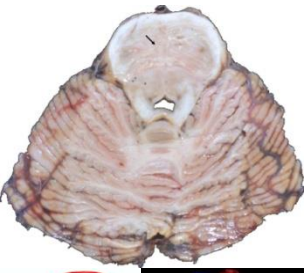
2017 CST-Astellas Canadian Transplant Fellows Symposium

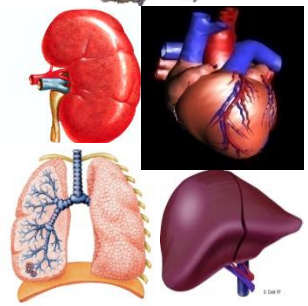
Optimizing use of organs from Increased Risk Donors

Atual Humar, MD

Atul Humar is a Professor in the Department of Medicine, University of Toronto. Dr. Humar received his medical degree from the University of Ottawa. He completed his residency and did further training in Transplant Infectious Diseases in Toronto and Boston. Dr. Humar's research interests are in virology with a focus on the pathogenesis of herpesvirus infections post-transplant. He is involved in both basic and clinical research assessing immunologic and virologic determinants of infection. Dr. Humar is the Director of Multi Organ Transplant Program at the University Health Network and the University of Toronto Transplant Institute. He is also active in the Canadian Society of Transplantation as a President and has been very active in both the AST and TTS. Dr. Humar operates a joint research lab with his wife, Dr. Deepali Kumar, who is also a faculty member at the University of Toronto.

Optimizing use of organs from Increased Risk Donors





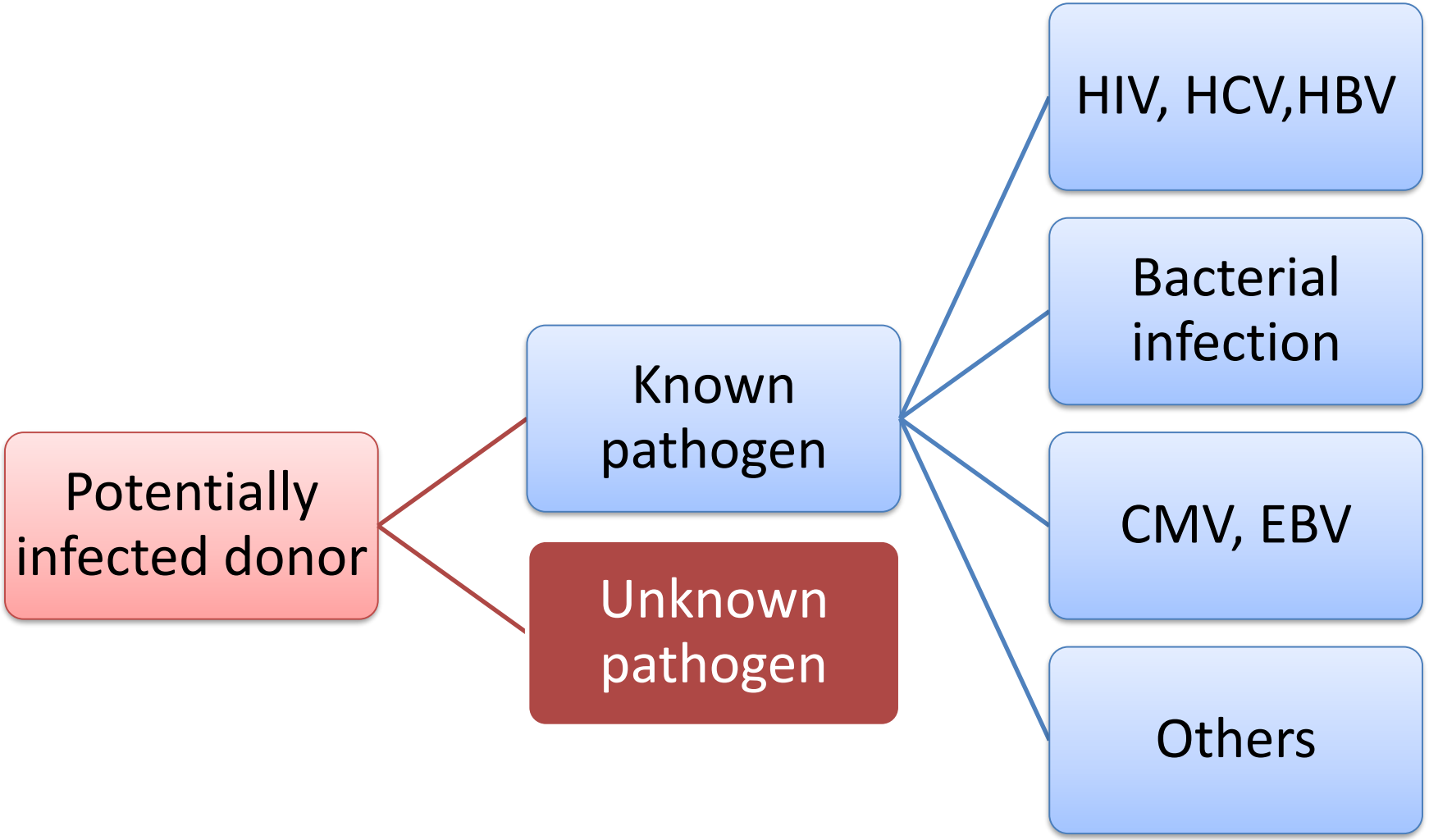
ATUL HUMAR M.D.

University Health Network

Toronto

Conflict of Interest Disclosure

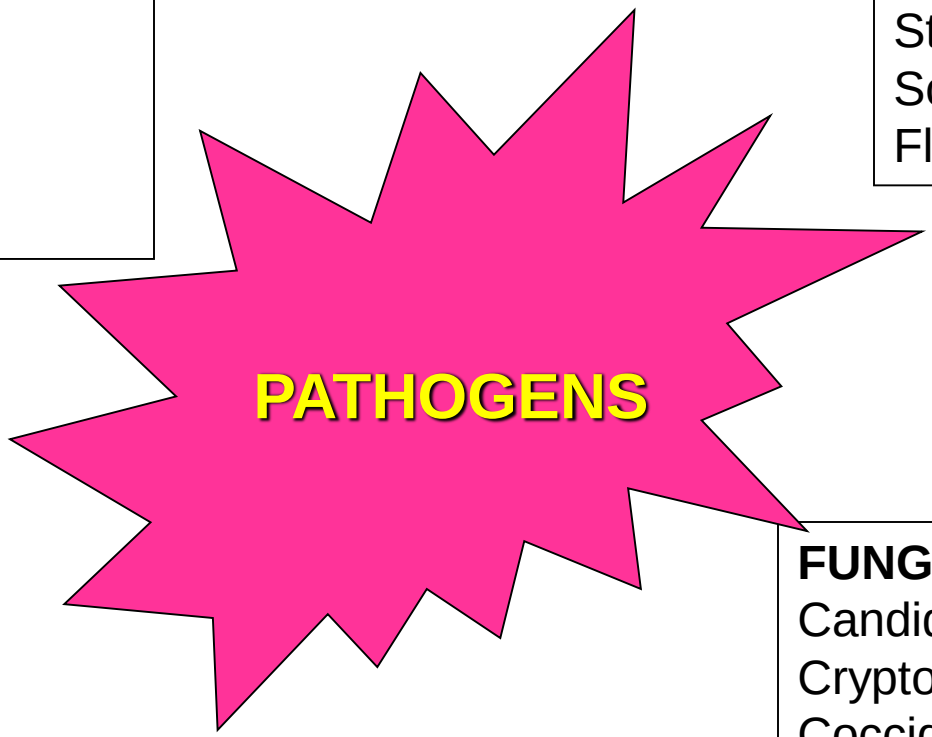
- No relevant COI for this talk


Potentially infected donor
Known pathogen
Unknown pathogen
HIV, HCV,HBV
Bacterial infection
CMV, EBV
Others

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

PRION
vCJD

FUNGAL
Candida
Cryptococcoccus
Coccidioides
Histoplasma
Aspergillus

Notable Organ Transplant-Transmitted Infections: 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, NY/PA 2005
- Chagas, 2006
- M. TB - 2008
- HIV/HCV 2007
- HCV 2009
- Balamuthia mandrillaris -2010
- HCV 2011
- HIV 2011

Standard Donor Testing 2017

- Step 1. Screening by history
- Step 2. Screening by laboratory results
  - HIV antibody [Ab/Ag assay]
  - Hepatitis B surface antigen, HepB core Ab
  - Hepatitis C antibody
  - syphilis serology
  - CMV antibody
  - EBV antibody
  - HTLV-I (and –II) (no HTLV testing in US)
  - Cultures

Additional Donor Testing

- NAT testing (geographic variation)
  - HIV, HCV, HBV
  - West Nile Virus
- Serologies
  - Fungal, Chagas/*T.cruzi*, *Strongyloides*
  - (selected situations)

Issues with Donor Testing 2017

- Serologies can be confounded
  - Blood products
  - Hemodilution
  - Recent exposure (window period)
- Turn around time – especially NAT
- Single tests done – especially NAT
- False positives – organ discard

CASE # 1: The High risk donor

- You are called about a 25 year old deceased donor
  - HCV Antibody negative
  - HIV Antibody negative
  - HBV testing negative [HbSAg]
- AST, ALT, ALP normal
- Donor found in a bathroom stall with a needle in arm
- In hospital x 1 day

CASE # 1

- NAT for HIV/HCV/HBV negative. Would you use the organs?

a) Yes for any consenting recipient
b) Yes “higher-status” or “special case” recipient only
c) Decline organs in most cases except certain exceptional circumstances

Summary of Canadian Standards Association increased-risk donor criteria

CSA criteria for increased-risk donors

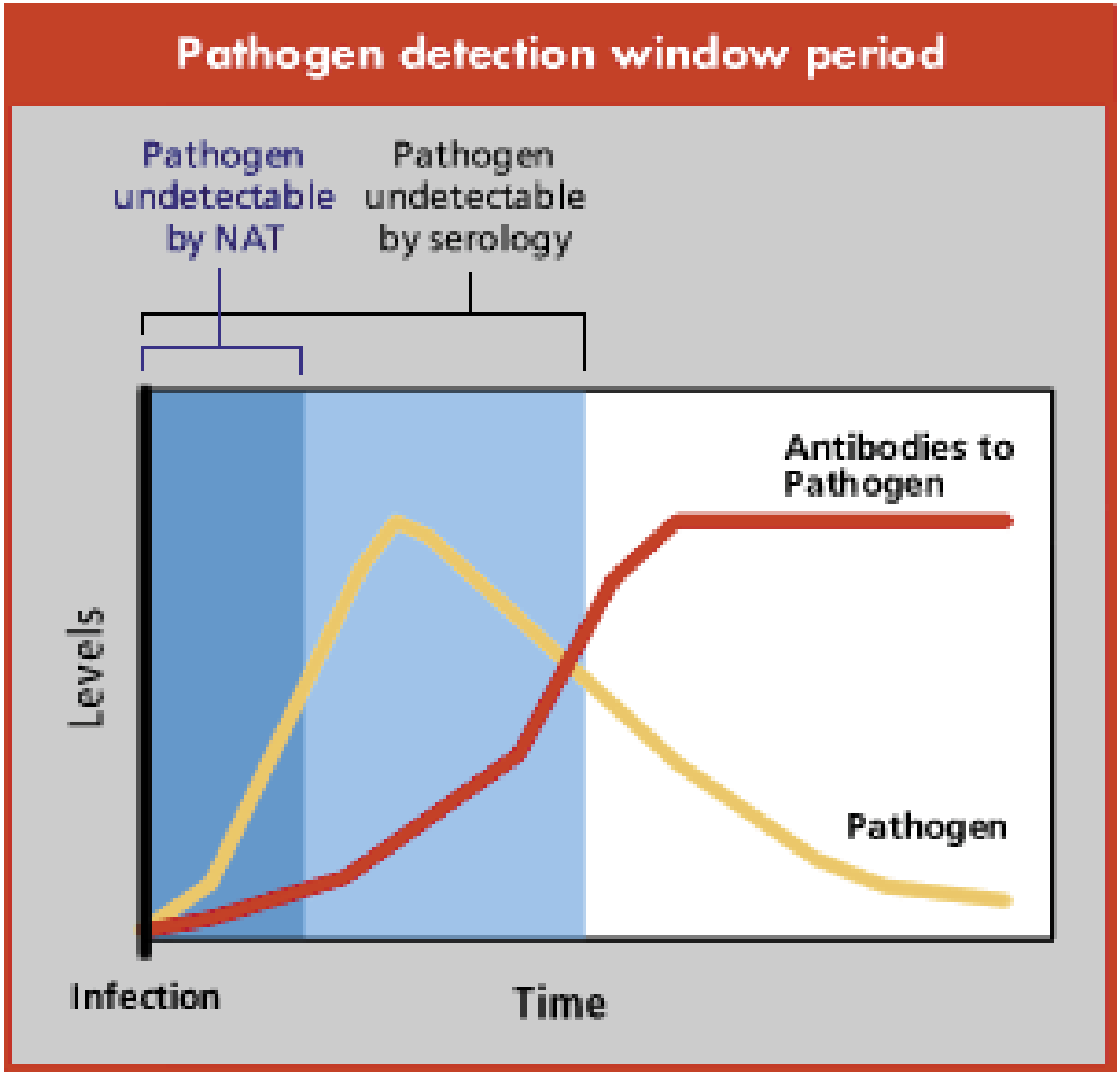
- Nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years
- Men who have had sex with another man in the preceding 5 years
- Persons who have engaged in sex in exchange for money or drugs in the preceding five years
- Persons who have had sex in the preceding 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

CHICAGO TRANSMISSION CASE

- 2007: Multiple organs transplanted from a single donor
- Donor HCV Ab and HIV Ab negative
- Classified as CDC-IRD (high risk donor)
- 4-recipients infected with HIV and HCV
- Retrospective testing of donor sera showed NAT + for HIV/HCV

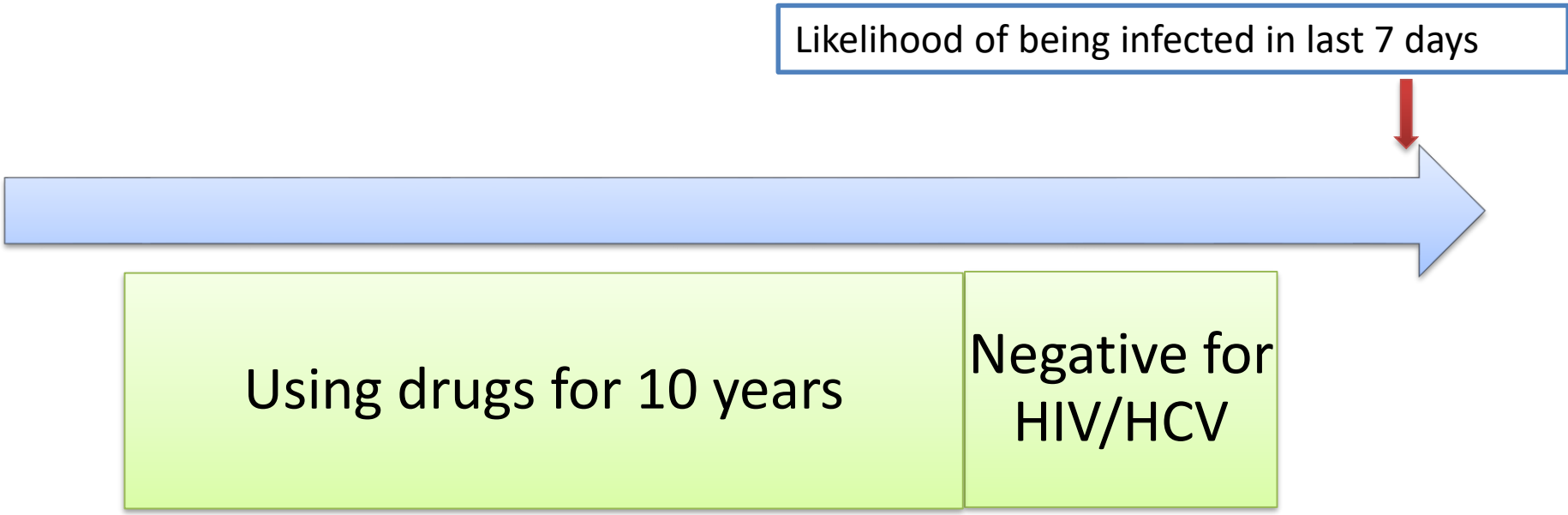
What is the “residual risk”?

- If the serology and NAT are negative – what is the risk of transmission?
- Answer – not very often but sometimes
  - Depends on risk behaviours in donor


Pathogen detection window period
Pathogen undetectable by NAT
Pathogen undetectable by serology
Antibodies to Pathogen
Pathogen
Levels
Infection
Time

What is the Window Period

Pathogen	serology	Nucleic Acid Testing
HIV	17-22 days	5-6 days
HCV	~ 70 days	3 –5 days (best test; many assume 7 days)
HBV	35-44 days	20-22 days


Likelihood of being infected in last 7 days
Using drugs for 10 years
Negative for HIV/HCV

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

Risk Category	ELISA Per 10,000	NAT Per 10,000	Risk of window period infection expressed as ratio
Men who have sex with men	5.8 (5.2-6.6)	2.4 (2.1-2.7)	1: 4167
Intravenous drug use	6.6 (6.1-7.2)	2.7 (2.5-3.0)	1:3704
Commercial sex worker	3.7 (3.0-4.8)	1.5 (1.2-2.0)	1:6667
Sex with a partner in above categories	0.7 (0.5-0.9)	0.3 (0.2-0.4)	1:33,333
HIV Exposed through blood	1.5 (0.8-2.4)	0.6 (0.4-1.0)	1:16,667
Incarcerated	1.0 (0.8-1.2)	0.4 (0.3-0.5)	1: 25,000

CST/CNTRP Consensus guideline; Transplantation 2014

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

Risk Category	ELISA Per 10,000	NAT Per 10,000	Risk of window period infection expressed as ratio
Men who have sex with men	14.3 (10.7-17.3)	1.5 (1.1-1.8)	1: 6667
Intravenous drug use	377.4 (346.0-412.1)	40.8 (37.4-44.6)	1:245
Commercial sex worker	270.8 (242.6-298.9)	29.1 (26.1-32.2)	1:344
Sex with a partner in above categories	168.3 (157.7-191.4)	18.0 (16.9-20.5)	1:556
Exposed through blood	13.9 (2.9-44.6)	1.4 (0.3-4.3)	1:7143
Incarcerated	107.8 (102.4-116.7)	11.5 (10.9-12.5)	1: 870

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

Estimated Canadian wait list numbers and mortality

	Number on the wait list	Death on the wait list
Heart	136	23%
Lung	245	19%
Liver	551	16%
Kidney	2732	3%
Kidney Pancreas	56	9%

Source: Canadian Organ Replacement Register, 2012, CIHI; Data extracted for year 2009

RISKY DONORS: CONSIDERATIONS

Individual

- Risk vs. benefit of transplantation
- Risk of waiting until next available offer
- Is patient on an alternate list [e.g. HCV +]

Societal

- Acceptance beneficial from a societal perspective (Schwietzer et al. AJT 2007) by adding organs into the pool

Programmatic

- An transmission incident may reflect poorly on a transplant program.

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, doctors are confronting complex medical and ethical questions.

Will Any Organ Do?

By Gretchen Reynolds

Last summer at one hospital in Dallas, four people died from rabies, an unheard-of level of incidence of this rare disease. As it turned out, each patient was infected by an organ or tissue — a kidney, a liver, an artery — that he or she received in a transplant several weeks earlier. Their shared

plant surgery was a dodgy, last-ditch response to end-stage kidney failure. But with the advent of better antirejection drugs and surgical techniques, transplantation has become the treatment of choice for a growing range of conditions, including chronic kidney failure, end-stage lung or liv-

The Chicago Maroon

NEWS

HIV–infected patient sues hospital after transplant

A University of Chicago Medical Center patient filed suit against the hospital and one of its surgeons Monday, charging medical negligence after receiving a kidney transplant in January 2007 that she later found infected her with HIV and Hepatitis C.

by Kelin Hall - Nov 21, 2008 10:03 am CST

A University of Chicago Medical Center patient filed suit against the hospital and one of its surgeons Monday, charging medical negligence after receiving a kidney transplant in January 2007 that she later found infected her with HIV and Hepatitis C.

The patient claims the hospital had known that the organ donor had participated in "homosexual sexual activity within the past five years" but had withheld this information from her, according to Thomas Demetrio, the plaintiff's attorney. The plaintiff filed suit anonymously.

Privacy laws prohibit the Medical Center from disclosing what it told its patients about the donor, and Medical Center officials declined to comment on the matter because of the pending lawsuit.

According to the Medical Center's website, the University has successfully completed 2,500 kidney transplants.

The kidney tested negative for both HIV and Hepatitis C when it was screened and transplanted, according to Demetrio, but current medical tests cannot always detect diseases immediately after infection. In some cases, tests can come up clean several weeks after infection has occurred.

According to the Chicago Tribune, the plaintiff didn't find out she had contracted the diseases until early this month. They report that she was brought to the hospital for testing after it was discovered that three other patients who received transplants from the same donor had contracted HIV.

Table 2: Donor characteristics, by PHS/CDC high-risk donor (HRD) status

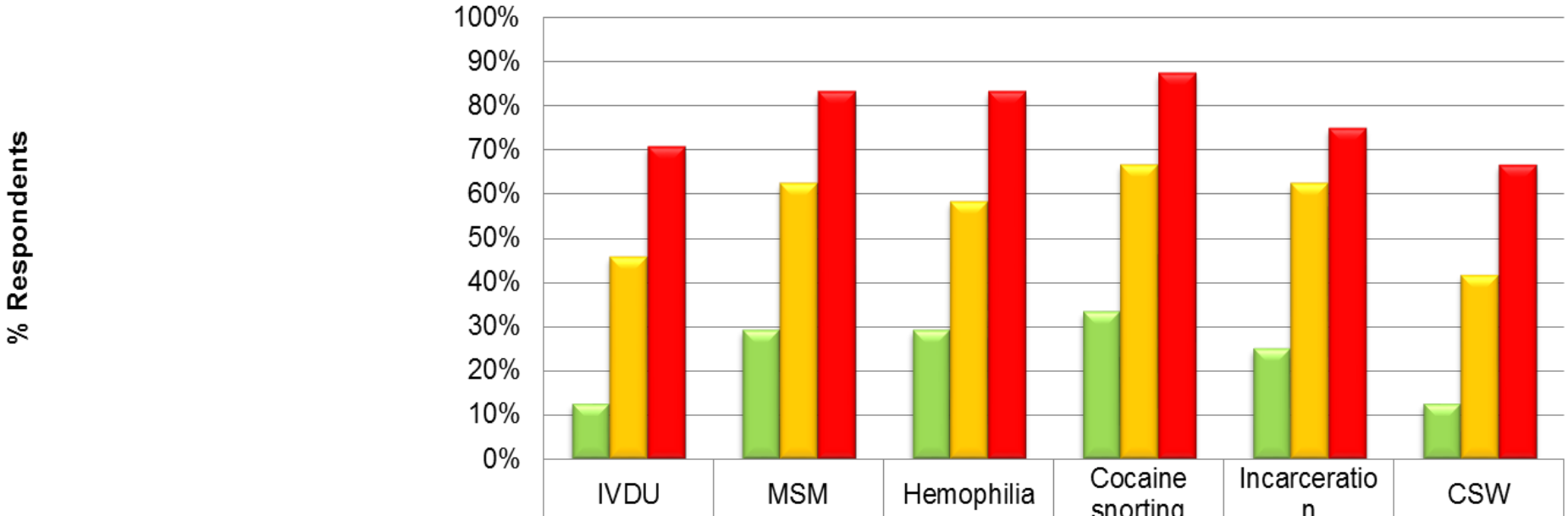
Characteristic	HRDs[1] (n = 2574)	Non-HRDs (n = 27 376)	p-Value[2]
Age (mean)	37.5	40.8	<0.001
Age category (%)			
<18	3.2	12.8	<0.001
18–30	34.0	20.2	
31–40	19.6	11.9	
41–50	25.1	19.8	
ECD (kidney definition, %)[3]	12.0	25.6	<0.001
[illegible]			
Comorbidities (%)			
History of cancer	2.7	3.8	0.006
History of MI	4.4	4.6	0.8
Hypertension	27.5	33.9	<0.001

Considerations

- Many donor are substance abuse but not IVDU – we count as HRD but lower risk
- In hospital time is important
  - In hospital x 7d with NAT means near normal risk
- History in donors often not reliable

Likelihood of accepting organ

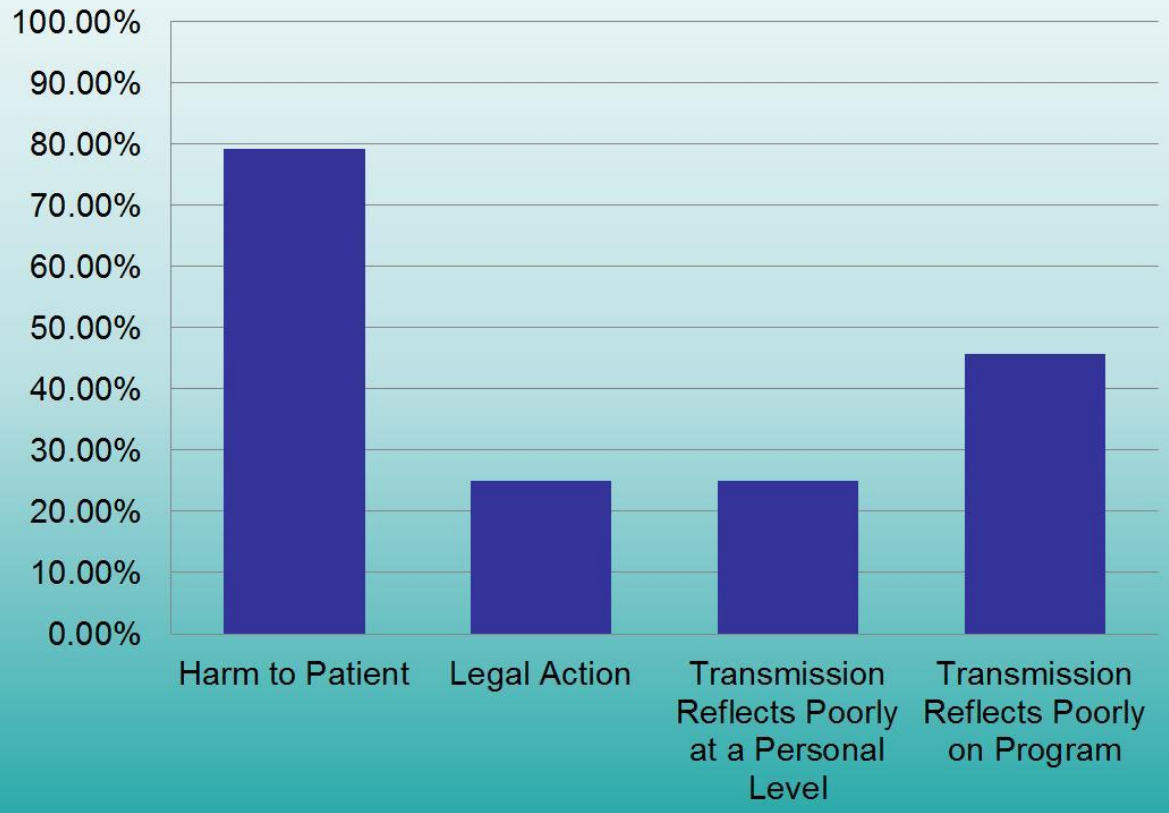
Figure 5: Acceptability of High Risk Donor depending on Donor Testing



	IVDU	MSM	Hemophilia	Cocaine snorting	Incarceration	CSW
IC+Negative Serology	12.50%	29.20%	29.20%	33.30%	25%	12.50%
IC+Neg Serology+Negative NAT	45.80%	62.50%	58.30%	66.70%	62.50%	41.70%
IC+Neg Serology+Neg NAT+No High Risk Behaviour in Window Period	70.80%	83.30%	83.30%	87.50%	75%	66.70%

Kumar et al. Transplantation 2015

REASONS FOR DECLINE



STANDARDIZED INFORMED CONSENT

Read from a script

Describe the risk to the patient

Provide the alternatives

Document the informed consent process

FOLLOW-UP TESTING IS ESSENTIAL

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

CST/CNTRP Consensus guideline; Transplantation 2014

What about the HCV positive donor?

HCV Ab + /NAT +

HCV Ab+ /NAT-ve

Recipient may also be any one of these

How many donors?

Estimated Risk of Human Immunodeficiency Virus and Hepatitis C Virus Infection among Potential Organ Donors from 17 Organ Procurement Organizations in the United States

Pathogen	Risk status[1]	N	Prevalence (%) for organ donors in study[2]	Prevalence (%) blood donors [3]
HIV	Normal risk	11245	0.10 (0.06–0.16)	0.011 (0.008–0.013)
	High risk	1180	0.50 (0.21–0.86)	0.011 (0.008–0.013)
	Missing risk status	1182	1.00 (0.57–1.54)	0.011 (0.008–0.013)
	All potential donors	13607	0.21 (0.15–0.29)	0.011 (0.008–0.013)
HCV	Normal risk	10997	3.45 (3.10–3.85)	0.17 (0.16–0.18)
	High risk	1169	18.20 (15.74–20.91)	0.17 (0.16–0.18)
	Missing risk status	1183	12.88 (10.83–15.08)	0.17 (0.16–0.18)
	All potential donors	13349	5.58 (5.15–6.06)	0.17 (0.16–0.18)

The overall adjusted prevalence for anti-HCV was 5.58% (CI = 5.15–6.06%). The adjusted anti-HCV prevalence was lowest for normal risk donors at 3.45% (CI = 3.10–3.85), and highest for high risk donors at 18.20% (CI = 15.74–20.91%).

Ellingsona K et al. AJT 2011; 11: 1201–1208

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

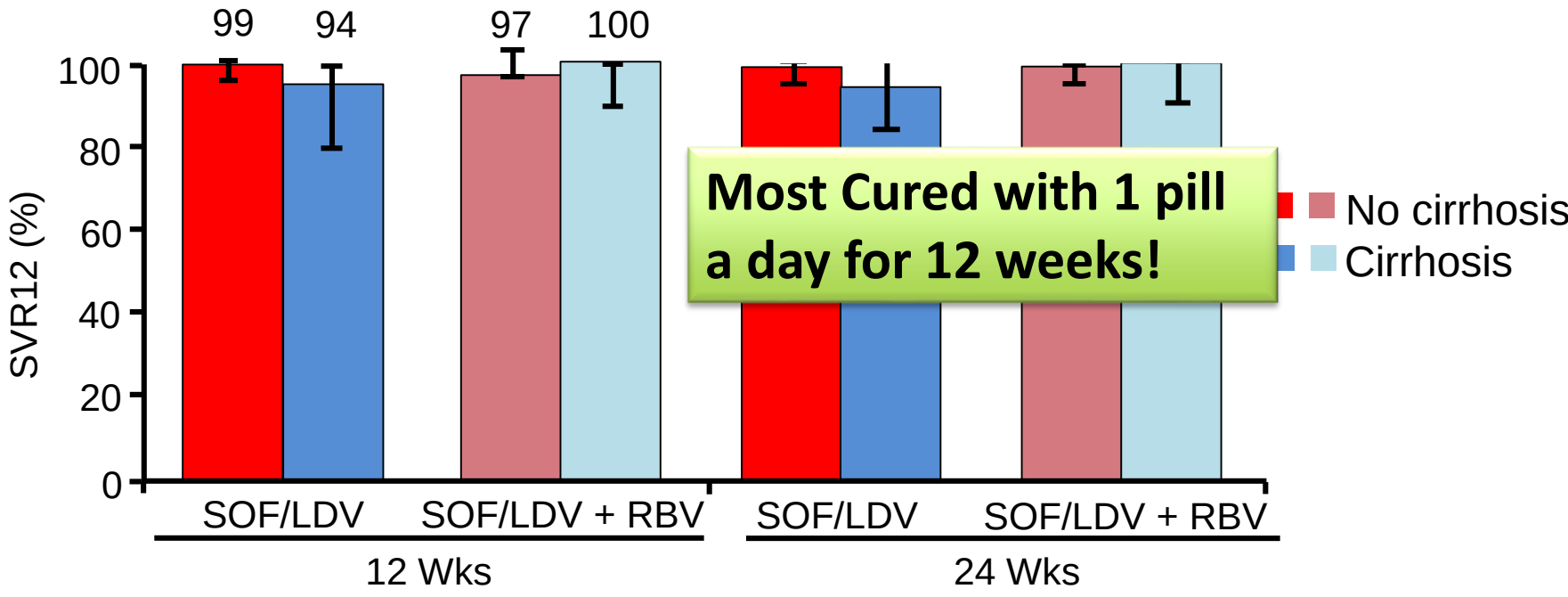
WHAT ABOUT THE HCV NAT POSITIVE DONOR?

ASSUME 100% RISK OF TRANSMISSION

ARE IMPLICATIONS OF TRANSMISSION CHANGING?

Sofosbuvir/Ledipasvir ± RBV for 12 weeks

Nuc Pol Inhibitor *NS5A Inhibitor*



ION 1 Study

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

Case 3

- Donor is 35 y.o. female
- NDD; ICH 2% to endocarditis from IVDU; in hospital x 2 weeks
- Adequate antibiotic treatment for strep viridans endocarditis
- LFTs, Cr, imaging normal
- HCV NAT+, HCV Ab+
- HIV NAT -ve

Would you:

a) Decline all together
b) Accept only for HCV NAT+ recipient
c) Accept for any recipient (HCV NAT -ve)
d) Accept for “special list” recipient (HCV NAT-ve but eg. highly sensitized, very sick etc)

HCV D+/R-

American Journal of Transplantation
AST AMERICAN SOCIETY OF TRANSPLANTATION ASTS
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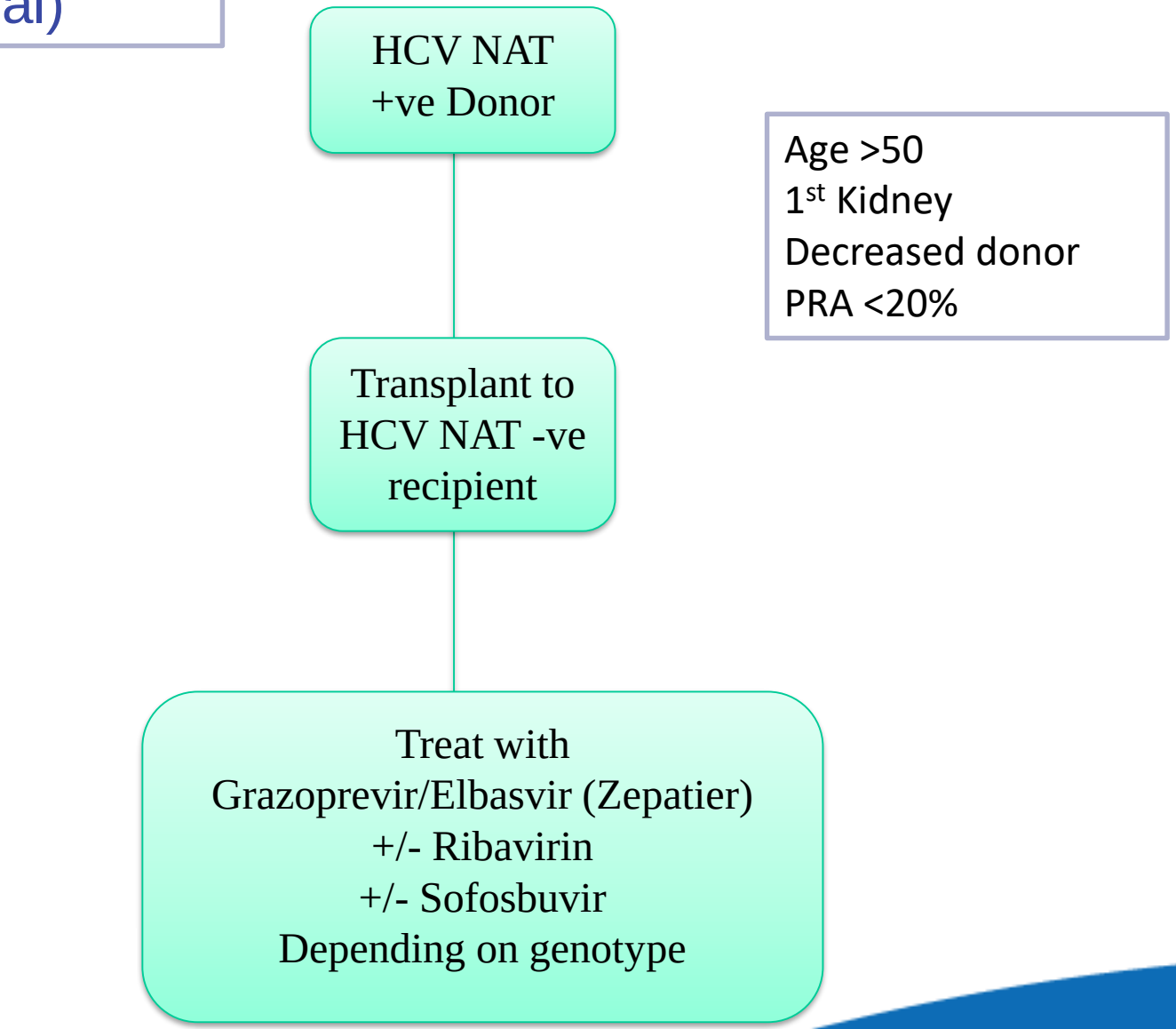
Case Report

Successful Lung Transplantation from Hepatitis C Positive Donor to Seronegative Recipient

Basha Khan, Lianne G. Singer, Cecilia Chaparro, Tereza Martinu, Stephen Juvet, Mauricio Pipkin, Thomas K. Waddell, Shaf Keshavjee, Atul Humar, Marcelo Cypel

Accepted manuscript online: 22 November 2016 Full publication history

HCV KIDNEY TRIAL (Goldberg et al)



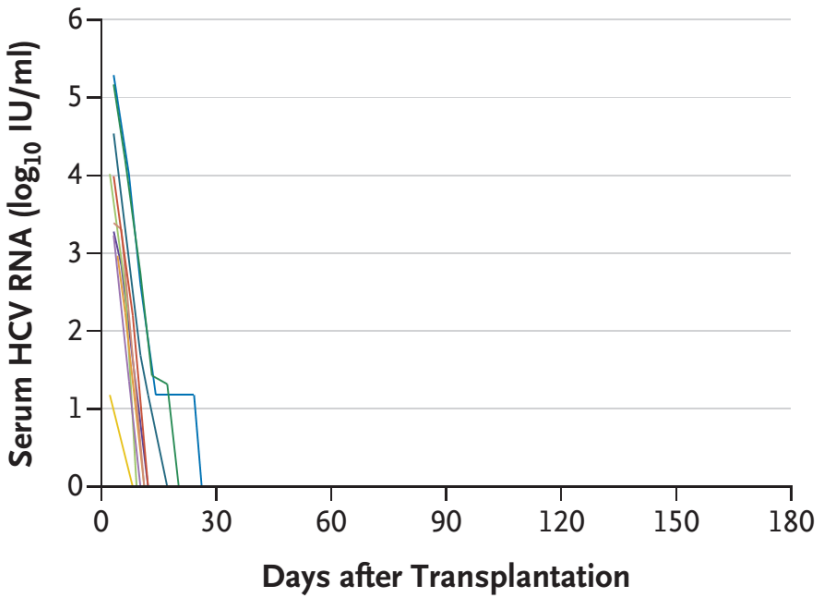


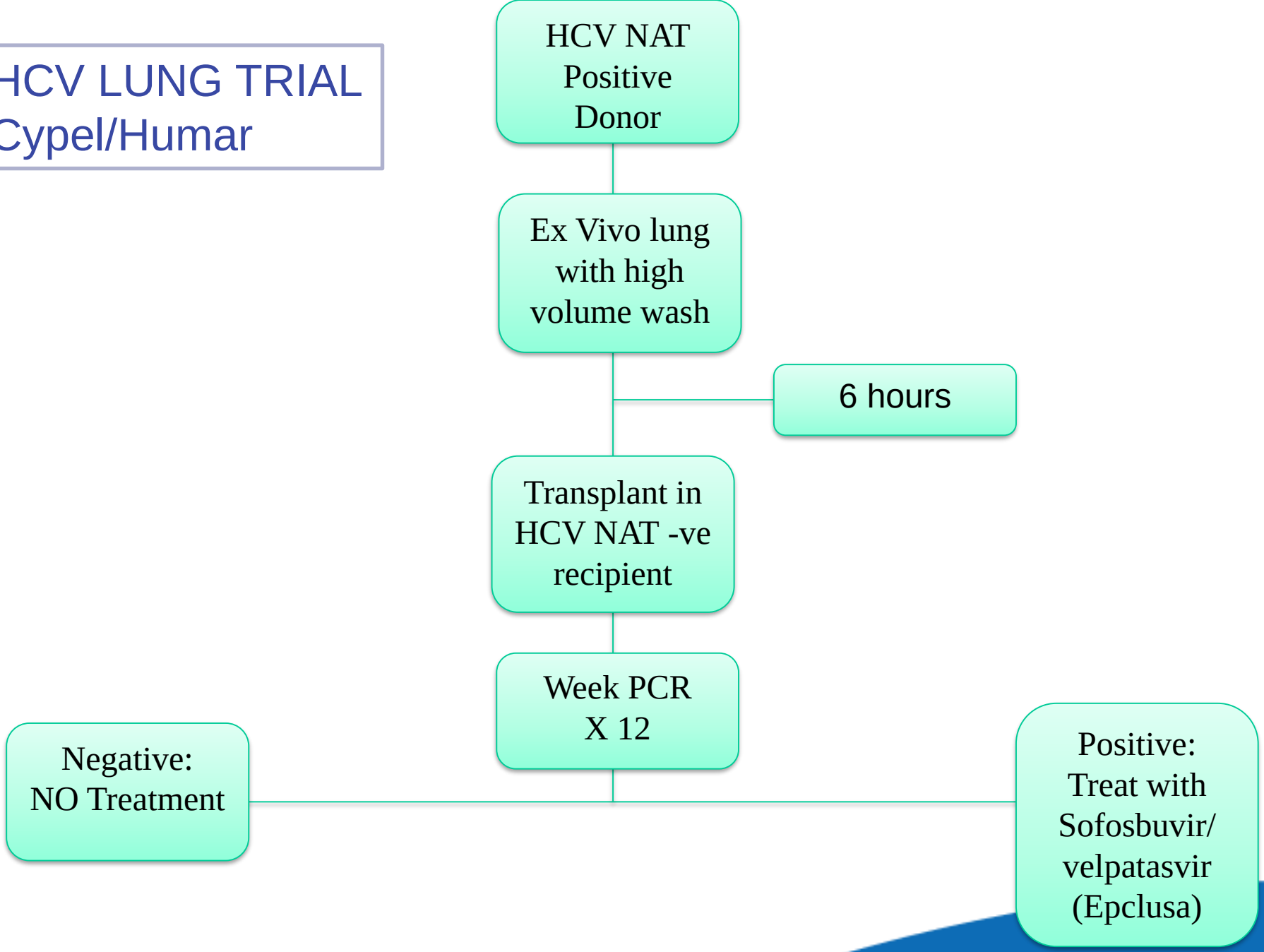
Figure 1. Hepatitis C Viral Load in 10 Kidney-Transplant Recipients.

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

10 patients
Median wait time
58 days
IAQR 53-100 days
Median KDPI score 42%

Goldberg et al. NEJM 2017

HCV LUNG TRIAL
Cypel/Humar



Recommendations for utilization of increased risk donors

- Transplant physicians and surgeons should consider the utilization of organs from IRDs.

- This should be done in conjunction with NAT testing for HCV and HIV, and HBsAg or NAT for HBV. Some development work is required to ensure that NAT is available across all jurisdictions in Canada (strong recommendation, moderate quality evidence).

- All potential recipients should be made aware of the option to consider accepting organs from IRDs and that declining such an offer will not impact their waiting time for a standard risk (non-IRD) organ.

Recommendations for utilization of increased risk donors

- Appropriate informed consent from potential recipients should be obtained. It is suggested that a standardized informed consent process be used
  - Information provided at the time of listing
  - Standardized IC at time of transplant

- Decisions around utilization or non-utilization may take into account the timing of increased risk behaviour, the window period for the specific test used, and the status of the recipient as well as other recipient-specific circumstances.

Recommendations RE HCV

- Definition of HCV positive donor should include NAT results (“HCV Viremic donor”)

- HCV Ab + / NAT negative donor
  - Consider using all organs for any appropriately consented recipient
  - Appropriate f/u testing important
  - We should keep a national database of such transplants

Recommendations

- HCV NAT Positive donor
  - Use preferentially in HCV NAT positive recipient
  - Consider using in selected NAT negative recipients with following considerations
    - For now should normally be in the context of a research study
    - May be very sick or special circumstance
    - Should have access to DAAs post transplant
    - We should track all such cases nationally

Thank You

Questions / Discussion

atul.humar@uhn.ca