organ donation
- Evolution of HCV treatment
- Use of HCV+ organs (to HCV+ and HCV-)
- Landscape of HCV+ organs (opioid, geographic differences)
- Trials vs practice
- Prophylactic vs pre-emptive
- THINKER trial and prelim data

# What is hepatitis c

- Hepatitis C is an RNA virus
- Passed by blood-to-blood contact
- Acute HCV
  - Flu-like illness
  - Rarely severe presentation
  - Can be severe in acute post-transplant setting
- Chronic infection:  cirrhosis, HCV, liver failure
- **Curable infection** (unlike CMV, EBV, HIV, …)
  - Long-term follow-up study of 344 patients[1]
    - Median f/u:  3.22 years (range 0.5-18.0)
    - 1,300 serum samples—RNA positive in 0/1300

1-Maylin S, et al. Gastroenterology2008; 135: 821-829

# Epidemiology of HCV

- Infectivity when acutely infected
  - 2/3 chronically infected, 1/3 spontaneously clear infection
  - Spontaneous clearance thought to represent no reservoirs of HCV
- Epidemiology
  - 1-1.5% of overall US population infected
  - 1 in 30 baby boomers infected
  - 3-5 million Americans infected

# How is HCV treated

- Pre-2011: IFN + Ribavirin (cure rates 30-40%)
- 2011-2013: IFN + TPV/BCV (cure rates 50-60%)
- 2014-present: all-oral regimens (>95% cure rates)
- Cure: Undetectable viral load 12 weeks after stopping therapy (SVR-12)
- Cure rates similar pre- vs post-transplant
- Treatments
  - Regimens based on genotype, renal function
  - Costly: $25,000-95,000 for round of therapy

# Interpreting HCV serologies

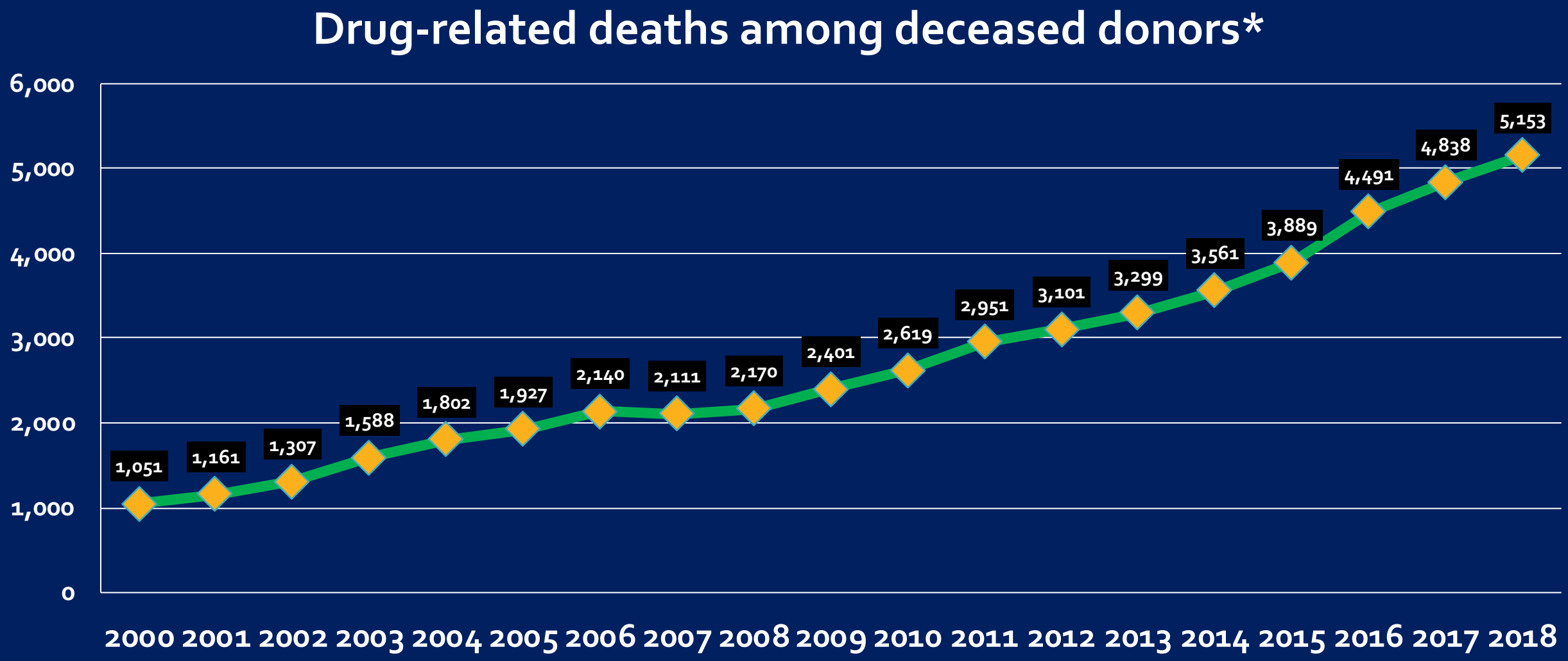
- HCV antibody: Prior exposure to virus
- HCV Nucleic Acid Test (NAT): Active virus in the blood
- Ab-/NAT-: Never exposed or window period
- Ab+/NAT-:
  - False (+) Ab
  - Active infection with low-level virus (acute or chronic)
  - On-treatment with viral suppression
  - Prior infection with spontaneous 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

# Evolution of donor hcv testing

# Historic utilization HCV-positive donors

- HCV-positive misleading term
- HCV-viremic donors
  - Livers: High utilization for HCV-infected patients
  - Kidneys: 2/3 discarded due to quality and small number of patients
  - Lungs/hearts: Historically near-universal discards
- HCV Ab+/NAT- donors
  - Treated like HCV NAT+
- Treatment
  - Liver: Cure rates in IFN era lower (20-30%)
    - Overall efficacy
    - Side effects
    - Interactions
  - Kidney, lung, heart: Challenge because of rejection

# Unfortunate reason I am giving this talk: opioid deaths




* Drug-related: 1) Mechanism of death coded as “drug intoxication”; b) “other” mechanism + IVDU; or 3) “other” mechanism + non-IV illicit drug use; According to OPTN/UNOS data as of April 1, 2019

# Identifying an opportunity in 2015

## Transplanting Hepatitis C–Positive Kidneys

Peter P. Reese, M.D., M.S.C.E., Peter L. Abt, M.D., Emily A. Blumberg, M.D., and David S. Goldberg, M.D., M.S.C.E.

Disposition of 6546 Kidneys from 3273 Deceased Donors with Hepatitis C Antibody between 2005 and 2014.*

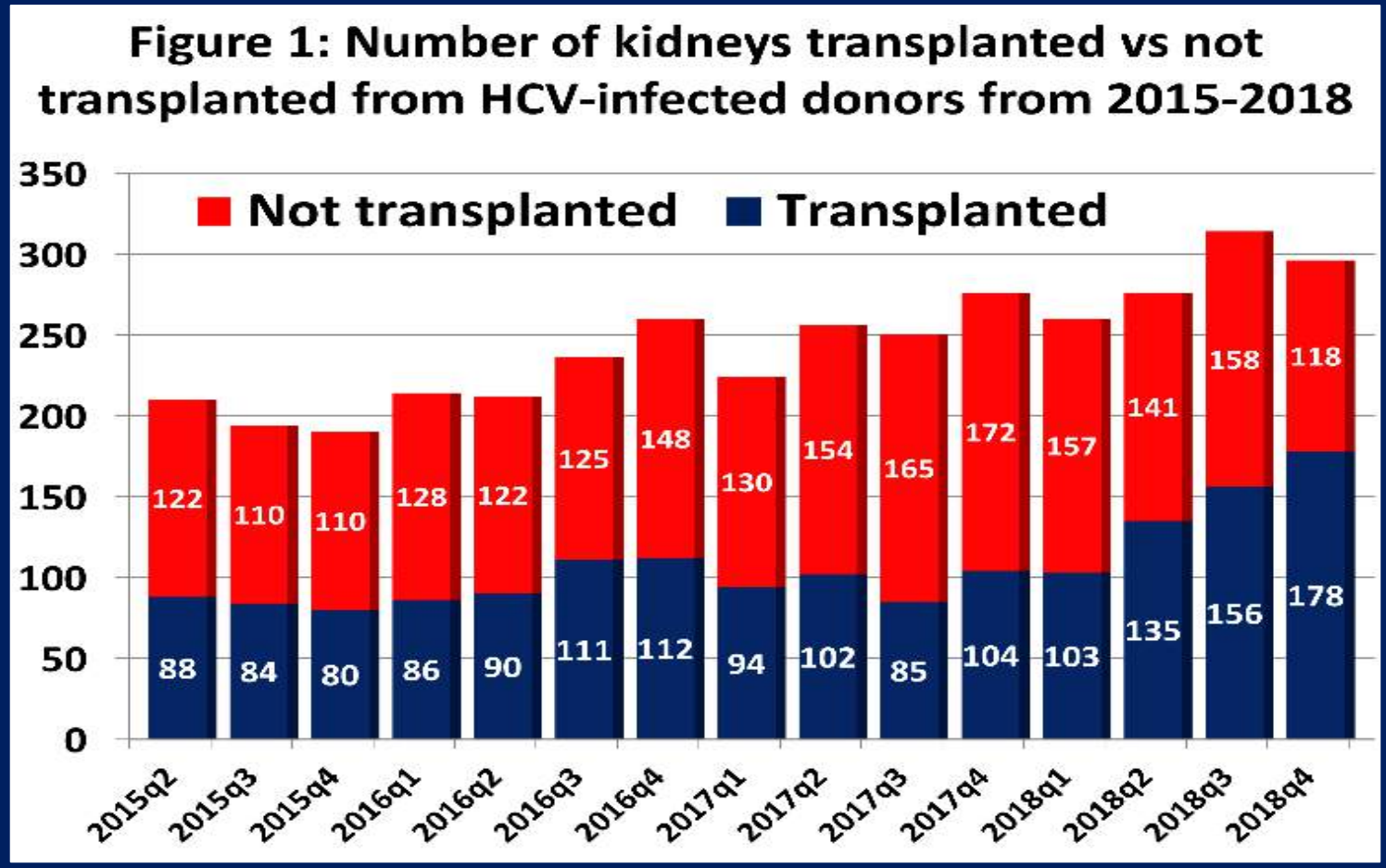
| Disposition of Kidney Pairs | No. of Donors (%) | No. of Kidneys Discarded | Median Kidney Donor Profile Index (IQR) | Estimated Additional Graft-Years Obtainable by Transplanting Both Kidneys | | |
|---|---|---|---|---|---|---|
| | | | | 1-Yr Survival | 3-Yr Survival | 5-Yr Survival |
| Both kidneys discarded | 1718 (52.5) | 3436 | 0.85 (0.67–0.96) | 3000 | 7637 | 10,301 |
| 1 kidney transplanted, 1 discarded | 708 (21.6) | 708 | 0.71 (0.54–0.87) | 636 | 1675 | 2,361 |
| Both kidneys transplanted | 847 (25.9) | 0 | 0.60 (0.43–0.77) | — | — | — |

* A hepatitis C virus (HCV)–positive donor was defined by a positive antibody test for hepatitis C; data are national registry data from the Organ Procurement and Transplantation Network. Discarded kidneys are those for which donation authorization was obtained but that were never procured, were procured for research purposes rather than transplantation, or were procured with the intent of transplantation but then discarded. Of the 4144 discarded kidneys, 2698 (65.1%) were procured with the intent of transplantation. The Kidney Donor Profile Index, indicating the quality of a donated kidney, ranges from 0 (highest quality) to 1 (lowest quality); the donor's HCV antibody status is considered in the score, which is based on data from an earlier era of HCV treatment. Estimates of additional graft-years obtainable by transplanting both kidneys were based on the median-quality kidney in each category. IQR denotes interquartile range.

Reese PP, Abt PL, Blumberg EA, Goldberg DS. Transplanting Hepatitis C-Positive Kidneys. NEJM 2015; 373(4): 303-305

# Underuse of organs continues

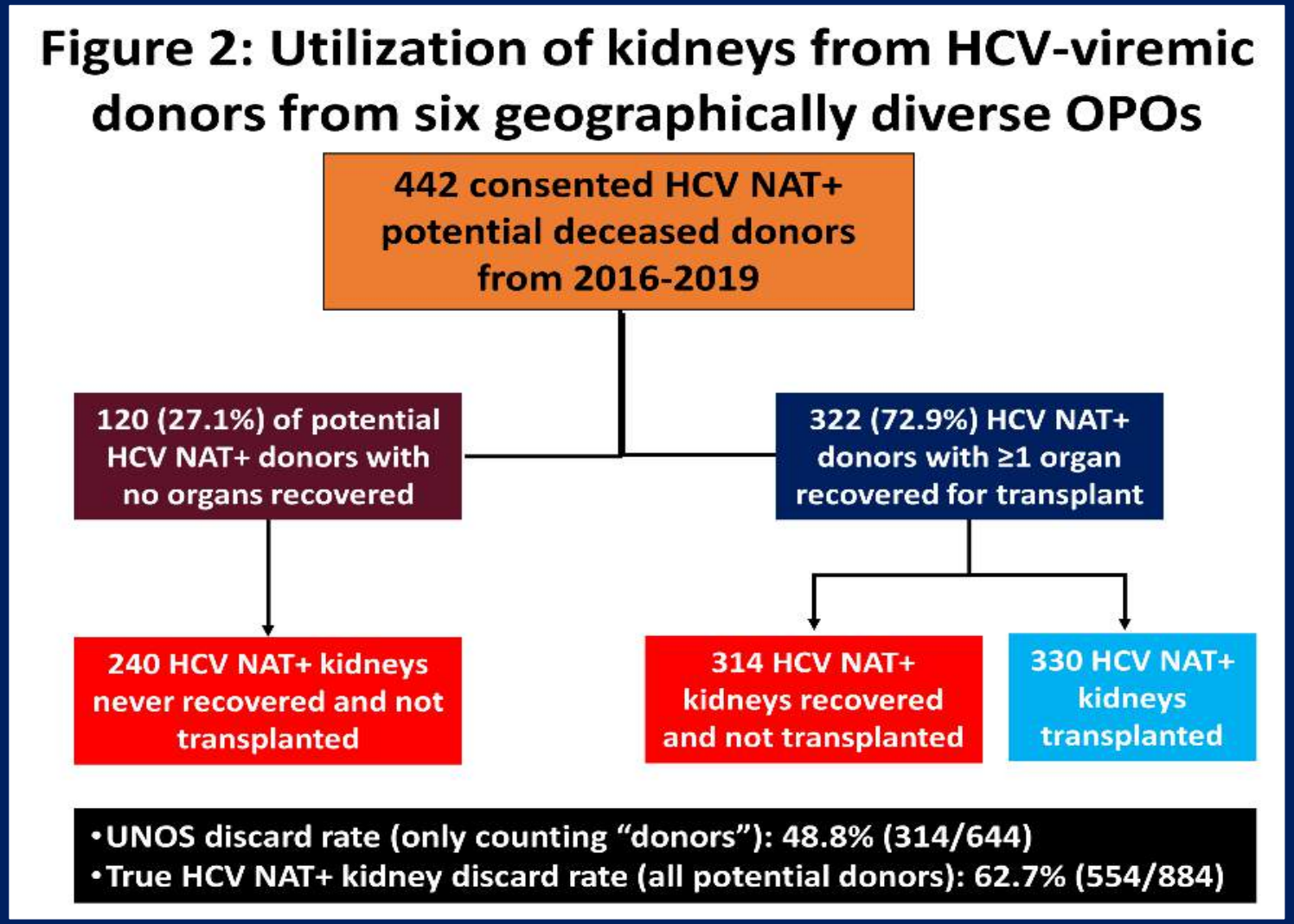
- Increase utilization but nearly 40% of kidneys from HCV-viremic 'donors' not transplanted (recovered + discarded or never recovered)



# 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

# Underestimating HCV donor potential: Data from 6 OPOs

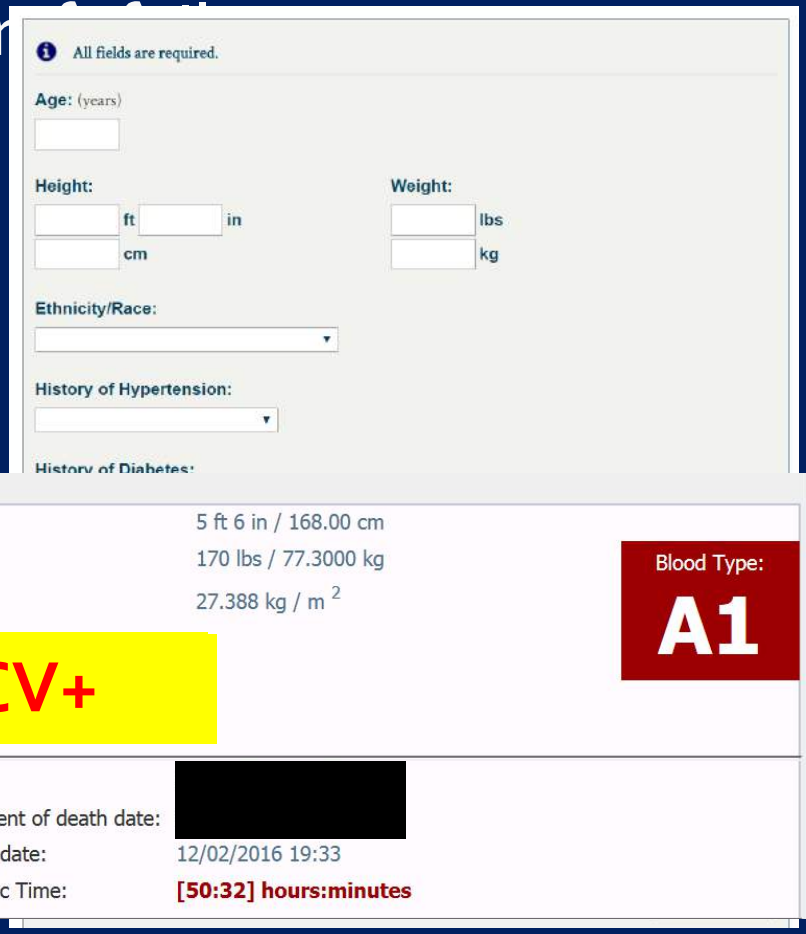


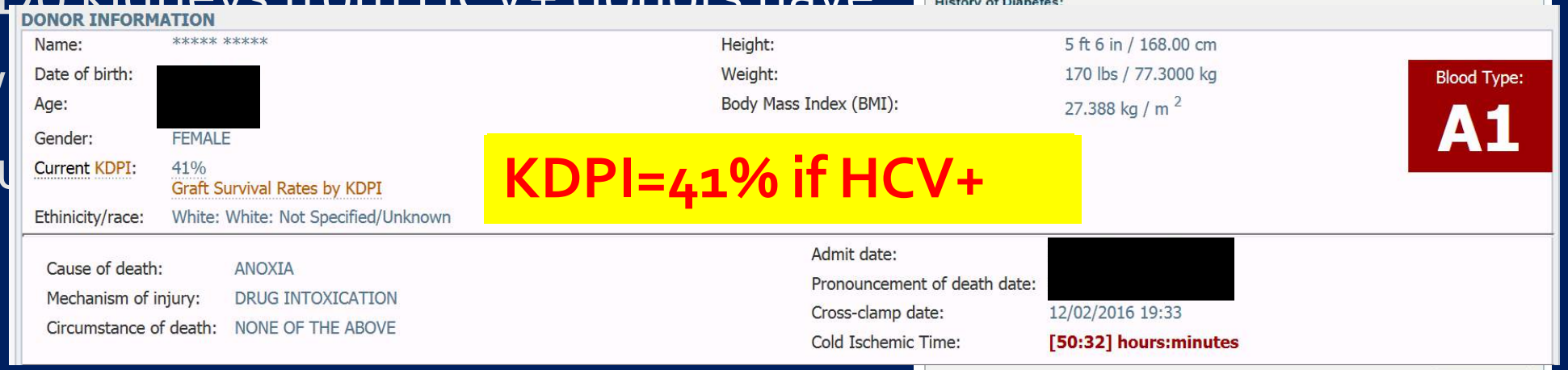
# Why were kidneys from HCV+ donors discarded so frequently

- 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 were kidneys from HCV+ donors discarded so frequently

- Limitations of KDPI
- 10 donor factors to measure risk of gr
- Low c-statistic (0.6-0.65)
- Doesn't differentiate donor vs recipient factors (i.e., HCV)
- Do kidneys from HCV+ donors have w
qu



# Published data from clinical trials or center case series

- Different treatment strategies
  - Prophylactic: On call to the OR or at the time of transplant
    - Benefits: Shorten therapy, prevent infection
    - Risks: Limited data on enteral administration, less real-world
  - Pre-emptive: Early after transplant
    - Benefits: Confirm infection, patient more stable
    - Risks: Acute hepatitis, immunologic complications
  - Reactive: When infection confirmed and insurance approves
    - Benefits: Relies on insurance, patient stable
    - Risks: Insurance delays or denials, FCH
- Prophylactic and pre-emptive require donated drug or hospital provision of drug

# Published data from clinical trials or center case series: Prophylactic kidney

- EXPANDER (Johns Hopkins)
  - First dose on call to the OR
  - Used Grazoprevir/Elbasvir
  - Sought to prevent infection
- 10/10 cured
- 5/10 without evidence of true infection
  - Caveat was day 1 testing
- No liver or renal complications
- REHANNA (AASLD abstract)
  - 4 weeks treatment starting on call to the OR
  - 9/10 cured (to date)

Durand CM, Bowring MG, Brown DM, et al. Direct-Acting Antiviral Prophylaxis in Kidney Transplantation From Hepatitis C Virus-Infected Donors to Noninfected Recipients: An Open-Label Nonrandomized Trial. *Annals of internal medicine.* 2018;168(8):533-540

# Published data from clinical trials or center case series: Prophylactic kidney

- Ultrashort therapy
  - Pilot: 1 dose pre and 1 dose post
  - Second phase: 1 dose pre and 3 doses post
- Results
  - Group 1: 3/10 required full-course therapy
  - Group 2: 3/40 required full course-therapy
  - 6 required full-course therapy
    - 3 cured with first-line therapy
    - 2 failed first line and cured with second line therapy
    - 1 failed two full courses of therapy ->unknown if any treatment options available

Gupta G, Yakubu I, Bhati C, et al. Ultra-short duration direct acting anti-viral prophylaxis to prevent virus transmission from hepatitis C viremic donors to hepatitis c negative kidney transplant recipients. *American journal of transplantation* 2019.

# Published data from clinical trials or center case series: Pre-emptive kidney

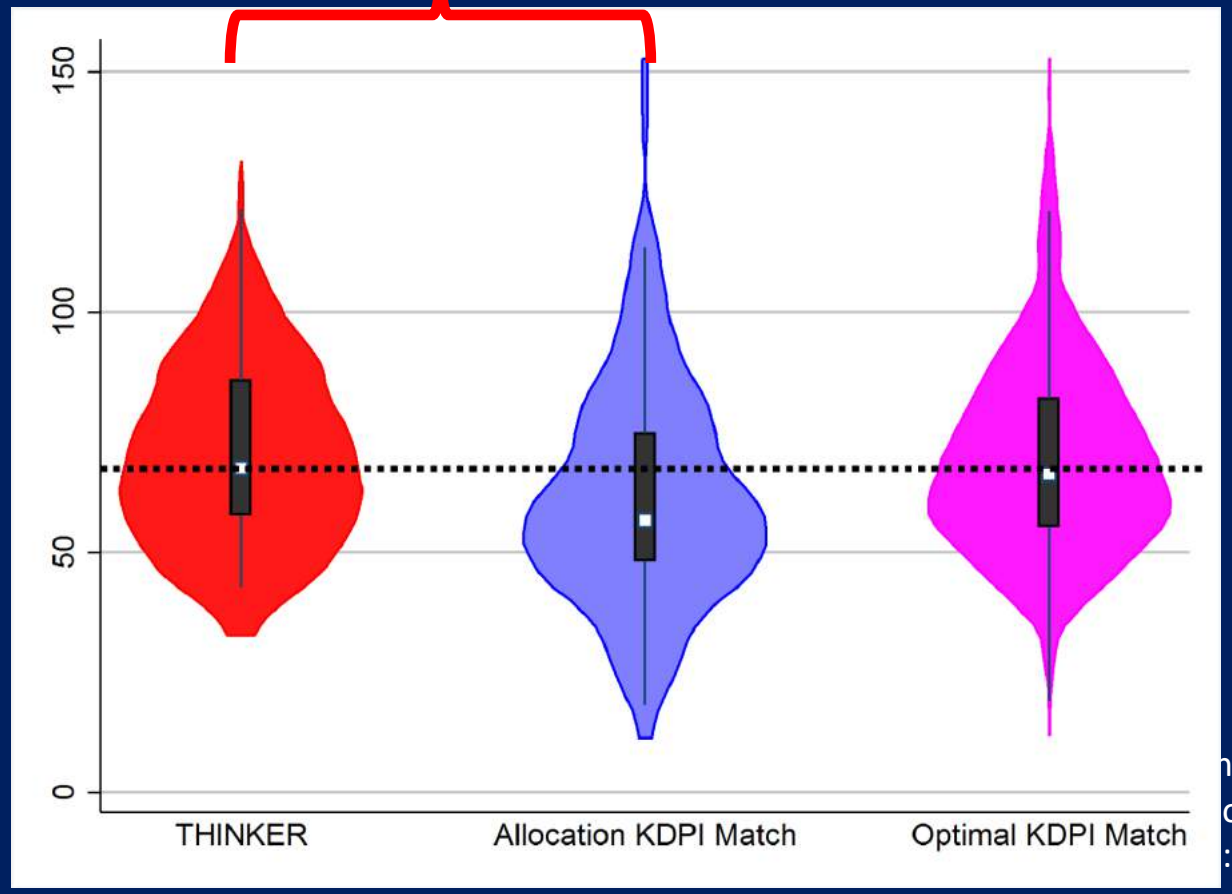
- THINKER studies
  - First cohort: 10 transplants
  - Second cohort: 20 total transplants
- Treatment on day 3 with Grazoprevir/Elbasvir for GT 1 or 4 disease
  - 20/20 cured with first-line therapy
  - No liver related complications
  - Excellent renal function

Goldberg DS, Abt PL, Blumberg EA, et al. Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients. *The New England journal of medicine.* 2017;376(24):2394-2395; Reese PP, Abt PL, Blumberg EA, et al. Twelve-Month Outcomes After Transplant of Hepatitis C-Infected Kidneys Into Uninfected Recipients: A Single-Group Trial. *Annals of internal medicine.* 2018;169(5):273-281.

# Published data from clinical trials or center case series: Pre-emptive kidney

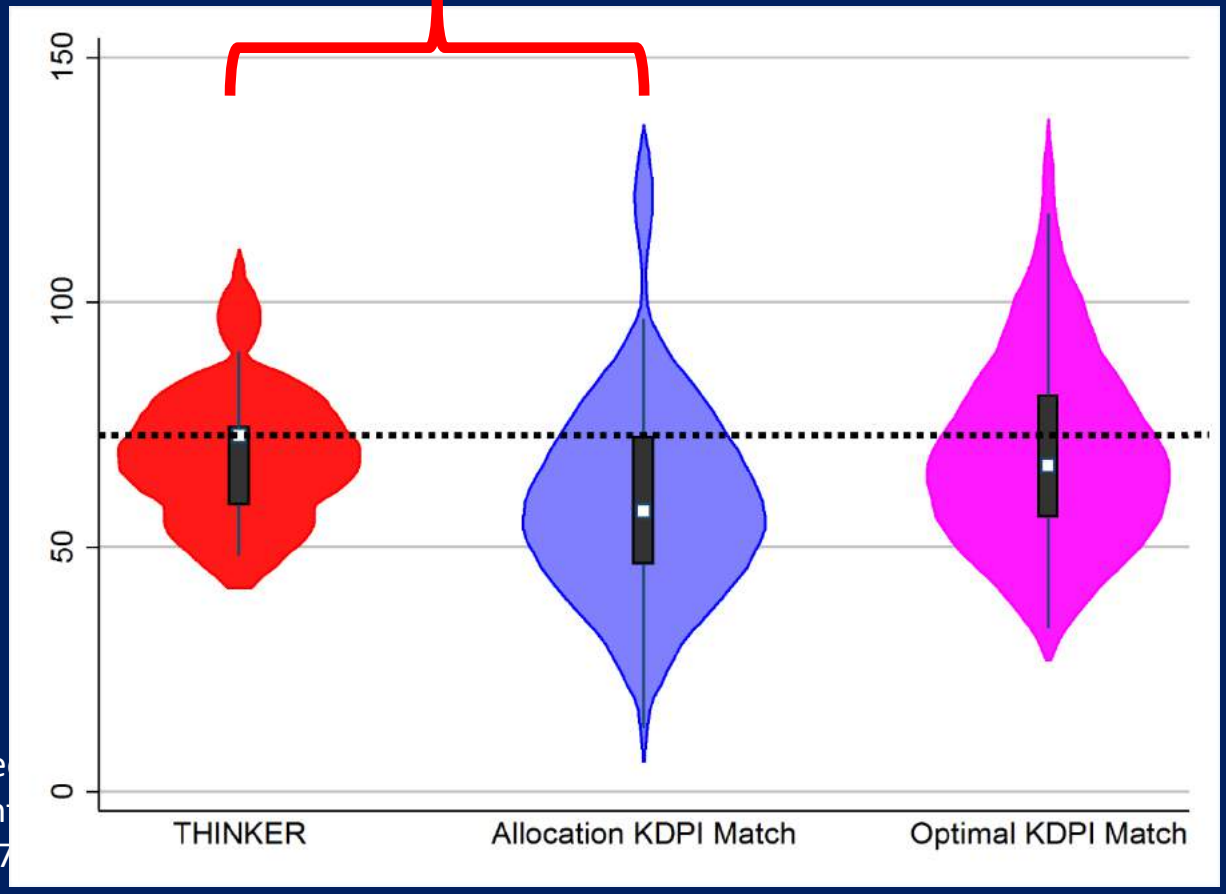
**6-month renal function**

**P=0.036**




**12-month renal function**

**P=0.016**



# Published data from clinical trials or center case series: Reactive kidney

- Methodist (Tennessee)
- ‘Standard-of-care’ approach
- Relied on insurance approval
- 53 kidney transplants
- Results
  - Median time between transplant and treatment initiation was 76 (IQR: 68-88) days
  - All 53 recipients became viremic
  - 19% experienced clinically significant increases (>3 times ULN) in aminotransferase levels
  - One patient developed fibrosing cholestatic hepatitis with complete resolution
  - 100% SVR rates
  - Unexpected: 57% with CMV viremia, 32% with BK viremia
-

Molnar MZ, Nair S, Cseprekal O, et al. Transplantation of kidneys from hepatitis C-infected donors to hepatitis C-negative recipients: Single center experience. *American journal of transplantation* 2019.

# Published data from clinical trials or center case series: Prophylactic thoracic

- Brigham and Women's
  - Immediately post-op and therapy for only 4 weeks
  - 44 transplants (36 lung and 8 heart)
  - SVR rate:  44/44 with 4 weeks of therapy
- Massachusetts General
  - On call to the OR for heart transplants
  - Continued for 8 weeks
  - 25/25 cured

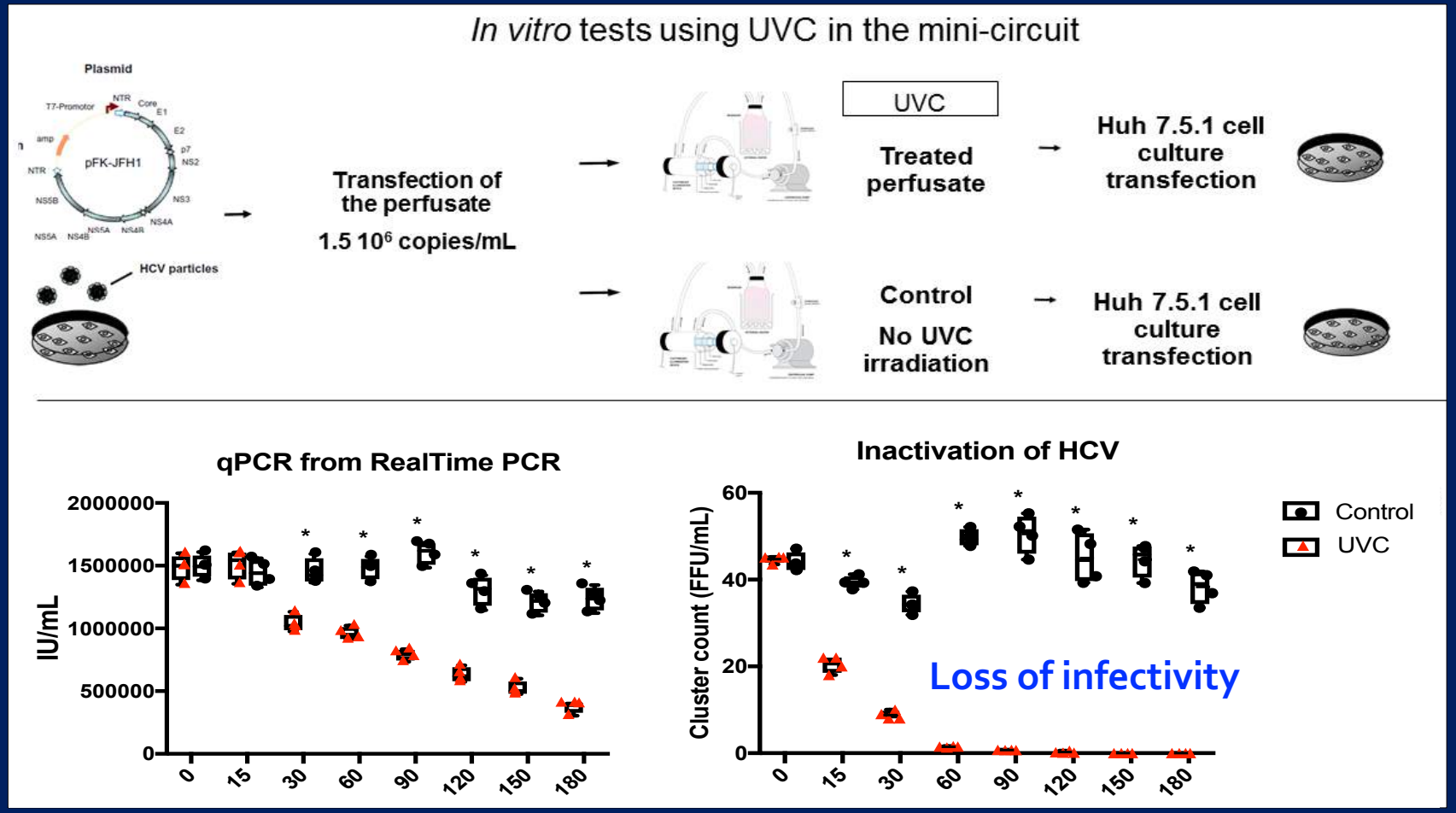
Woolley AE, Singh SK, Goldberg HJ, et al. Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. *The New England journal of medicine.* 2019;380(17):1606-1617.; Bethea ED, Gaj K, Gustafson JL, et al. Pre-emptive pangenotypic direct acting antiviral therapy in donor HCV-positive to recipient HCV-negative heart transplantation: an open-label study. *The lancet Gastroenterology & hepatology.* 2019;4(10):771-780.

# Published data from clinical trials or center case series: Reactive and pre-emptive lung

- Toronto General Hospital
  - Study #1: Focus on transmission using EVLP + UV light
    - EVLP + UV prevented transmission Brigham in 2/22
    - 2/20 with viremia had FCH after relapse and required second treatment
  - Study #2: Focus on prevention with EVLP + therapy on call to the OR and continued for 1 week
    - AASLD abstract
      - Lung: EVLP + UVS
      - Heart, liver kidney, standard donor
      - Recipient: Ezetimibe + 1 week therapy
      - 100% (25/25) cure rate

Cypel M, Feld JJ, Galasso M, et al. Prevention of viral transmission during lung transplantation with hepatitis C-viraemic donors: an open-label, single-centre, pilot trial. *The Lancet Respiratory medicine.* 2019.; Galasso M, Feld JJ, Watanabe Y, et al. Inactivating hepatitis C virus in donor lungs using light therapies during normothermic ex vivo lung perfusion. *Nature communications.* 2019;10(1):481.

# Marked effect of UV light on HCV infectivity




UV light leads to **loss of infectivity>>>decline in HCV RNA ie HCV RNA may underestimate effect**

Galasso Nat Comm 2019; slide courtesy of Jordan Feld, MD

# Published data from clinical trials or center case series: Pre-emptive therapy

- USHER study (Penn)
  - Day 3 with Grazoprevir/Elbasvir for GT 1 or 4 HCV
  - 9/10 cured (1 died prior to SVR-12 but had EOT response)
  - No heart-related issues
  - 3 required NGT administration

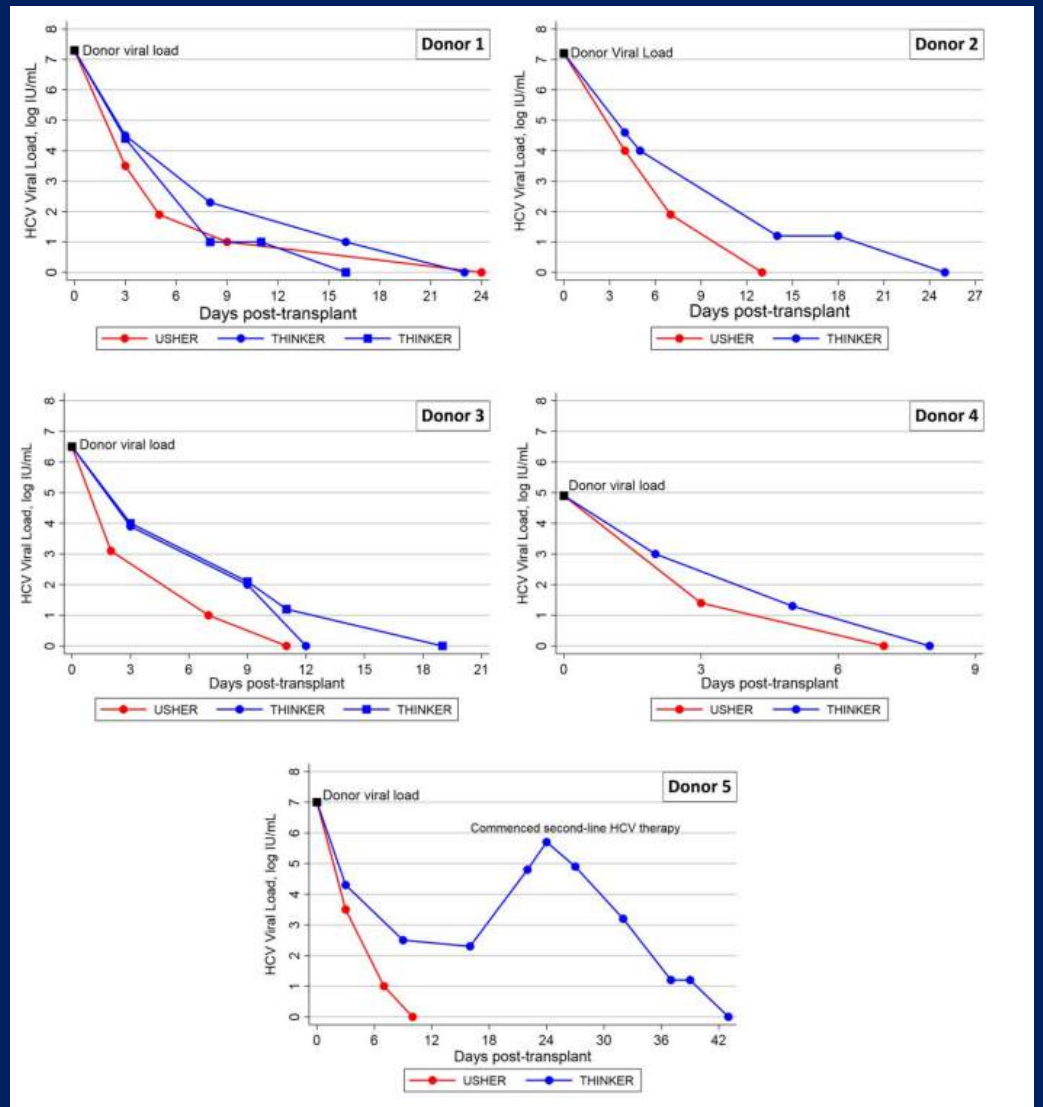
McLean RC, Reese PP, Acker M, et al. Transplanting hepatitis C virus-infected hearts into uninfected recipients: A single-arm trial. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2019;19(9):2533-2542.

# Published data from clinical trials or center case series: Reactive heart

- Vanderbilt: First published heart study
  - Initial study with 10 transplants: 9/10 cured (1 died)
  - Extended to >50 transplants
- UCSD: 19 transplants
  - All cured (with available data)
  - No heart-related complications

Schlendorf KH, Zalawadiya S, Shah AS, et al. Early outcomes using hepatitis C-positive donors for cardiac transplantation in the era of effective direct-acting anti-viral therapies. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* 2018;37(6):763-769; Aslam S, Yumul I, Mariski M, Pretorius V, Adler E. Outcomes of heart transplantation from hepatitis C virus-positive donors. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* 2019.; Gernhofer YK, Brambatti M, Greenberg BH, Adler E, Aslam S, Pretorius V. The impact of using hepatitis c virus nucleic acid test-positive donor hearts on heart transplant waitlist time and transplant rate. *The Journal of heart and lung transplantation* 2019;38(11):1178-1188.

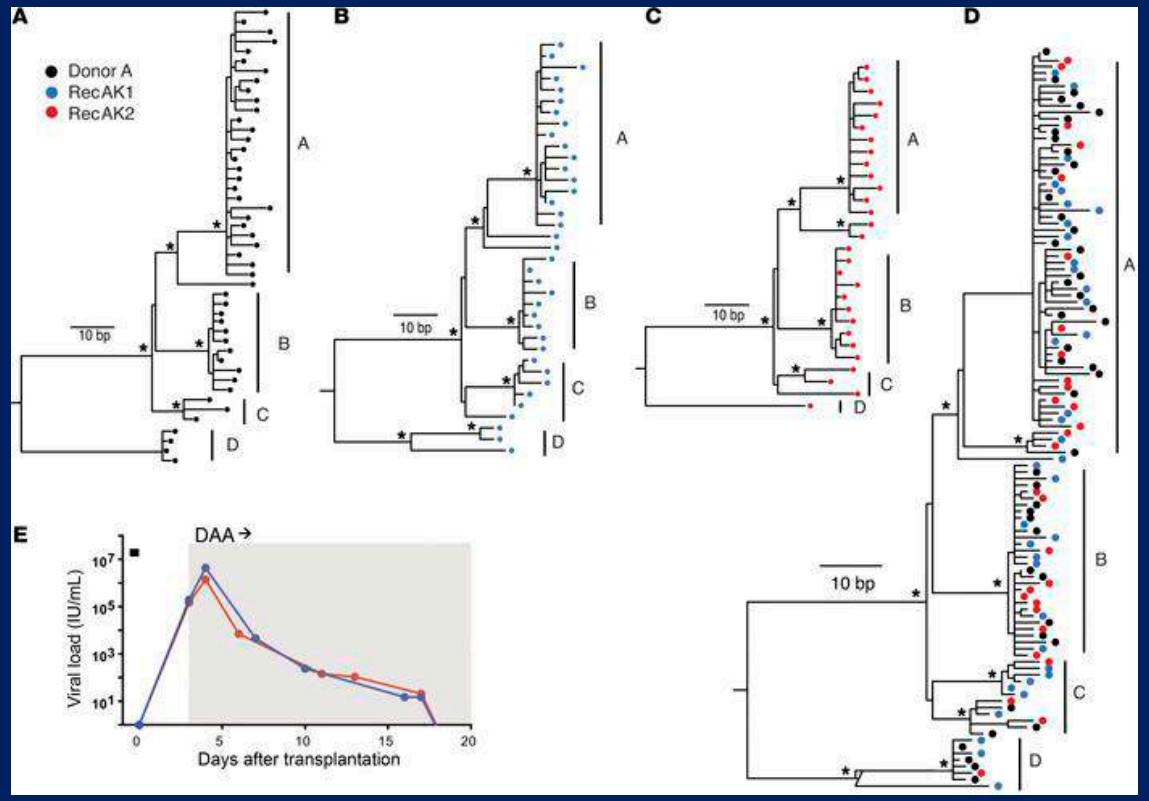
# Other interesting clinical observations: Viral transmission differs in hearts and kidneys

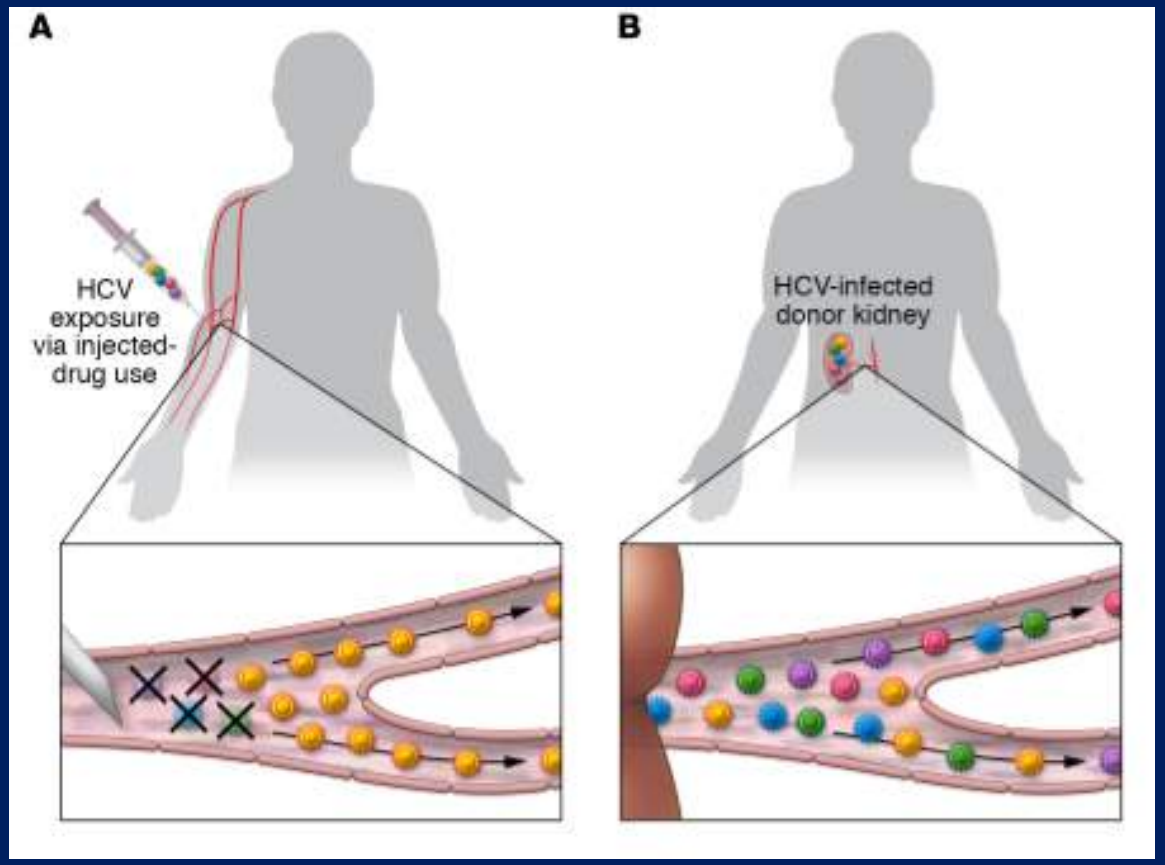



McLean RC, Reese PP, Acker M, et al. Transplanting hepatitis C virus-infected hearts into uninfected recipients: A single-arm trial. *American journal of transplantation.* 2019;19(9):2533-2542.

# Other interesting clinical observations: Unique viral bottleneck

**Highly permissive HCV transmission process**

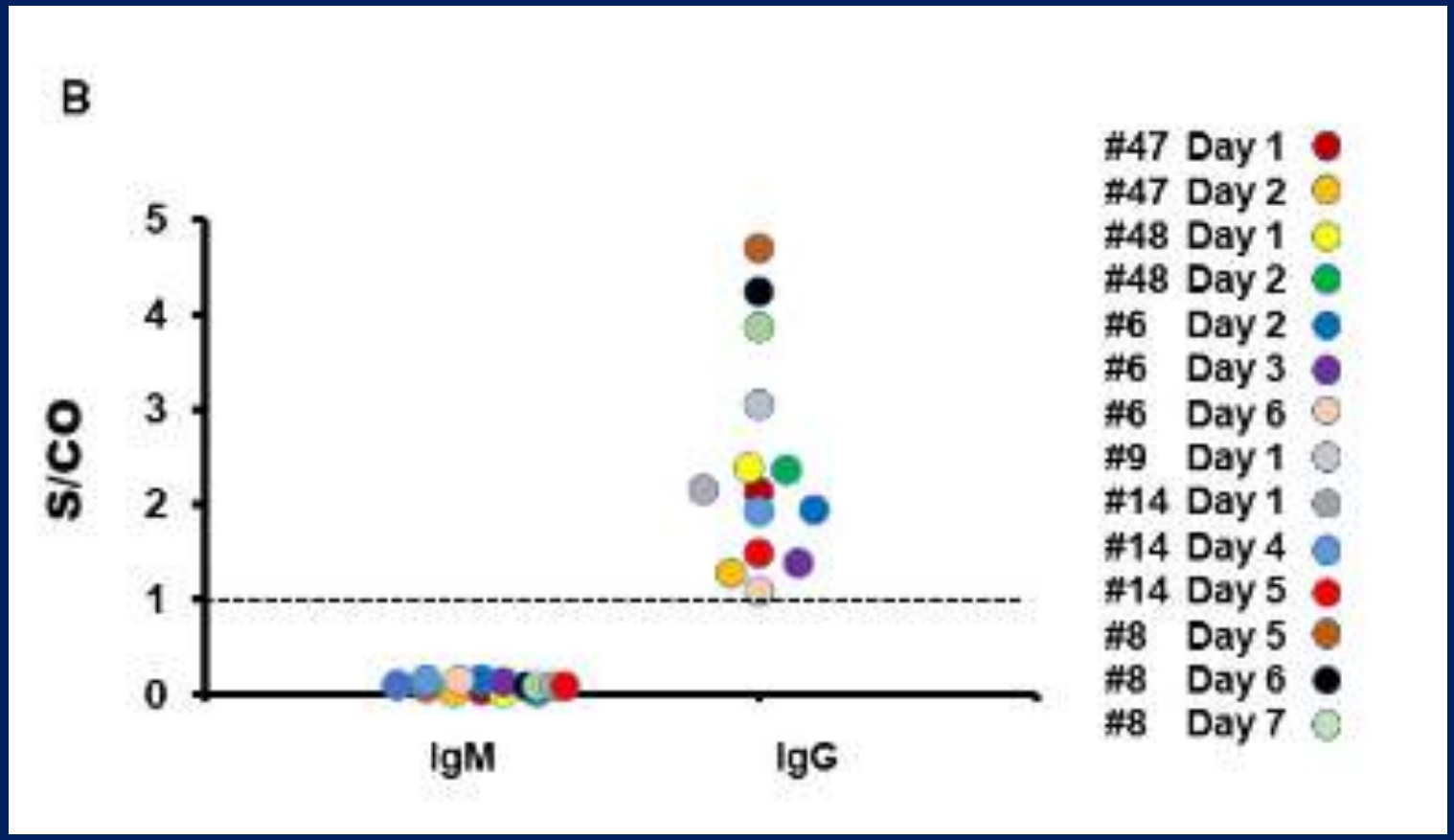



Durand & Chattergoon, J Clin Invest 2019;129:3038–3040, Zahid, et al. J Clin Invest 2019;129: 3134-39

# Other interesting clinical observations: HCV Ab transmission

**Transmission of donor-derived HCV Ab in 45% (18/40) cases**




Porrett…Goldberg DS. American Journal of Transplantation 2019; 19(9): 2525-2532

# While outcomes good, it's not all rosy: Rejection

| 1st Author | Organ | Timing of DAA | #Rejection/Total (%) | # Denovo DSA/Total (%) |
|---|---|---|---|---|
| Reese | Kidney | Upon viremia | | 1/20 (5%) |
| Molnar | Kidney | Median 76 days post transplant | 3/53 (6%) ACR<br>1/53 (1.9%) ACR/AMBR | 16/53 (30%) |
| Kwong | Liver | Insur authorization (11-84 days) | 2/10 (20%) ACR<br>1/10 (10%) AMR | |
| McLean | Heart | Upon viremia | 2/10 (20%) ACR<br>1/10 (10%) AMR (+ X-match) | |
| Schlendorf | Heart | Insur authorization | 1/12 AMR (8.3%) | |
| Woolley | Heart | Pre-emptive | 6/11 (55%) ACR<br>1/11 (9%) AMR | |
| | Lung | Pre-emptive | 11/18 (61%) ACR (2 yrs)<br>1/42 (2%) AMR (1 yr) | |
| Cypel | Lung | ≥ 2 weeks post tx | 11/22 (50%) ACR | |

Reese, et al, Ann Intern Med 2018; Molnar, et al. Am J Transplant 2019; Kwong, et al, Am J Transplant 2018; McLean, et al Am J Transplant 2019; Schlendorf, et al J Heart Lung Tx 2018; Woolley, et al, NEJM 2019; Cypel, et al, Lancet Resp Med 2019

# While outcomes good, it's not all rosy: Viral complications

- Treatment failures
  - Penn kidney (1/50)
  - Toronto lung (2/20)
  - VCU (3/6) with 1 failing second-line therapy (unclear if treatment options)
- Fibrosing cholestatic HCV
  - Methodist: 1/53
  - Cleveland Clinic: 2/75
  - Toronto: 2/20 after failing first line therapy
- Other viral complications
  - Mayo-Jacksonville: Acute MPGN with renal failure
  - CMV and BK: Methodist

# What we know based on available data

- Transmission universal from viremic donors
- Donor viral load correlates with recipient viral load
- Cure rates similar to chronically infected
- Potential for short-course therapy (but there may be a limit)
- Organs being utilized more to save more lives
- Variable practice across the US (trial vs standard of care)
- Insurance approval is not universal
- Short-term impact on grafts minimal

# What we don’t know based on available data

- What are true cure rates
  - Unknown as no registry of all patients
- What is informed consent process like for patients?
  - No specific policy or oversight
- How many other viral complications are there?
- How is HCV transmitted in non-hepatic transplants
- What are long-term impacts to the graft
- What are the true risks of other viral infections?
- What is optimal time course for therapy
- Does it matter if therapy starts late

# How should this be done currently

- Depends who you ask (and depends on the organ)
- Personal opinion
  - Ideal scenario: IRB-approved research protocol
    - Practice and protocol vetted for patient safety and proper informed consent
    - Evaluation for higher-risk features (liver disease)
  - Reasonable alternative
    - Formal education and informed consent process
    - Appropriate patient selection
    - Pre-transplant assessment of liver disease (e.g., Fibroscan)
    - Guaranteed drug coverage (insurance + health system safety net)
  - Treatment: Epclusa or Mavyret

# Considerations in patient selection

- Do we need to screen for pre-existing liver disease
  - Clinical trials (e.g, THINKER, EXPANDER, Toronto): Yes
    - Undiagnosed liver disease (e.g., NASH)->especially in renal patients
  - What are risks of HCV infection with pre-existing liver disease?
  - Are risks magnified if reactive treatment approach?
- What if requires enteral administration (limited published data; lung)
- What if on amiodarone (heart and use of Sofosbuvir)
- What if have prolonger hyperbilirubinemia (liver; G/P)
- What if insurance denies or delays?

# What are financial and logistical barriers

- Who will pay for therapy
  - If prophylactic treatment: Requires hospital coverage
- Overarching concern: Need universal insurance approval
  - “Daily dose wallet” or blister packaging complicates dispensing from inpatient pharmacy->can be done
  - In 2017, 65% of state Medicaid programs still had fibrosis restriction
  - DAAs are not FDA approved for acute HCV
  - Peri-operative treatment initiation would require insurance approval prior to HCV infection
    - Currently all anecdotes suggest insurance will not approve therapy until patient has been infected
      - Some require documentation of infection
      - Some insurers will allow for donor data
      - Some outright refuse

# Conclusions

- Transplanting organs from HCV+ donors into HCV- patients is important potential mechanism to:
  - Save more lives
  - Increase number of transplants
  - Improve utilization of scarce resource
- Highly potent DAAs should change us to rethink how we view HCV in the setting of transplantation (i.e., HBV Core Ab+)
- Informed consent process is critical
- Need to define operational factors for broader utilization
  - Insurers
  - Optimal patient selection
  - Unexpected risks

# Acknowledgments


- Co-Principal Investigator: Peter Reese, MD, MSCE
- Co-Investigators: Peter Abt, MD and Emily Blumberg, MD
- Collaborators
  - K. Rajender Reddy, MD
  - Roy Bloom, MD
  - Matthew Levine, MD, PhD
  - Paige Porrett, MD, PhD
  - Ali Naji, MD, PhD
  - Susanna Nazarian, MD, PhD
  - Deirdre Sawinksi, MD
  - Jennifer Trofe-Clark, PharmD
  - Vivianna Van Deerlin, MD, PhD
  - Midhat Farooqi, MD, PhD
  - Rick Hasz, BS
  - Gift of Life Donor Program
  - Maureen McCauley, BS
  - Anna Sicilia, BS
  - Adam Mussell, BS
  - Mary Kaminski, PA
- Patients