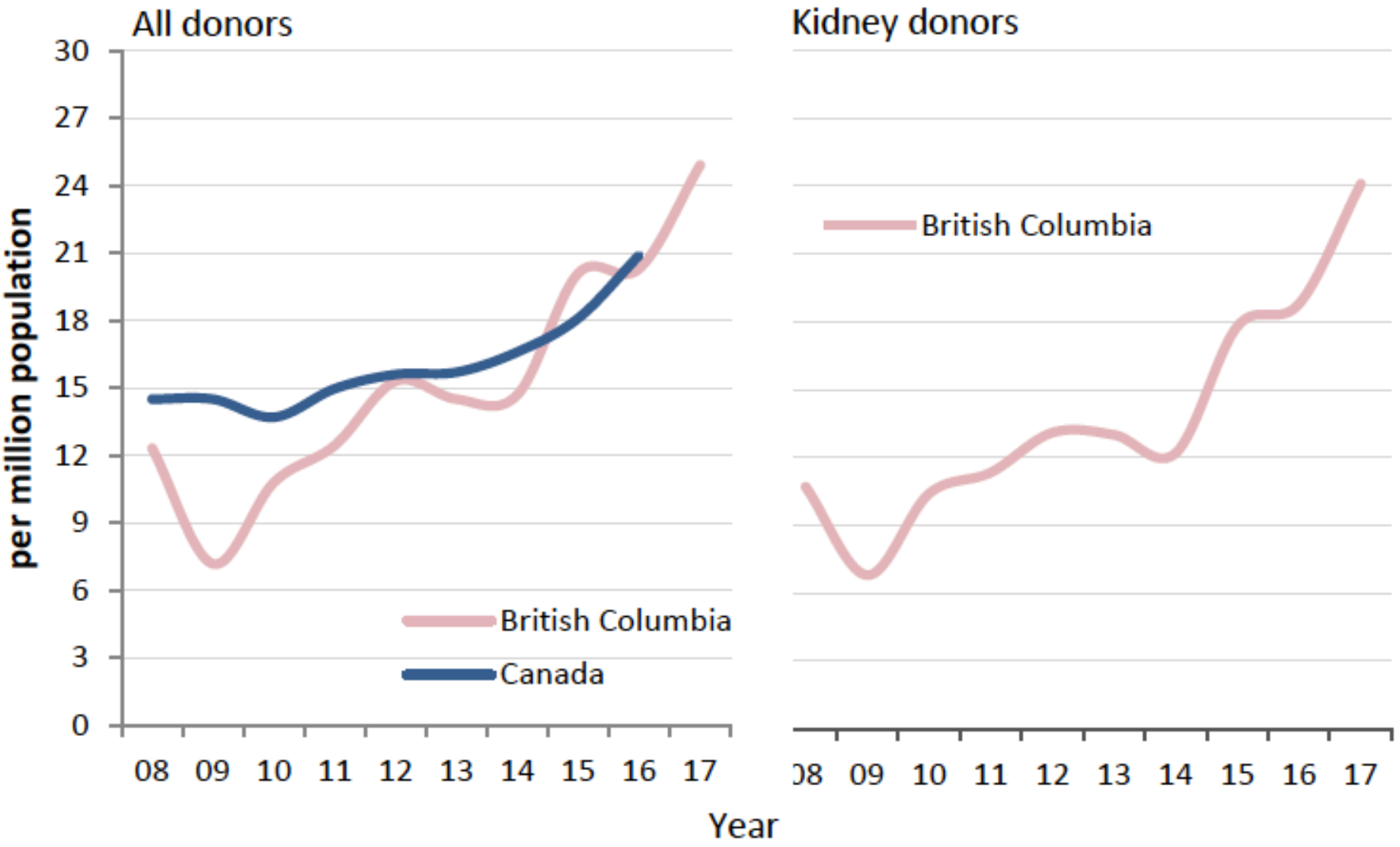
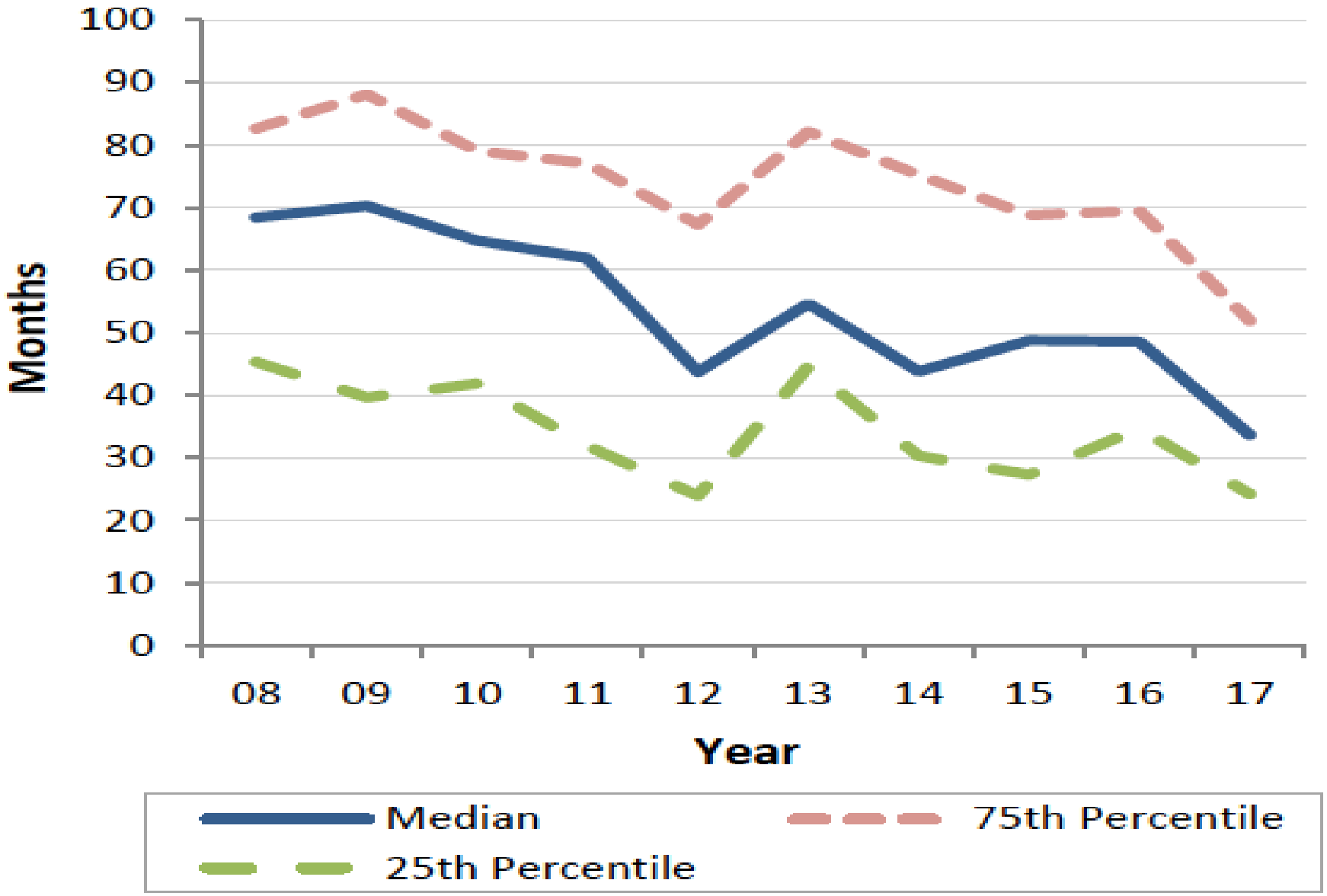
Increased Risk Donors

November 1, 2018
BC Kidney Days

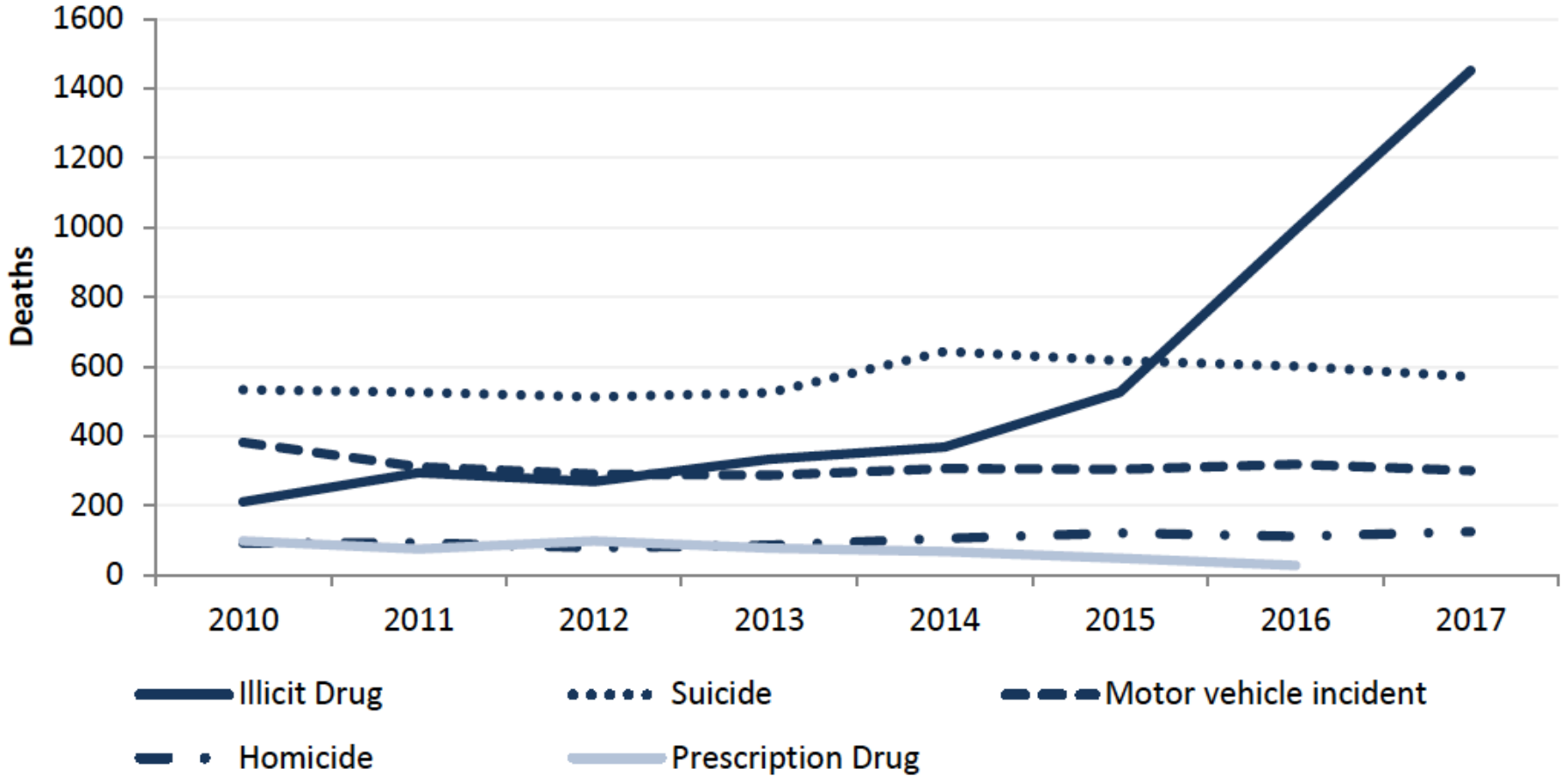
Jagbir Gill MD MPH
Associate Professor of Medicine
UBC


All donors
Kidney donors
per million population
30
27
24
21
18
15
12
9
6
3
0
British Columbia
Canada
08
09
10
11
12
13
14
15
16
17
Year



Median dialysis exposure prior to DDKT

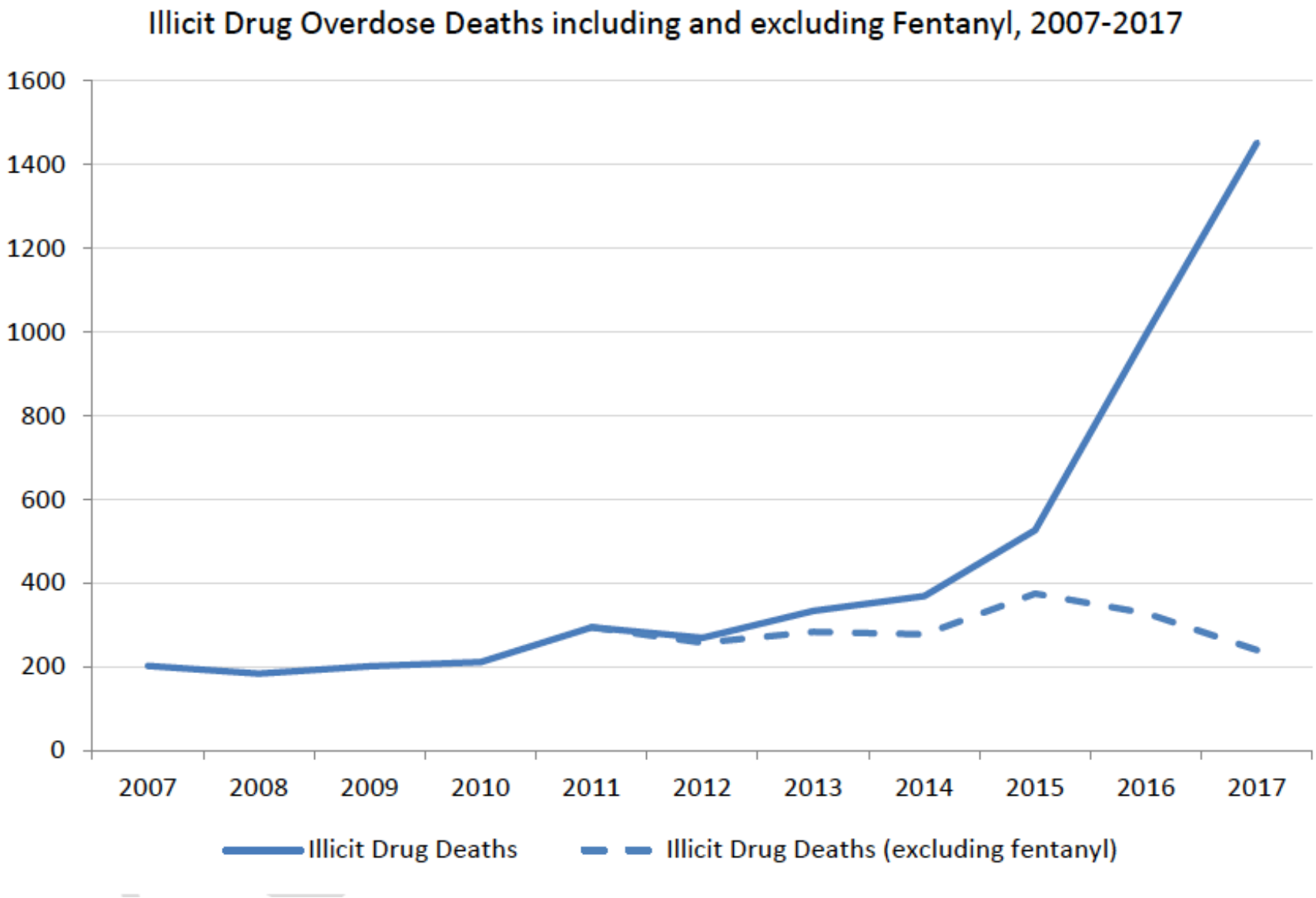
Major Causes of Unnatural Deaths in BC

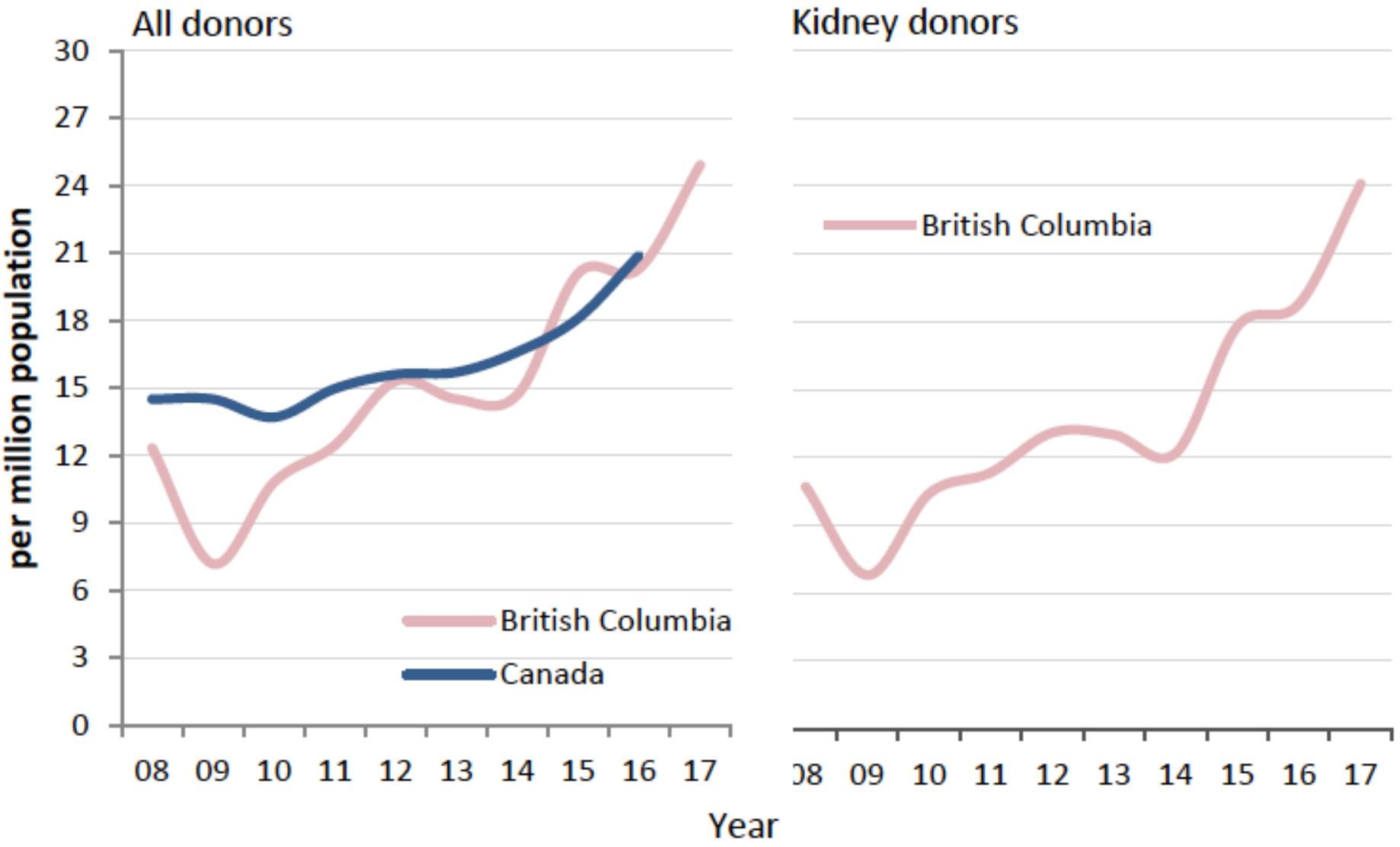


BC Coroners Service

Posting Date Sept 27, 2018

Illicit Drug Overdose Deaths in BC
January 1, 2008 to August 31, 2018


Illicit Drug Overdose Deaths including and excluding Fentanyl, 2007-2017
1600
1400
1200
1000
800
600
400
200
0
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Illicit Drug Deaths
Illicit Drug Deaths (excluding fentanyl)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British Columbia
Canada
08
09
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11
12
13
14
15
16
17
Year

Case scenarios

Which donors should we accept kidneys from?

Case 1

- 54 yo man
- NDD – subarachnoid hemorrhage
- SCR 87 umol/L
- Social history – was in prison for 3 years 4 years ago
- No known drug use or high risk sexual behaviors in the last year according to friend

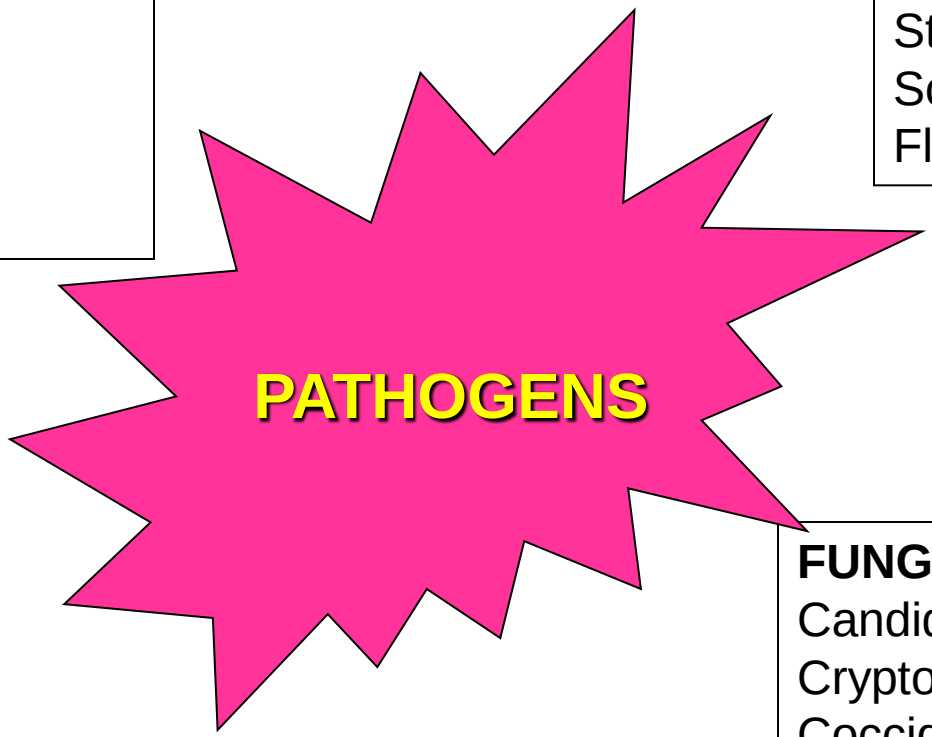
Case 2

- 24 yo man
- NDD – anoxic brain injury (overdose)
- SCR 62umol/L
- Social history – IV drug use in the last 2 weeks (in hospital for 8 days)

Potential DDI Pathogens

VIRAL
Hepatitis A, B, C, D…
HIV
HHV 1 - 8
Rabies
West Nile Virus
LCMV

PARASITIC
Malaria
Chagas disease
Strongyloides
Schistosomiasis
Flukes



BACTERIAL
Gram positive
Gram negative
Mycobacterial
Spirochetes

FUNGAL
Candida
Cryptococcoccus
Coccidioides
Histoplasma
Aspergillus

PRION
vCJD

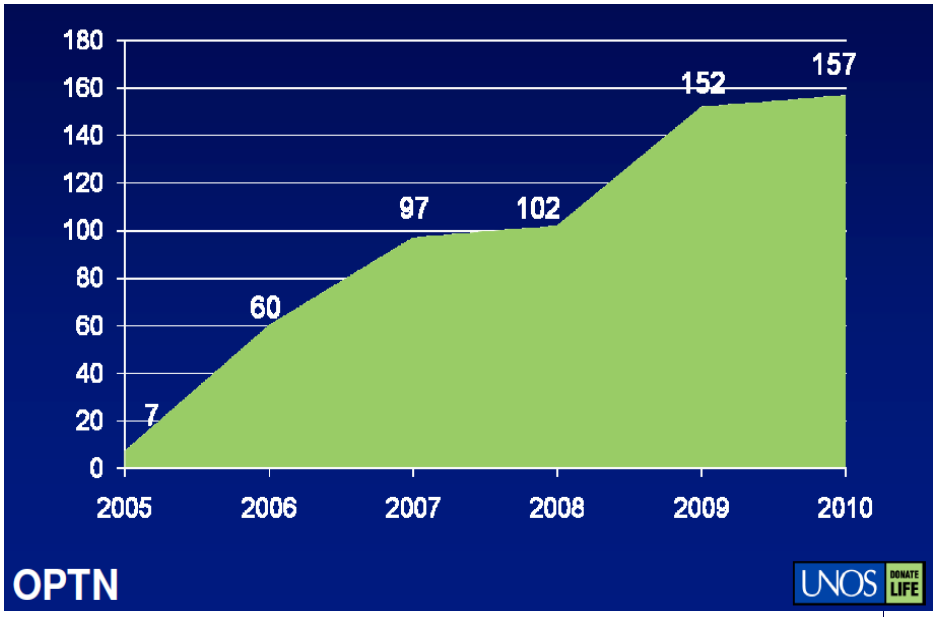
Courtesy: Dr. A. Humar

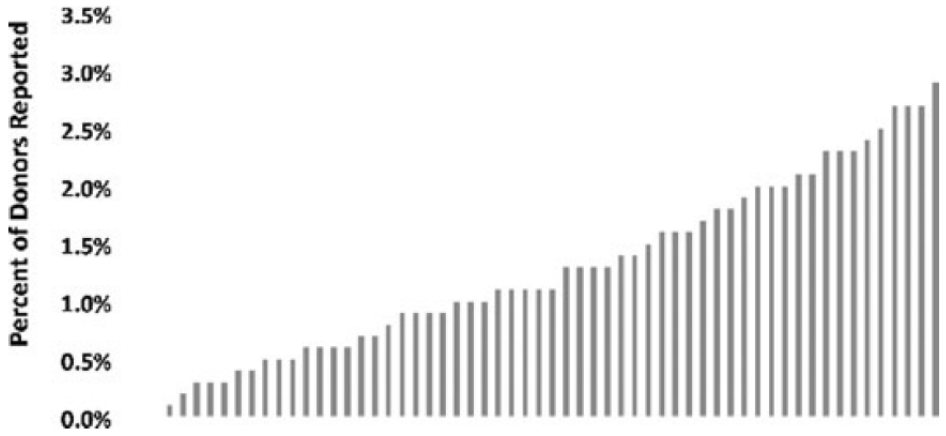
Notable DDI: Published literature

- HIV, 1985
- HCV, 2000
- Chagas Disease (T. cruzi), 2001
- West Nile Virus (WNV), GA 2002
- Lymphocytic Choriomeningitis Virus (LCMV) 2003; 2005
- Rabies, 2004, 2005
- WNV, MY/PA 2005
- Chagas, 2006
- M. TB – 2008
- HIV/HCV 2007
- HCV 2009
- Balamuthia mandrillaris – 2010

Courtesy: Dr. A. Humar

Rare events - but likely underreported





Ison, et al AJT 2011

- Nearly 160 DDI reported between 2005-10
- Variable reporting
- Tissues
  - 20 cases from 1998-2006
  - 1 million tissue transplants per year

The New York Times

Transplant surgeons are increasingly using organs from drug users, the obese and the very ill. But with little known for certain about the consequences,

Will Any Organ Do?

By Gretchen Reynolds

doctors are confronting complex medical and ethical questions.

Chicago, 2007

- Donor HCV and HIV negative on serologic tests
- Had high risk social characteristics (classified as high risk donor)
- 4 recipients infected with HIV and HCV - 2 died
- Retrospective testing of donor sera showed NAT positive for HIV/HCV

Infection Reports to DTAC, 2005-2010

Disease	# of Donor reports	# of recipients with confirmed transmission	# of DDI-Attributable recipient deaths
Virus	122	34	9
Bacteria	75	31	9
Fungus	56	37	10
Mycobacteria	37	11	2
Parasitic	30	18	6
Total Infections	**320**	**131**	**36**

Ison et al. AJT 2011

Trends of DDI in the US

- Bacterial transmission
  - likely underrecognized and underreported
  - Often involves resistant bacteria
- Fungi
  - Endemic mycoses and cryptococcus increasing
  - High morbidity and mortality
- Mycobacteria is increasingly important
- Parasites
  - Increase in strongyloides, chagas, and amoeba – reflects a more international pool of donors
- Viral transmissions
  - Increased recognition of PB 19, LCMV
  - HIV, HCV testing needs to be optimized (NAT)

Ison et al. AJT 2011

Critical Balance with DDI

Ensure patient safety

Critical Balance with DDI

Ensure patient safety

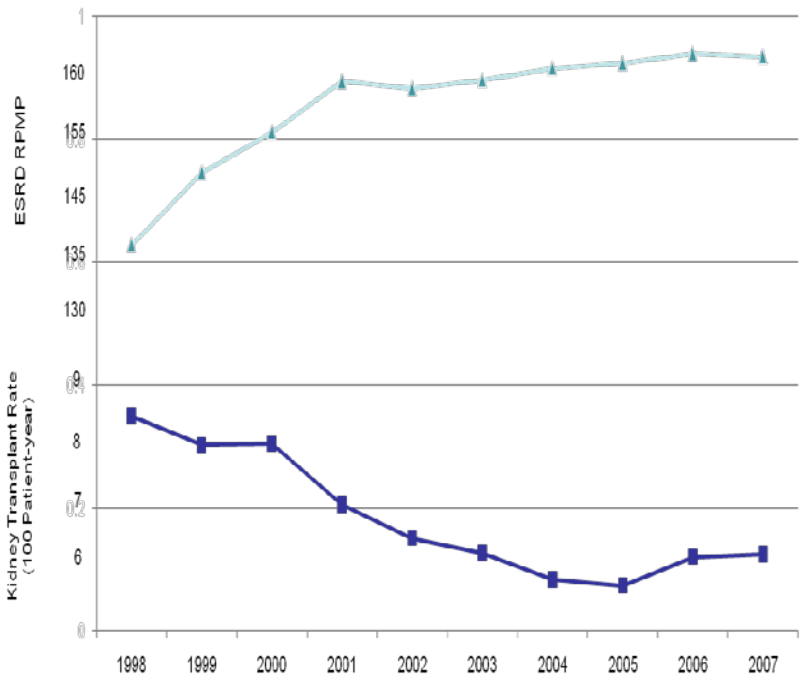
YET

Balance patient safety with the need to expand the pool of deceased organ donors

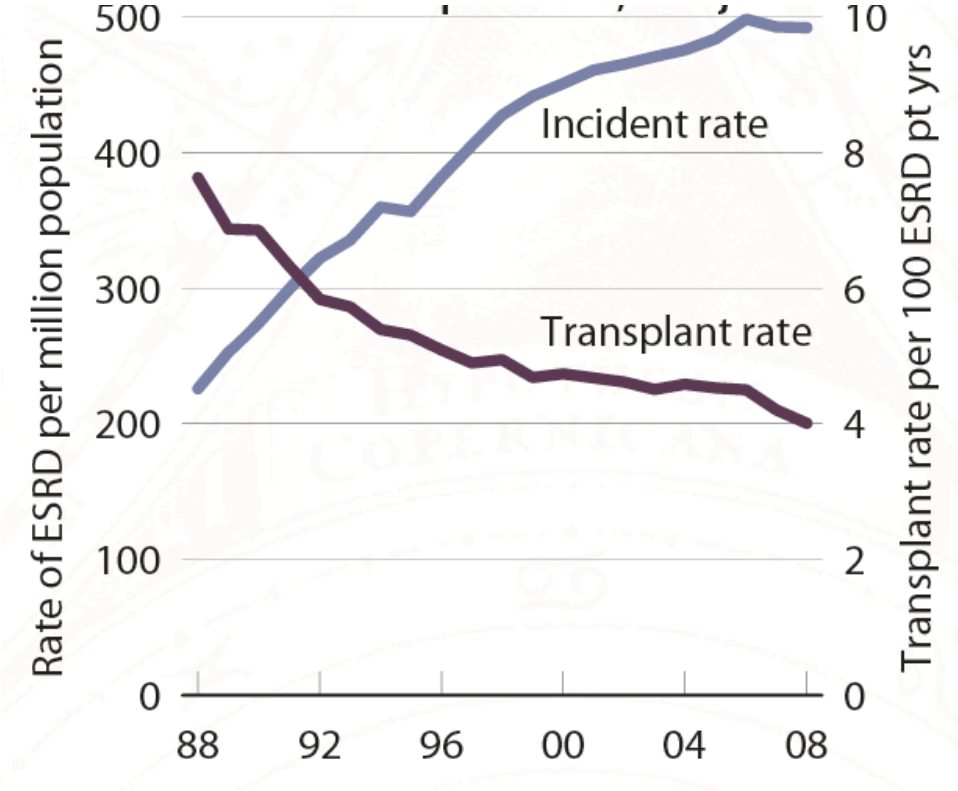
Demand for transplantation

Incident ESRD RPMP and Kidney Transplant Rate/100 Patient-years

CANADA



UNITED STATES



Transplantation is more complex→ greater risk of DDI

- Donor characteristics
  - Broader geographic backgrounds
  - Antibiotic exposures (MDR)
  - Prolonged hospitalizations and shifts in nosocomial flora over time
- Recipient Characteristics
  - Higher degree of immunosuppression
  - Increased use of medical devices (LVADs)
  - More complex patient population (more prone to multiorgan failure)
- Transplant programs
  - Increased number of programs
  - Geographic variability

Transplantation is more complex→ greater risk of DDI

- Donor characteristics

PRE DONATION SCREENING

socomial flora over

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socomial flora over

- Recipient Characteristics

POST DONATION MONITORING

rone to multiorgan

- Transplant programs
  - Increased number of programs
  - Geographic variability

Transplantation is more complex→ greater risk of DDI

- Donor characteristics

PRE DONATION SCREENING

socomial flora over

- Recipient Characteristics

POST DONATION MONITORING

rone to multiorgan

- Transplant programs

COMMUNICATION

Standard Donor Testing

- Screening by history
- Screening by laboratory results
  - HIV antibody
  - Hepatitis B Surface Ag, Hepatitis B Core Ab
  - HCV antibody
  - Syphilis serology
  - CMV antibody
  - EBV antibody
  - HTLV-1 (not in US as of 2010)
  - Toxoplasma antibody (select donors)
  - Cultures

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ADDITIONAL TESTING AVAILABLE

- **Serologic testing of less common pathogens Fungal, chagas/T.cruzi, Strongyloides**
- **Nucleic Acid Test (NAT) for HIV, HCV, HBV, WNV**

Challenges with donor screening

- History unreliable – i.e. next of kin may not be aware of high risk behaviours
- Serologies may be confounded (blood products, recent exposures)
- Cost and logistical limitations to advanced (NAT) testing (turn around time, after hours testing)

Challenges with diagnosing DDI in recipients

- Appropriate diagnosis requires recognition of potential for DDI – ie appropriate donor screening
- Atypical presentations of infections in donors and in recipients
- Emerging infections harder to detect
- Requires diligent reporting

Case scenarios

Which donors should we accept kidneys from?

Case 1

- 44 yo man
- NDD – subarachnoid hemorrhage
- SCR 87 umol/L
- Social history – released from prison 8 months ago
- No known drug use or high risk sexual behaviors in the last year according to friend

Case 2

- 24 yo man
- NDD – anoxic brain injury (overdose)
- SCR 62umol/L
- Social history – IV drug use in the last 2 weeks (in hospital for 8 days)

Who is a “high risk” donor?

CSA criteria for increased-risk donors

- Nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years
- Men who have had sex with another man in the preceding 5 years
- Persons who have engaged in sex in exchange for money or drugs in the preceding five years
- Persons who have had sex in the preceding 12 months with any of the above persons or a person known or suspected to have HIV, HCV or HBV infection.
- Exposure in preceding 12 months through percutaneous inoculation or open wound
- Prison, lock up, jail or juvenile detention >72 hours in the past 12 months
- Non-sterile tattooing, piercings in the past 12 months
- Close contact with anyone with clinically active viral hepatitis (living in the same house where kitchen and bathroom are shared) in the past 12 months

What are the actual risks?

Behaviour	Prevalence %	Incident Rate (per 100 p-years)
IV Drug User		
HIV	18	2
HCV	38	2.1
Men Sex with Men		
HIV	25	3
HCV	4	0.2
Commercial Sex Worker		
HIV	24	10
HCV	12	10
Inmates		
HIV	2	0.2
HCV	23	1

American Journal of Transplantation 2007; 7: 1515–1525

How reliable are serologic tests?

- Serologic tests will rule out most infected donors
- So the concern is about false negatives
  - The window period for detection is key

Virus	Serology
HIV	17-22 days
HCV	~70 days
HBV	35-44 days

Humar, et al. NAT consensus conference. AM J Trans 2010

How reliable are serologic tests?

- Serologic tests will rule out most infected donors
- So the concern is about false negatives
  - The window period for detection is key

Virus	Serology	NAT
HIV	17-22 days	5-6 days
HCV	~70 days	3-5 days
HBV	35-44 days	20-22 days

Humar, et al. NAT consensus conference. AM J Trans 2010

NAT testing in high risk

- Improves detection of HIV, HCV in high risk individuals
- Should be utilized in donors with high risk characteristics (IVDU, CSW)

Advantages of NAT

- Reduction in inadvertent transmission
- Increased organ utilization from increased risk donors
  - US-wide survey found chance of using a high risk donor is higher if OPO used NAT testing
- Improved public perception of transplantation safety

Kucirka et al AJT 2009

Disadvantages of NAT

- Loss of donors due to false positive NAT
  - In average risk donor, there will **76** false positive donors identified for one true positive for HIV and **45** for one with HCV
- Detection level varies with assay – no uniform standardization
- Logistical issues (after hours testing, single sample testing) may prolong CIT
- Cost

NAT Consensus Conference

- There is insufficient evidence to recommend routine NAT for HIV HCV and HBV as standard of care for ALL deceased donors
- For increased risk donors, NAT should be considered to reduce the risk of disease transmission and potentially increase utilization.
- HCV yield is highest, but HBV and HIV will also reduce risk

Humar, et al. NAT consensus conference. AM J Trans 2010

BCT Guidelines

- NAT testing in donors
  - Deceased donors
    - NAT for HIV and HCV in all high risk donors regardless of time relative to transplant
  - Living donor
    - NAT for HIV and HCV for all living donors within 2 weeks of donation

HBV

- Prevention of HBV infection is based on effective vaccination
- Hep B sAg → high risk of transmission → inferior graft outcomes
- Hep B cAB pos with sAB pos→ low risk of transmission
  - Ensure serologic evidence of adequate immunity in recipient prior to transplantation
  - Prophylaxis versus preemptive screening (monitoring for viremia)

What is the risk of transmission to the recipient, even when the NAT testing is negative?

Risk per 10,000 donors of an HIV infection occurring during the window period, by ELISA and NAT

Risk Category	Risk of window period infection expressed as ratio
Men who have sex with men	1: 4167
Intravenous drug use	1:3704
Commercial sex worker	1:6667
Sex with a partner in above categories	1:33,333
HIV Exposed through blood	1:16,667
Incarcerated	1: 25,000

CST/CNTRP Consensus guideline; Transplantation 2014

Courtesy: Dr. A. Humar

Risk per 10,000 donors of an **HCV** infection occurring during the window period, by ELISA and NAT

Risk Category	Risk of window period infection expressed as ratio
Men who have sex with men	1: 6667
Intravenous drug use	1:245
Commercial sex worker	1:344
Sex with a partner in above categories	1:556
Exposed through blood	1:7143
Incarcerated	1: 870

Courtesy: Dr. A. Humar

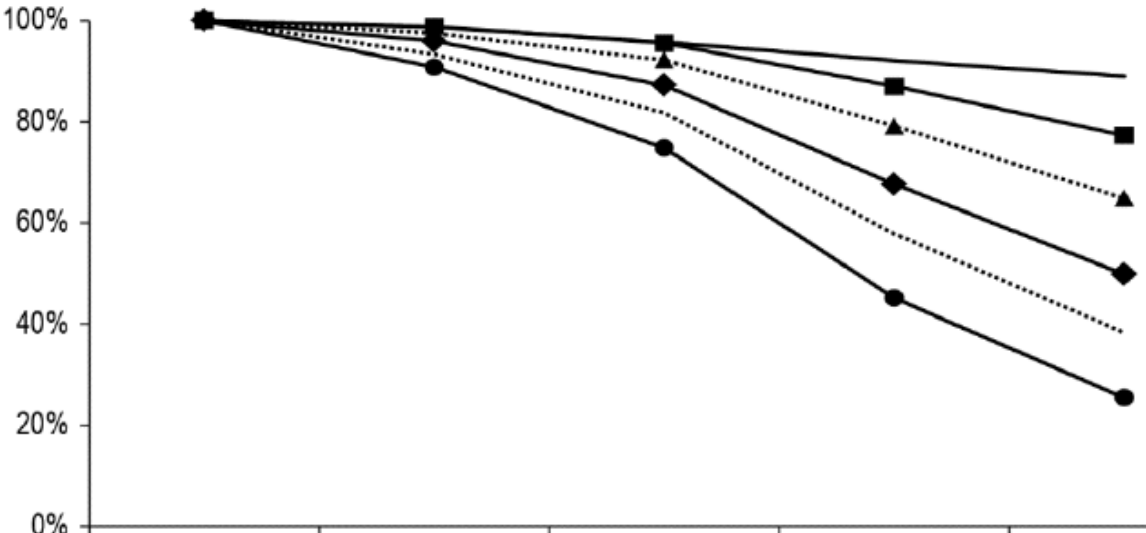
HOWEVER HCV NOW VERY TREATABLE

Risk Category	Risk of window period infection expressed as ratio	Chance of cure with DAA	Chance of chronic HCV infection
Men who have sex with men	1: 6667	95	1: 133,340
Intravenous drug use	1:245	95	1: 4,900
Commercial sex worker	1:344	95	1: 6,800
Sex with a partner in above categories	1:556	95	1: 11,120
Exposed through blood	1:7143	95	1: 142,860
Incarcerated	1: 870	95	1: 17,400

Courtesy: Dr. A. Humar

Patient Survival on dialysis

Figure 3: Unadjusted Three-Month and One-, Three- and Five-Year Survival Rates in Dialysis Patients, by Age Group, Canada, 2002 to 2011 (Percentage)



	0	3 Months	1 Year	3 Years	5 Years
Age 0–17	100	98.7	95.7	92.1	89.0
Age 18–44	100	98.8	95.5	87.0	77.3
Age 45–54	100	97.5	92.2	79.1	64.8
Age 55–64	100	95.9	87.2	67.6	49.8
Age 65–74	100	93.3	81.7	57.8	38.3
Age 75+	100	90.8	74.8	45.1	25.4

Source

Canadian Organ Replacement Register, 2012, Canadian Institute for Health Information.

Who do we offer these organs to and how?

- Key considerations:
  - Need to communicate risk to recipient
  - Need to ensure informed consent and document this
  - Need adequate follow-up plan for surveillance

Post-transplant followup

Post-transplant Test	Timing of Test
HIV, HCV NAT	At 1 and 3 months post-transplant
HBV NAT or HBsAg	
Anti-HBs, anti-HBc, and either HBV NAT or HBsAg	At 12 months post-transplant

Courtesy: Dr. A. Humar

Can we utilize HCV positive organs?

HCV to HCV

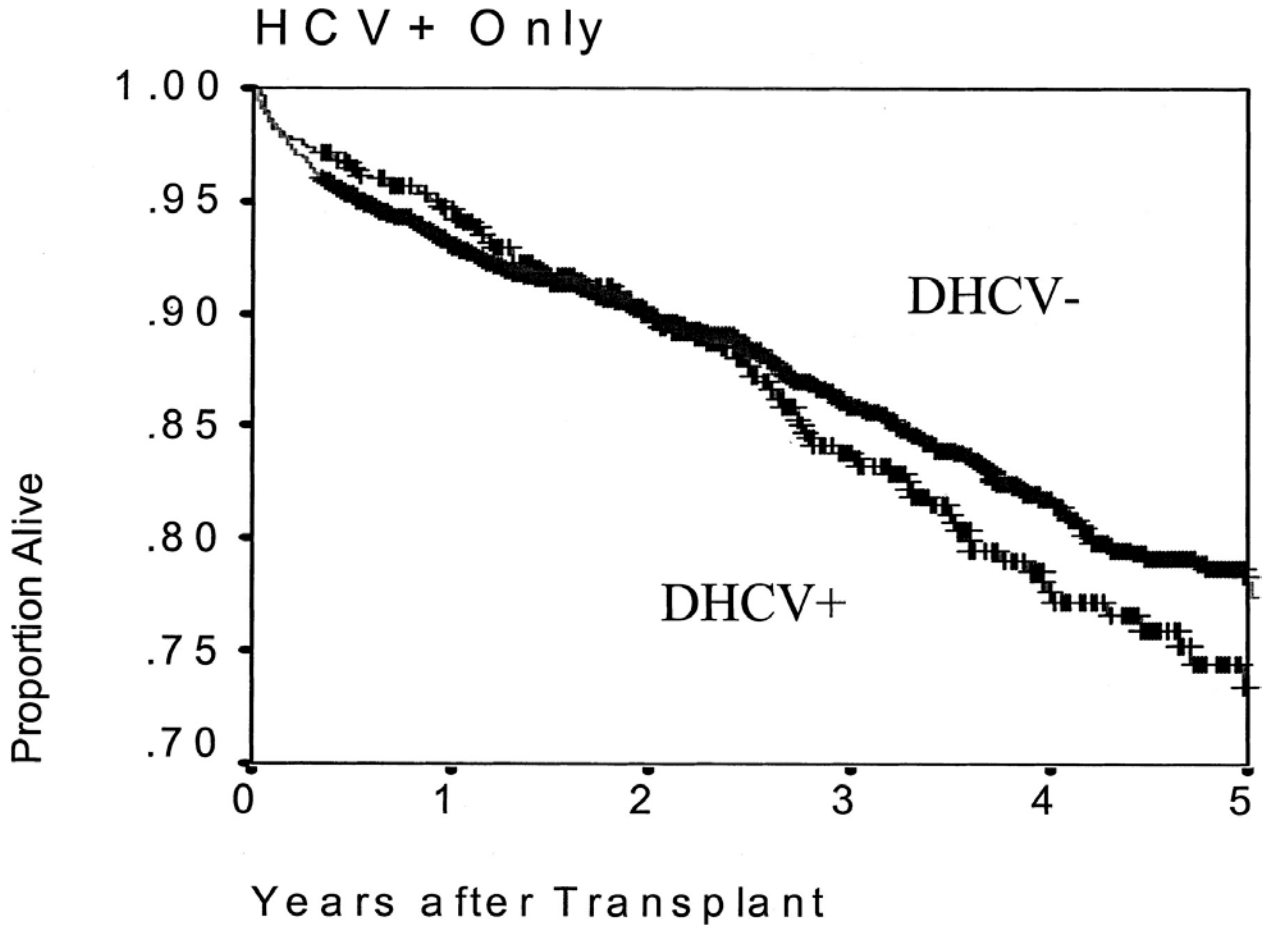


Figure 1. Kaplan-Meier plot of patient survival after renal transplantation, hepatitis C–positive (HCV+) recipients only (n = 2525), stratified by receipt of a kidney positive for hepatitis C (DHCV+) or negative for hepatitis C (HCV−).

Abbott K C et al. JASN 2003;14:2908-2918

Can we allocate HCV serology positive NAT negative donors to anyone?

If you are HCV Ab+ / NAT negative is there residual virus?

sponse (SVR). ***Methods:*** In this long-term follow-up study, including chronic hepatitis C patients who achieved SVR after interferon-based therapy, the presence of residual HCV RNA in serum, liver, and peripheral blood mononuclear cells (PBMCs) was assessed, using transcription-mediated amplification (sensitivity, <9.6 IU/mL). The benefit of SVR on liver

- This result strongly suggests that SVR may be considered to show eradication of HCV infection.

Maylin et al. Gastroenterology 2008

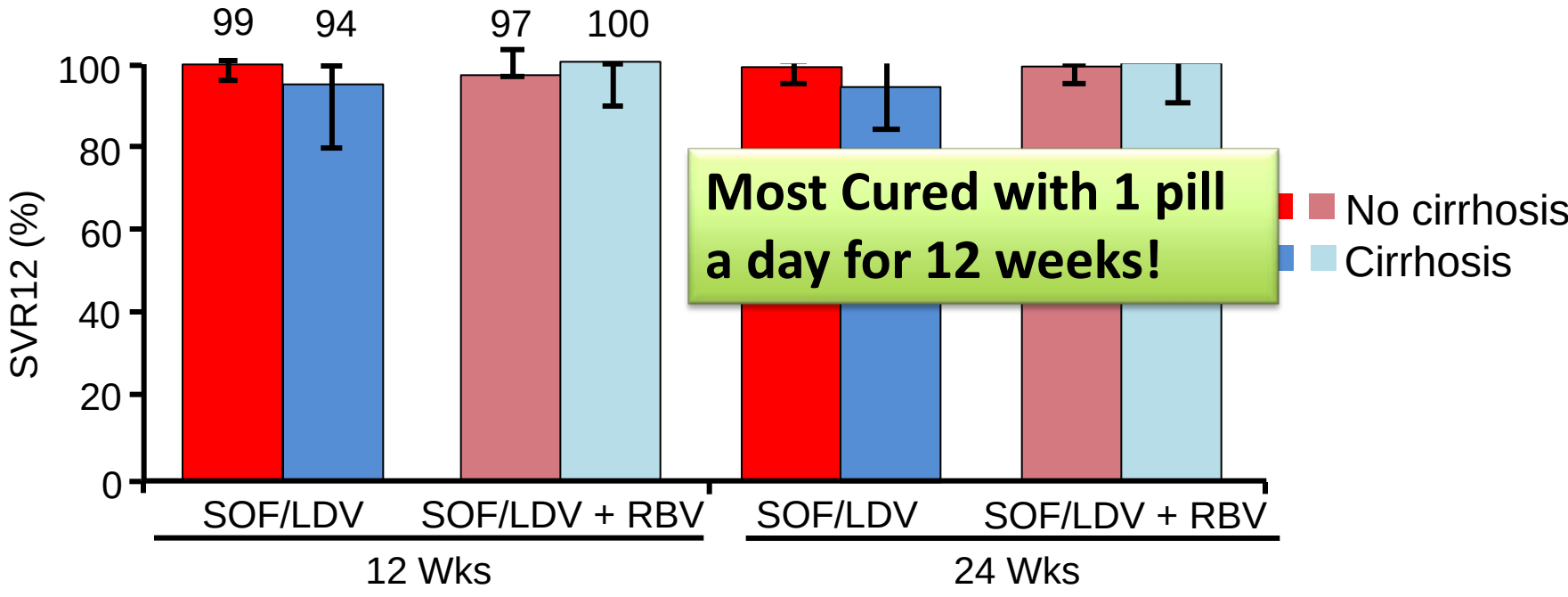
Courtesy: Dr. A. Humar

Can we allocate HCV serology positive NAT POSITIVE donors to anyone?

ARE IMPLICATIONS OF TRANSMISSION CHANGING?

Sofosbuvir/Ledipasvir ± RBV for 12 weeks

Nuc Pol Inhibitor *NS5A Inhibitor*



ION 1 Study

Courtesy: Dr. A. Humar

Afdhal N, et al. N Engl J Med. 2014;370:1889-1898.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients

David S. Goldberg, M.D.
Peter L. Abt, M.D.
Emily A. Blumberg, M.D.
Vivianna M. Van Deerlin, M.D., Ph.D.
Matthew Levine, M.D., Ph.D.
K. Rajender Reddy, M.D.
Roy D. Bloom, M.D.
Susanna M. Nazarian, M.D., Ph.D.
Deirdre Sawinski, M.D.
Paige Porrett, M.D., Ph.D.
Ali Naji, M.D., Ph.D.
University of Pennsylvania, Philadelphia, PA

Richard Hasz, M.F.S.
Lawrence Suplee, M.S.
Gift of Life Donor Program, Philadelphia, PA

Jennifer Trofe-Clark, Pharm.D.
Anna Sicilia, B.S.
Maureen McCauley, B.A.
University of Pennsylvania, Philadelphia, PA

Midhat Farooqi, M.D., Ph.D.
Children's Mercy Hospital, Kansas City, MO

Caren Gentile, M.S.
Jennifer Smith, B.S.
Peter P. Reese, M.D.
University of Pennsylvania, Philadelphia, PA

HCV NAT + kidneys

N=10 HCV negative recipients

Treat with
Grazoprevir/Elbasvir (Zepatier)
+/- Ribavirin
+/- Sofosbuvir
Depending on genotype

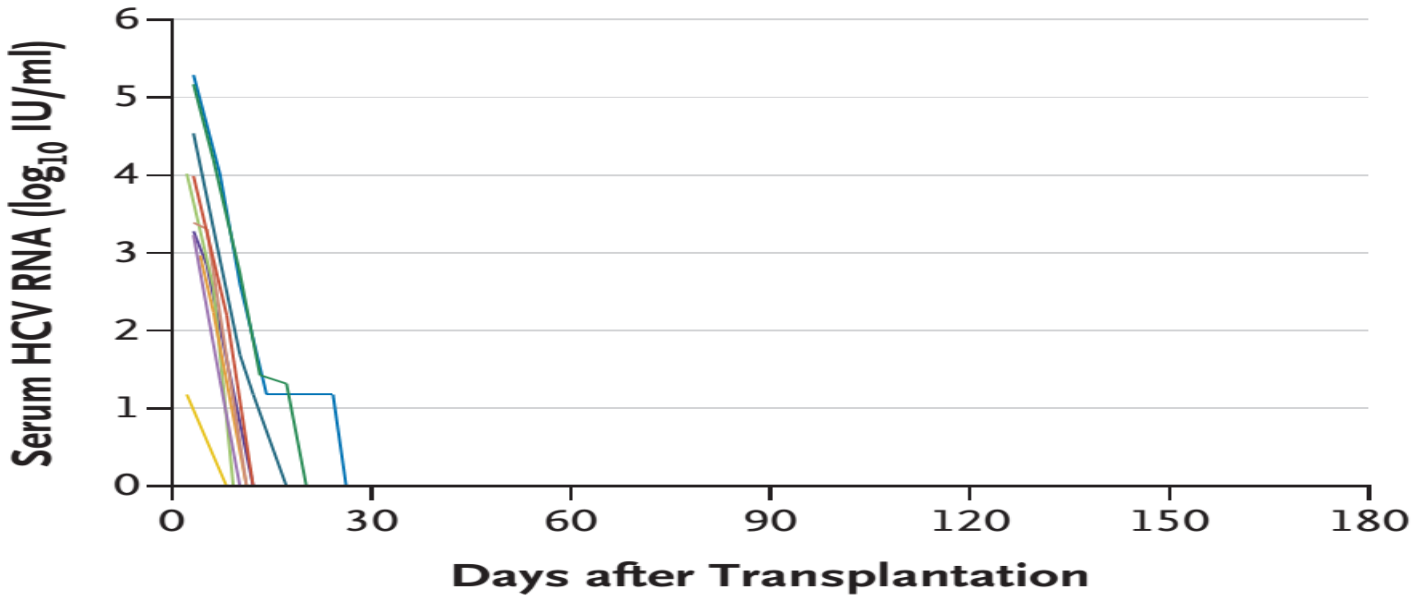


Figure 1. Hepatitis C Viral Load in 10 Kidney-Transplant Recipients.

The hepatitis C viral load was measured by means of polymerase chain reaction. Each curve represents a transplant recipient.

Twelve-Month Outcomes After Transplant of Hepatitis C–Infected Kidneys Into Uninfected Recipients: A Single-Group Trial

Table 2. Comparison of eGFRs and Creatinine Levels at 6 and 12 Months Between THINKER Participants and Matched Comparator Recipients of Kidneys From HCV-Negative Donors

Variable	Median Value (IQR)			Difference Between Matched Sets of THINKER Recipients and Allocation Comparators (95% CI)‡	*P* Value for Comparison With Allocation Comparators‡	Difference Between Matched Sets of THINKER Recipients and Optimal Comparators (95% CI)‡	*P* Value for Comparison With Optimal Comparators‡
	THINKER Recipients (*n* = 10 or 20)*	Matched Allocation KDPI Comparators (*n* = 50 or 100)*	Matched Optimal KDPI Comparators (*n* = 50 or 100)*†				
6-mo outcomes							
Creatinine level					<0.001		0.37
μmol/L	103 (90 to 118)	117 (95 to 150)	106 (88 to 124)	−20 (−29 to −11)		−4 (−11 to 4)	
mg/dL	1.2 (1.0 to 1.3)	1.3 (1.1 to 1.7)	1.2 (1.0 to 1.4)	−0.2 (−0.3 to −0.1)		−0.04 (−0.1 to 0.1)	
eGFR, mL/min/1.73 m^2	67.5 (57.8 to 85.7)	56.6 (48.3 to 74.6)	66.2 (55.3 to 81.9)	10.5 (4.8 to 16.2)	<0.001	1.6 (−4.2 to 7.5)	0.56
12-mo outcomes							
Creatinine level					<0.001		0.33
μmol/L	98 (84 to 111)	106 (95 to 141)	97 (80 to 115)	−21 (−31 to −12)		−4 (−12 to 4)	
mg/dL	1.1 (1.0 to 1.3)	1.2 (1.1 to 1.6)	1.1 (0.9 to 1.3)	−0.2 (−0.4 to −0.1)		−0.04 (−0.1 to 0.1)	
eGFR, mL/min/1.73 m^2	72.8 (58.6 to 74.4)	57.7 (46.0 to 68.6)	67.2 (55.8 to 78.3)	13.6 (7.9 to 19.2)	<0.001	1.4 (−7.2 to 9.8)	0.76
Delayed graft function, *n* (%)	5 (25)	45 (45)	32 (32)	NA	0.076	NA	0.59

eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; IQR = interquartile range; KDPI = kidney donor profile index; NA = not applicable; THINKER = Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients.

* As expected, 20 THINKER recipients had creatinine and eGFR values at 6-mo follow-up and 10 THINKER recipients had creatinine and eGFR values at 1-y follow-up. Each THINKER recipient was matched to 5 comparators.

† This group comprised recipients of kidneys with KDPI scores that were recalculated as if donors were HCV-seronegative.

‡ For between-group comparisons of creatinine level and eGFR, the comparator value was subtracted from the THINKER value. The differences, CIs, and *P* values were calculated using m-statistics (see the Methods section in Supplement 1 [available at Annals.org]), which account for small numbers of THINKER recipients and the 1:5 matching. For between-group comparisons of delayed graft function, the *P* values were calculated using conditional logistic regression.

Table 1. Characteristics of Kidney Transplant Recipients in the THINKER Study (*n* = 20)

Variable	Value
Mean age at consent (SD), *y*	56.3 (6.7)
Female, *n (%)*	6 (30)
Black, *n (%)*	8 (40)
Cause of end-stage renal disease, *n (%)*	
Diabetes	9 (45)
Hypertension	3 (15)
Polycystic kidney disease	3 (15)
IgA nephropathy	2 (10)
Congenital obstructive nephropathy	1 (5)
Chronic interstitial nephritis	1 (5)
Secondary focal and segmental glomerulosclerosis	1 (5)
Blood type, *n (%)*	
A	6 (30)
B	1 (5)
O	13 (65)
Median calculated panel reactive antibody level (range)	0 (0–48)
History of diabetes, *n (%)*	10 (50)
Prior transplant, *n (%)*	0 (0)
Median time receiving dialysis at enrollment (IQR), *d*	352.5 (232–403)
Median weight (IQR), *kg*	86.2 (77.6–98.9)
Highest education level, *n (%)*	
High school diploma	6 (30)
Some college/trade school	4 (20)
College degree	6 (30)
Master's degree or higher	4 (20)

IQR = interquartile range; THINKER = Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients.

Options to allocate:

a) Any recipient (HCV NAT -ve)
b) Special list of recipients (HCV NAT-ve but eg. highly sensitized, very sick etc)

Original Clinical Science—General

Race, Risk, and Willingness of End-Stage Renal Disease Patients Without Hepatitis C Virus to Accept an HCV-Infected Kidney Transplant

Maureen McCauley, BS,[1] Adam Mussell, MA,[1] David Goldberg, MD, MSCE,[1,2] Deirdre Sawinski, MD,[3] Rodolfo N. Molina, MD,[4] Ricarda Tomlin, BA,[4] Sahil D. Doshi, BA,[5] Peter Abt, MD,[6] Roy Bloom, MD,[3] Emily Blumberg, MD,[7] Sanjay Kulkarni, MD,[4] Gabriela Esnaola,[8] Justine Shults, PhD,[1] Carrie Thiessen, MD, PhD,[4] and Peter P. Reese, MD, MSCE[1,3,9,10]

>80% of recipients would accept an HCV positive kidney under certain circumstances

Factors associated with increased willingness to accept an offer

Multivariable analysis of willingness to accept HCV-infected kidney (n = 181)

	Odds ratio	95% CI	*P*
HCV cure 95% (vs 75%)	3.49	2.33-5.24	<0.01
HCV cure 90% (vs 75%)	2.10	1.57-2.80	<0.01
20-year-old donor (vs 60 years)	2.34	1.91-2.88	<0.01
Wait 5 years for HCV-negative kidney (vs 2 years)	1.43	1.22-1.67	<0.01
Race x Cure rate interaction			
Black race (vs white)	0.96	0.55-1.67	0.87
Nonblack, nonwhite race (vs white)	0.63	0.25-1.55	0.31
Black race x HCV 90% cure rate	0.77	0.51-1.16	0.21
Black race x HCV 95% cure rate	0.56	0.34-0.93	0.03
Nonblack, nonwhite race x HCV 90% cure rate	0.82	0.47-1.41	0.47
Nonblack, nonwhite race x HCV 95% cure rate	0.55	0.27-1.13	0.11
Other participant covariates			
Male	1.84	1.10-3.10	0.02
Age 18 to 45 years (reference)			
46 to 60 years	1.06	0.59-1.90	0.86
≥60 years	2.38	1.17-4.85	0.02
Prior transplant	3.03	1.15-7.80	0.03
Re-evaluation patient (vs new evaluation)	0.64	0.38-1.08	0.10
University of Pennsylvania (vs Yale)	0.52	0.29-0.94	0.03
Lowest tertile of trust in physicians (reference)			
Intermediate trust in physicians	0.88	0.46-1.68	0.69
High trust in physicians	0.51	0.28-0.93	0.03

BCT Pilot Project

Summary

- Increased infectious risk donors are, in part, contributing to the increase in organ donors and associated improved access to transplantation
- Risk of transmission is low with negative NAT testing, but careful informed consent and close follow-up is required
- HCV positive donors may result in an additional pool of potential donors