Transplantation of Organs from HCV-Infected Donors into HCV-Negative Recipients

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- Research grant support (Gilead, Merck, AbbVie) paid to my institution for studies of transplanting organs from HCV-infected donors into HCV-negative patients
- My wife’s best friend’s daughter is 5 years s/p LDLT and my college roommate is 4 years s/p DDLT

Objectives

- Discuss background data that led to developing trials of transplanting organs from HCV-infected donors into HCV-negative recipients
- Review published data from recent studies and case series exploring transplanting of organs from HCV-infected donors into HCV-negative recipients
- Discuss barriers to making this practice standard-of-care

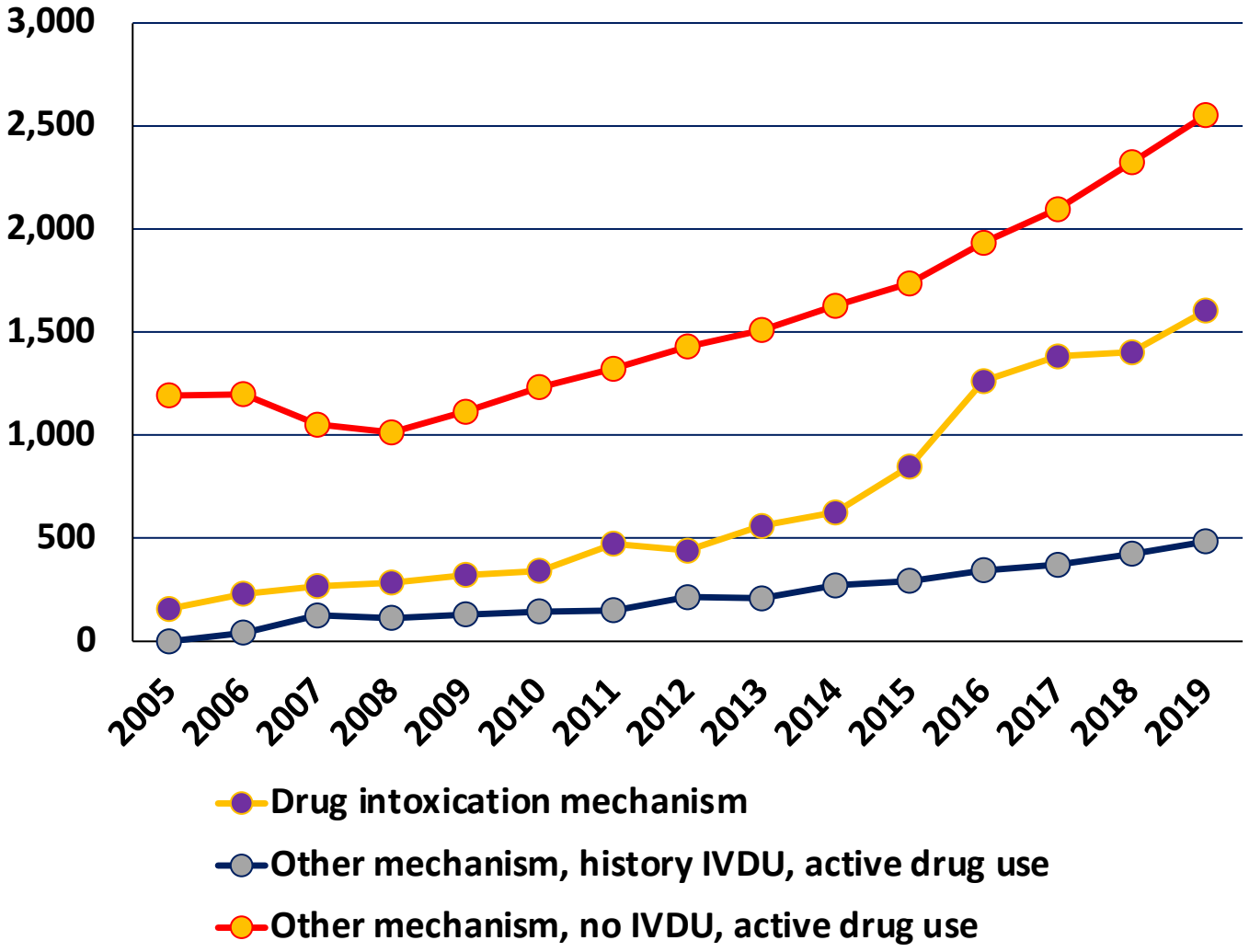
Defining HCV ‘positivity’ in organ donors

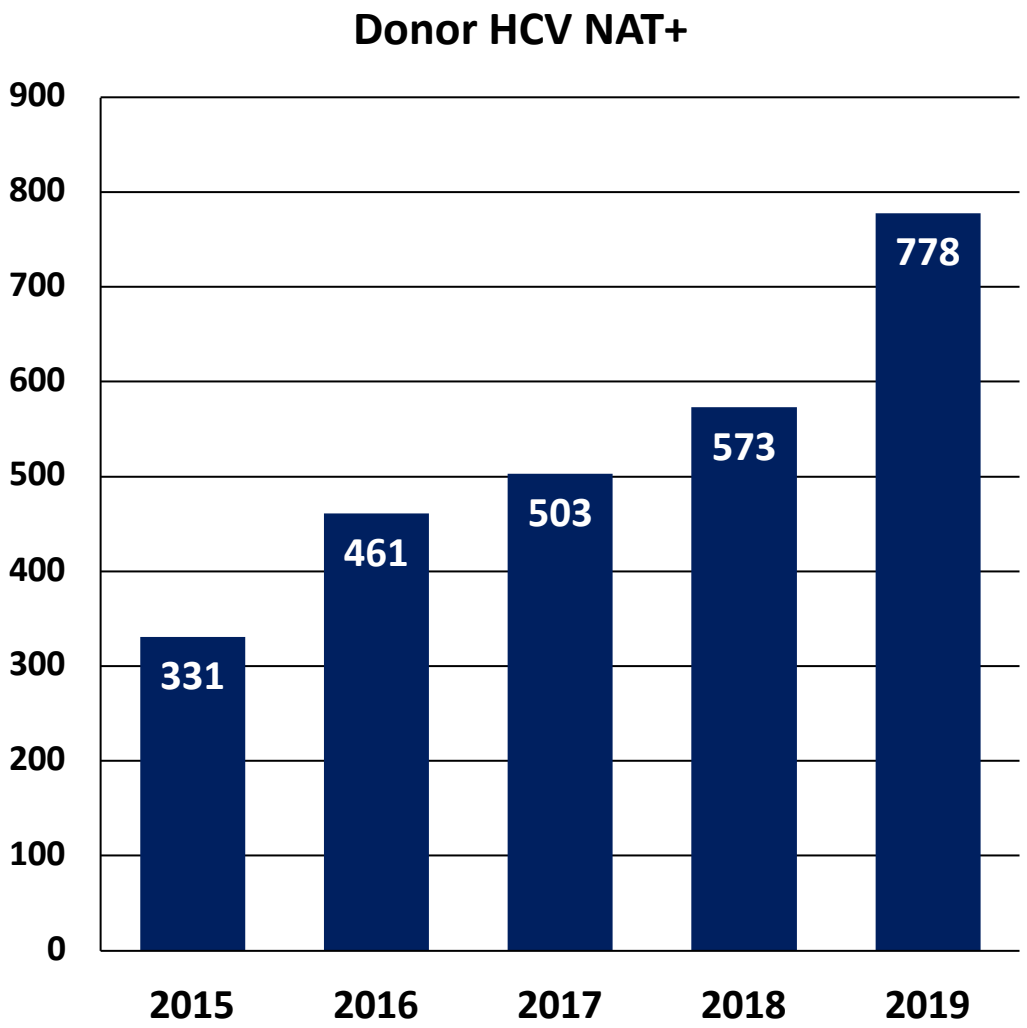
- Pre-2014 HCV NAT (RNA) testing not mandatory and variable
  - Donor HCV positivity defined largely by HCV Ab
  - One-third of previously infected/exposed patients without disease
- HCV Ab+ ≠ active HCV infection
  - Ab is a red herring
    - False (+)
    - Prior infection (spontaneously cleared or treated)
    - Chronic infection with fluctuating viral load (rare)

Defining HCV ‘positivity’ in organ donors

- Ab does not mean increased risk transmission
  - All data on published Ab+/NAT- transmissions
    - Increased risk donors in window period
    - Some HCV NAT+ on pre-donation sample
- Studies using OPTN/UNOS data pre-2015 are based solely on HCV Ab positivity
- **HCV ‘positive’ in this talk=HCV-viremic**

Important changes to the donor pool





Use of HCV-viremic organs prior to 2016

- Liver: High utilization
  - Large pool of recipients
- Kidney: Limited utilization for HCV+ recipients (recipient genotype restricted)
  - Did not want to give GT 2/3 recipient a GT 1 donor (genotype switch)
  - IFN and Ribavirin post-transplant challenging
  - Increasing utilization in 2014/2015 (HCV-infected recipients)
- Lung and heart: Rarely used
  - HCV as co-morbidity in recipients
  - Worse outcomes

First pilot trials of HCV D+/R- DDKTs using Grazoprevir/Elbasvir

- THINKER trial (Penn)[1,2]
  - Required real-time donor genotyping
  - Added complexity (donor blood)
    - Organ refusals (no specimen, wrong genotype)
  - Treatment on day 3->10/10 SVR-12 (cure)
    - Expanded and published data on 40 patients (39/40 cured with 1st line therapy)
- EXPANDER trial (Hopkins)[3]
  - Grazoprevir/Elbasvir + Sofosbuvir if GT 2 or 3
  - Started treatment on-call to OR
  - 10/10 SVR-12; 7/10 never with detectable HCV

1-Goldberg DS, et al. NEJM 2017; 376(24): 2394-2395; 2-Reese PP, et al. Annals of Internal Medicine 2018; 169(5): 273-281; 3-Durand CM, et al. Annals of Internal Medicine 2018; 168(8): 533-540

Selection of other published studies of HCV D+/R- transplants: Abdominal

- Cleveland Clinic: 'Real-world' experience of kidneys and livers[1]
  - 64 DDKTs->41 achieved SVR-2, 10 with EOTR, 7 on treatment
- Methodist University (Memphis, TN): 'Standard-of-care' approach[2]
  - 53 transplant with treatment 1-3 months; 53/53 cured
- Stanford: Non-trial experience[3]
  - 10 HCV D+/R- liver transplants
  - 10/10 with SVR-12

1-Kapila N, et al. Hepatology 2020; 2-Molnar MZ, et al. American Journal of Transplantation 2019; 3-Kwong A, et al. American Journal of Transplantation 2018

Selection of other published studies of HCV D+/R- transplants: Thoracic

- Vanderbilt University with ‘standard-of-care’ with special consent[1]
  - 70 recipients of heart from HCV NAT+ donor
  - Median days activation to transplant: 4 days (IQR: 1-18)
  - 1-year survival: 90.4%; all surviving to SVR-12 mark with cure
- Brigham and Women’s (formal trial)[2]: Short-course (4-week) of Epclusa within few hours post-transplant
  - Lung: 36/36; Heart: 8/8
- Toronto General Hospital: Protocol with EVLP + UV perfusate irradiation[3]
  - EVLP + UV led to lower viral loads with 2/11 not developing HCV

1-Schlendorf KH, et al. JAMA Cardiology, 2019; 2-Woolley AE, et al. NEJM 2019; 3-Cypel M, et al. Lancet Respiratory Medicine 2019

Novel Treatment Approaches

- Short-course G/P + Ezetimibe for 7 days (started 6-12h pre-transplant)[1]
  - Ezetimibe may serve to block HCV entry into cells
  - 30 transplants (13 lung, 10 kidney, 6 heart, 1 kidney-pancreas)
  - 30/30 SVR-12 (2 patients had end-of-treatment viremia)
- Ultra-short duration with adaptive approach (all received 1 dose on call to OR)[2]
  - Group 1: 1 day post-transplant: 3/10 developed viremia
  - Group 2a: 2 days post-transplant: 2/15 developed viremia
  - Group 2b: 2 days post-transplant: 1/25 developed viremia
  - Full-course if not cured with short course
    - 3/6 cured with first-line full-course
    - 2/6 failed first-line and cured with second-course
    - 1/6 failed first- and second-line therapies->likely now incurable
- Short-course (4 week) G/P for 4 weeks post-kidney transplant[3]
  - Started on-call to the OR
  - 10/10 cured

1-Feld JJ, et al. Lancet Gastroenterology Hepatology 2020; 5(7): 649-6572; Gupta G, et al. Am J Transplantation 2020; 20(3): 739-751; 3-Durand C, et al. Annals of Internal Medicine 2020, online 9/8/2020

Current landscape of HCV D+/R- organ transplants in the US

- Some centers offering this as “standard of care”
  - No IRB approval except for data collection
  - Variable consent process
  - Plan to apply to insurance company for approval
    - Some health systems agree to pay if insurance declines
- Variable information provided to patients
- Emerging publications of potential unanticipated risks
  - Methodist: Increased BK/CMV[1]
  - Methodist + Cleveland Clinic: Risks of FCH[1,2]
  - VCU: Multiple treatment failures (2 rounds)
  - Toronto: 10% relapse rates (2/20)
  - Mayo Jacksonville: Renal failure + insurance delay[3]
  - Insurance denials at Ohio State: 35% kidneys with initial refusal, 10% livers[4]
- Disturbing early pattern of disparities in utilization of kidneys from HCV-viremic donors[5]
  - Decreased use in racial and ethnic minorities, women, and those with less education

1-Molnar MZ, et al. American Journal of Transplantation 2019; 2-Kapila N, et al. American Journal of Transplantation 2019; 3-Wadei HM, et al. American Journal of Transplantation 2019; 4-Daloul R, et al. American Journal of Transplantation 2020; 5-Nguyen T, et al. Transplantation 2020, in press

How to implement practice of HCV D+/R- transplants

- Personal opinion: IRB-approved research protocol vetted for safety and informed consent
  - Evaluation for higher-risk features (liver disease)
  - Many unknowns: HCV cure rates with narrow CI, survival benefit/risks, CMV and BK, long-term graft outcome
- Reasonable alternative
  - Formal education and informed consent process that does not disproportionately leave out one group of patients
  - Pre-transplant assessment of liver disease (e.g., Fibroscan)
  - Guaranteed drug coverage (insurance + health system safety net)
- Treatment regimen: Epclusa or Mavyret
- Treatment duration: Full-course
  - Cost savings not worth the risk of potential treatment failures

Logistical barriers to implementing HCV D+/R- transplants in clinical practice

- Universal insurance approval
  - In 2017, 65% of state Medicaid programs still had fibrosis restriction
  - DAAs are not FDA approved for acute HCV
  - Denials and delays common[1]
- Timing of treatment initiation
  - Earlier the better[2]
  - Peri-operative treatment initiation would require either:
    - Insurance approval prior to HCV infection
      - Authorization for entire list?
      - Will insurance approve without documentation of HCV in donor or recipient
    - Health system “eats” the cost
      - What if recipient without detectable viremia?
      - Will insurance approve based on donor viremia?

1-Daloul R, et al. American Journal of Transplantation 2020; 2-AASLD-IDSA Hepatitis C Guidance Panel. Hepatology 2020

THINKER-NEXT Trial

- NIH U01 DK126654 (8-center NIDDK-funded U01)
  - Penn, Miami, Wash U, Hopkins, Vanderbilt, Columbia, Cincinnati, and MGH
- https://www.thinkernextstudy.org/tn-sites.html
- Key unanswered questions in HCV D+/R- kidney transplants
  - HCV cure rates with narrow confidence intervals
  - Compared to well-matched HCV-negative comparators
    - Post-transplant allograft function
    - Survival benefit of accepting kidneys from HCV-infected donors
    - Post-transplant risk of CMV
    - Chronic kidney disease pathology in donor kidneys

Key Takeaways

- 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
  - Informed consent process is critical
- Need to define operational factors for broader utilization
  - Insurers
  - Optimal patient selection
  - Unexpected risks