
بسم الله الرحمن الرحيم

Hepatitis C in Transplant, Donor and Recipient Issues

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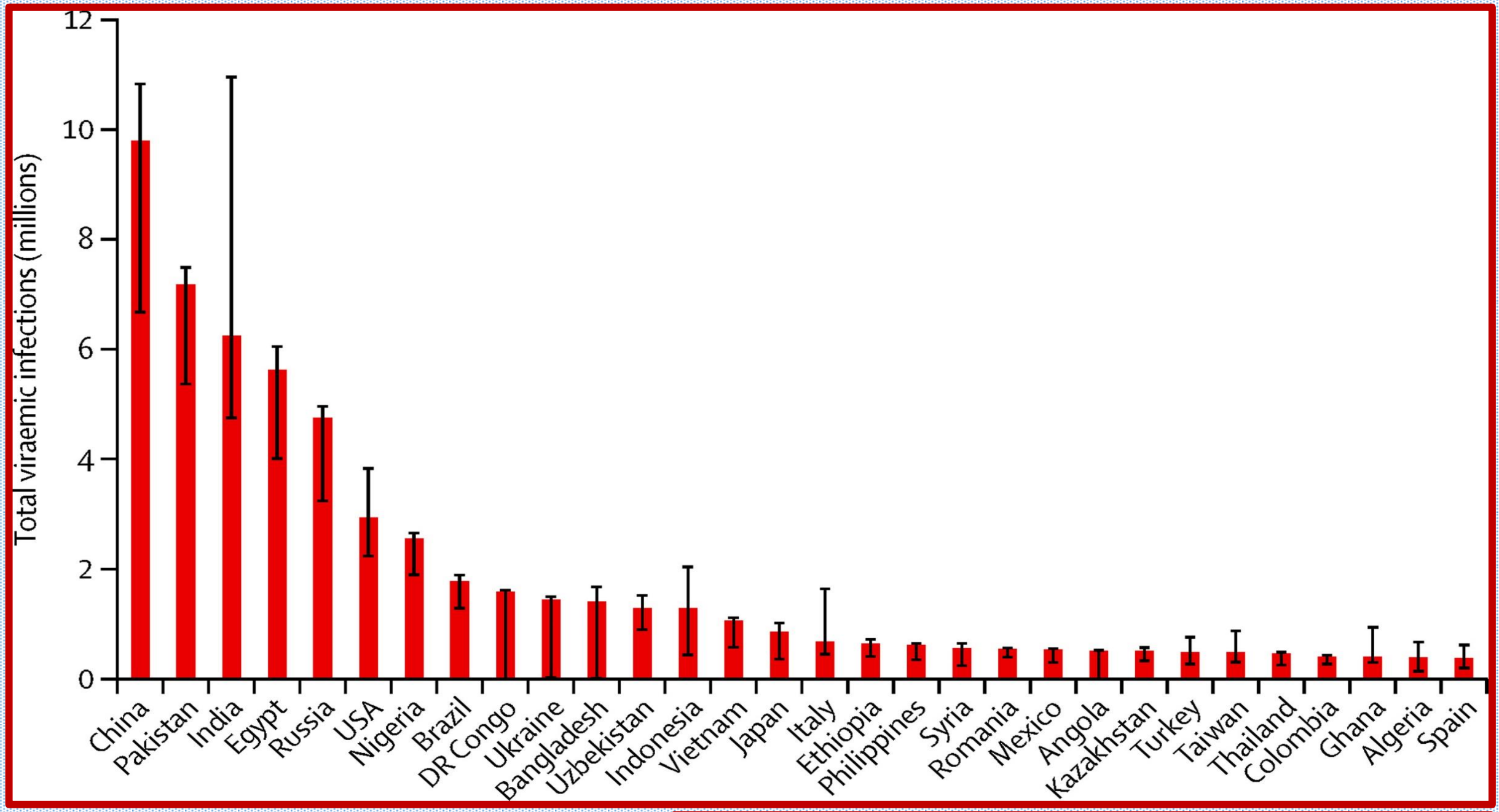
Viral hepatitis is the 7th leading cause of mortality worldwide with HCV accounting for about half of this mortality.

Global anti-hepatitis C virus prevalence and number of infected individuals (all ages)

Continent	Anti- HCV prevalence (%)	Viraemic rate (%)	2013 population (millions)	Anti- HCV infected (millions)	Viraemic HCV infected (millions)
Africa	2.9	70.5	927.0	26.9	19.0
North Africa/Middle East	2.7	68.8	469.0	12.7	8.7
America	1.3	74.0	953.7	12.4	9.2
Asia	2.8	64.4	3985.0	111.6	71.9
Australasia	1.8	74.8	28.0	0.5	0.4
Europe	1.8	72.4	742.5	13.4	9.7
Total	2.5	67.0	7105.2	177.5	118.9

World J Gastroenterol. 2016; 22(34): 7824–7840.



The Lancet Gastroenterology & Hepatology 2017, 161-176

Epidemiology of Hepatitis C in Iran

Hepatitis C infection prevalence has decreased dramatically in Iranian HD population during the last decade.

- **14.4% in 1999**
- **4.5% in 2006**

Alavian 2008

The latest incidence of HD pts with HCV Ab positive: 2018

- **Overall incidence: 542 pts (1.7%)**
- **Lowest incidence: 0%**
- **Highest incidence: 5.4%**

Unpublished data

HCV Infection in Organ Transplant Recipients

Organ	Prevalence (%)
Liver	21
Kidney	6.3
Heart	2.1
Lung	1.7

SRTR 2015 Annual Report, Am J Transplant 2017, Kumar *et* al, Am J Cardiol 2016, Englum *et al*, J Heart Lung Transplant 2016

HCV – RENAL TRANSPLANTATION

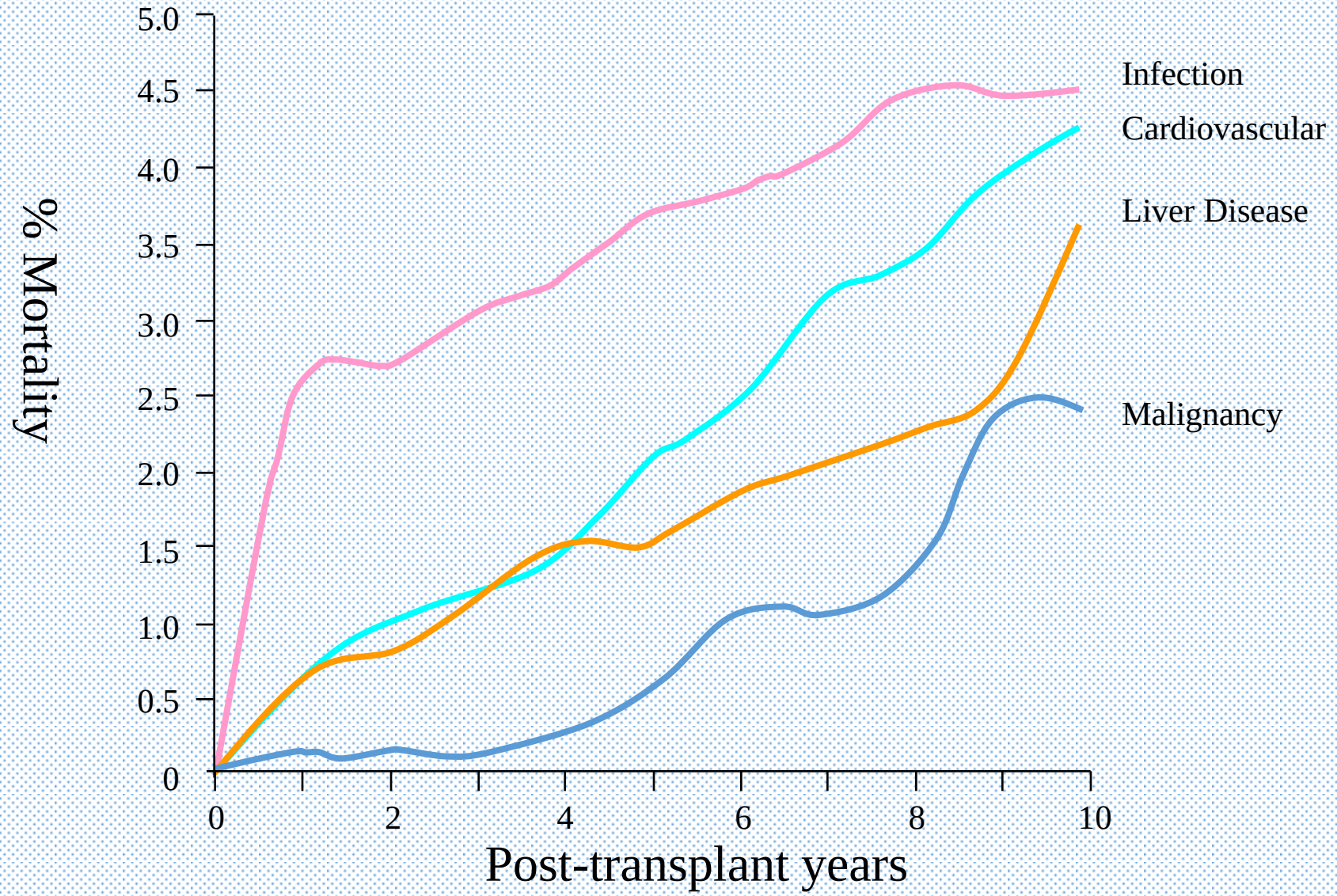
RELEVANCE

- **High prevalence in renal population (Dialysis/Tx)**

- **Liver diseases are the 4º cause of death for RT patients**

Renal Transplant 1978-1997 (n =1390)

Cumulative Risk of Mortality



Most renal transplant recipients (RTRs) have acquired HCV infection prior to transplantation.

Romero E, et al. Transplant Proc. 2008;40(9):2933-5.

Comparison of pretransplant factors between HCV-positive and HCV-negative pts

	Anti-HCV Ab Positive (*n*=41)	Anti-HCV-Ab negative (*n*=868)	*P*-value
Duration on HD (months)	39.6±6.0	18.4±1.9	0.001
Retransplantation (yes/no)	9/32 (21.9%)	61/807 (7.0%)	0.001

Einollahi B, et al. J Gastroenterol Hepatol. 2003;18:836–840.

There is a wide range of HCV infection prevalence (2.6-66%) among RTRs living in different countries.

Moghaddam SM, Alavian SM, Kermani NA. Rev Med Virol. 2008;18(6):375-86.
Einollahi B, et al. J Gastroenterol Hepatol. 2003;18:836–840.
Fehr T, et al. Am J Kidney Dis. 2003;42:193-201.
Mitwalli AH, et al. Nephron Clin Pract. 2006;102:72-82.

Prevalence of HCV infection among Renal Transplant Recipients:
1.8 to 8 percent

Baid-Agrawal et al. Am J Transplant 2014

HCV prevalence was 3.45 percent among normal-risk potential donors and 18.2 percent among high-risk potential donors.

Ellingson K, et al Am J Transplant 2011

Natural history of HCV infection in RTRs

RT improves overall survival in HCV pts on HD

the relative risk of mortality was 0.36 for RTRs, a 64% lower risk of death than wait-listed dialysis individuals

Kokado Transplant Proc. 2000;32:1940–3

Natural history of HCV infection in RTRs

RT improves overall survival in HCV pts on HD

pre-transplantation HCV infection does not adversely affect medium-term patient and graft survivals in RTRs .

No significant difference in 5-yr survival for HCV +ve RT recipients

Einollahi B. J Gastroenterol Hepatol. 2003;18:836–40

Natural history of HCV infection in RTRs

RT improves overall survival in HCV pts on HD

N

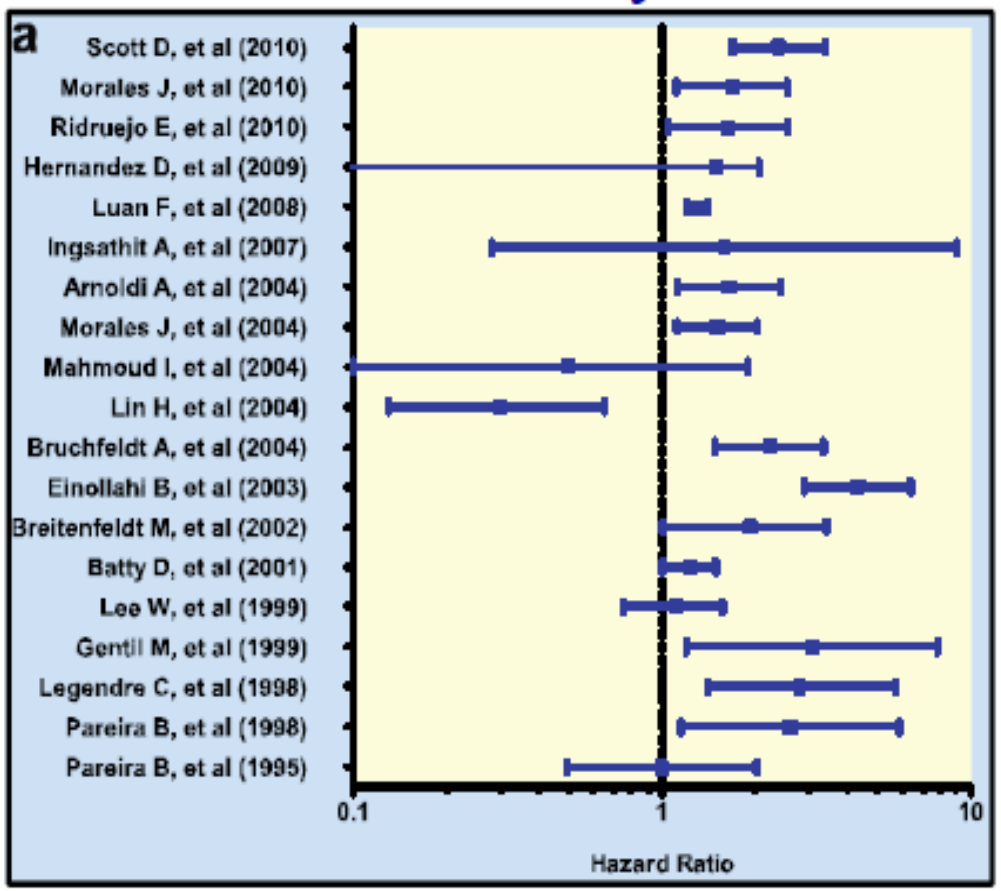
the survival rate of HCV-positive recipients appeared to decrease gradually over the long term, especially in the second decade following transplantation.

Significantly lower survival at 10 years,
Patient survival (P=0.001) 65%±5% versus 85%±3%
Graft survival (P=0.01) 49%±5% versus 69%±4%

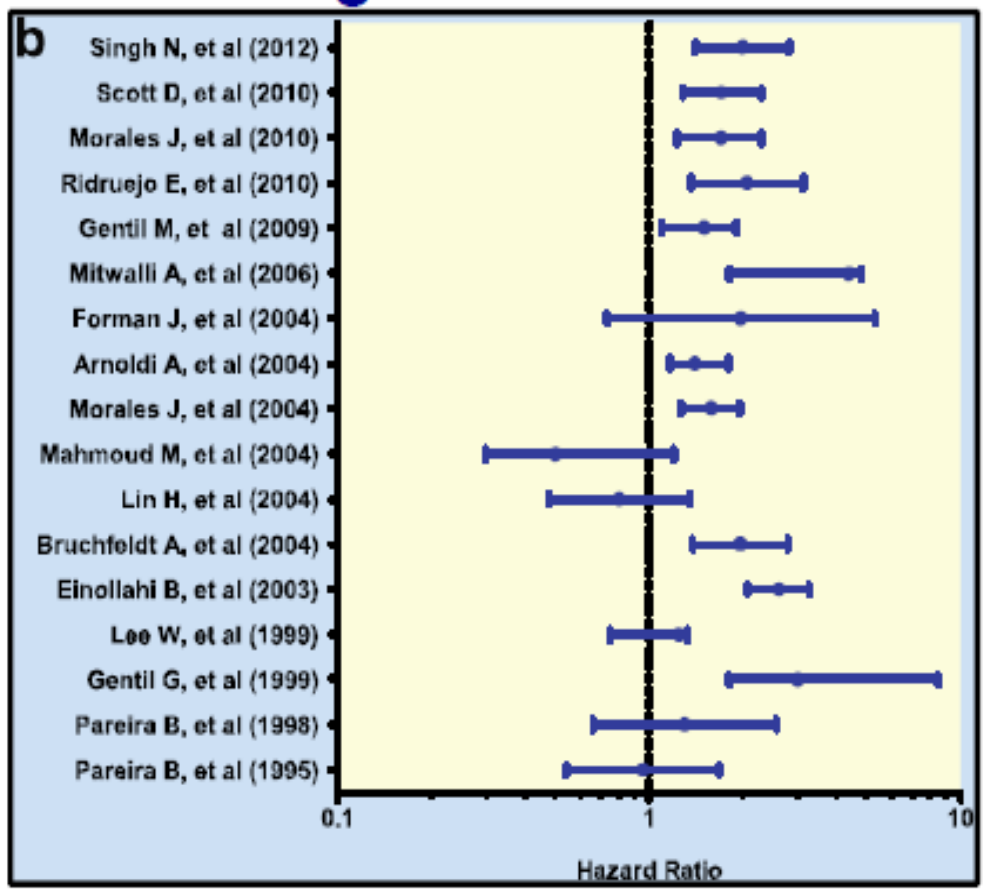
Einollahi Transplant Proc. 2007;39:907–10
Kokado Transplant Proc. 2000;32:1940–3

Inferior Outcomes in HCV+ Kidney Recipients

Mortality



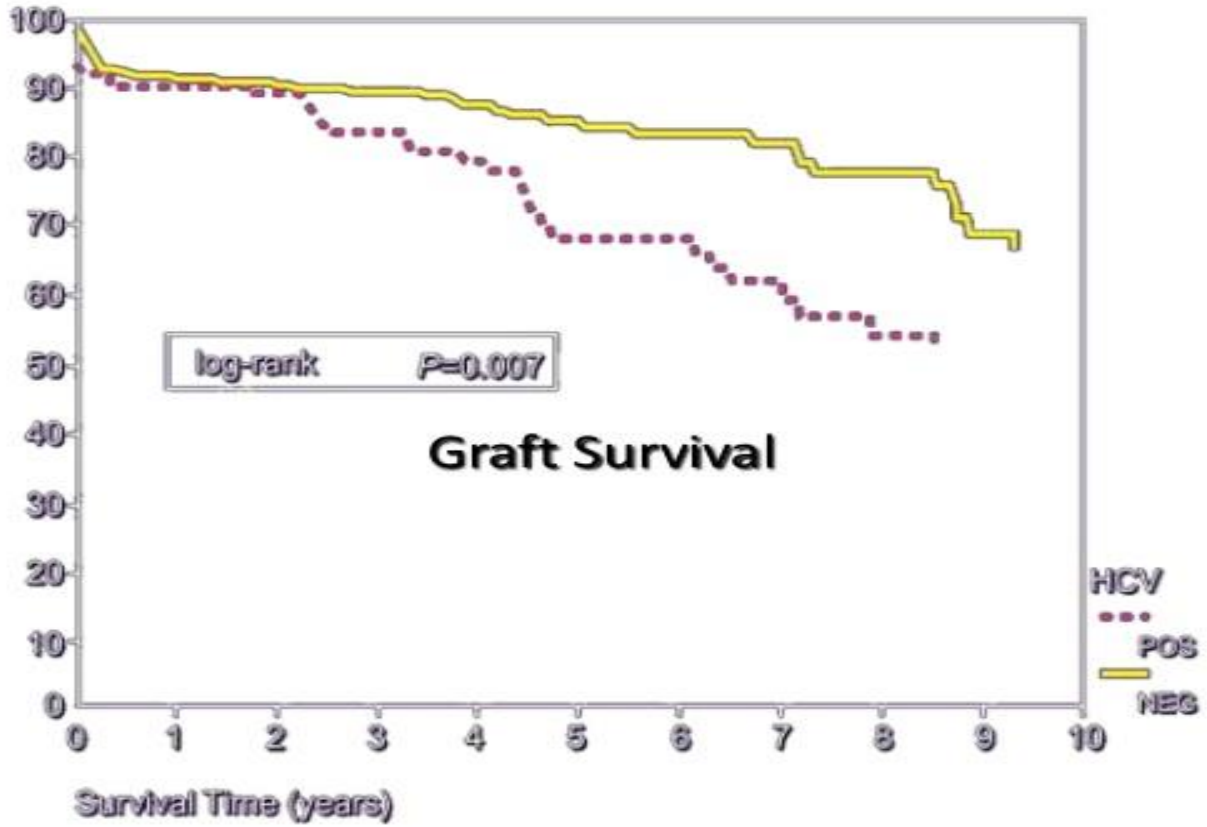
Allograft survival

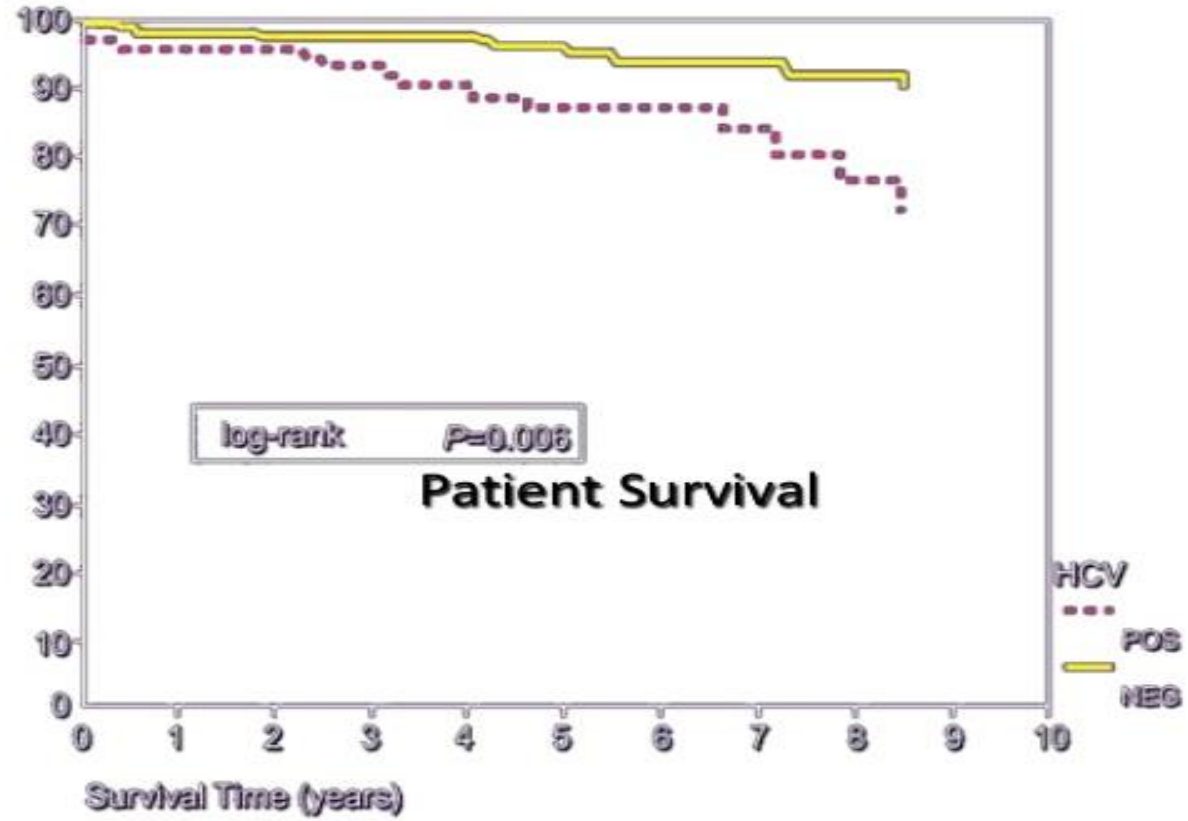


Adapted from meta-analyses of observational studies, comparing to HCV- recipients

From Baid-Agarwal et al, Am J Transplant 2014

HCV infection is associated with lower graft and recipient survival

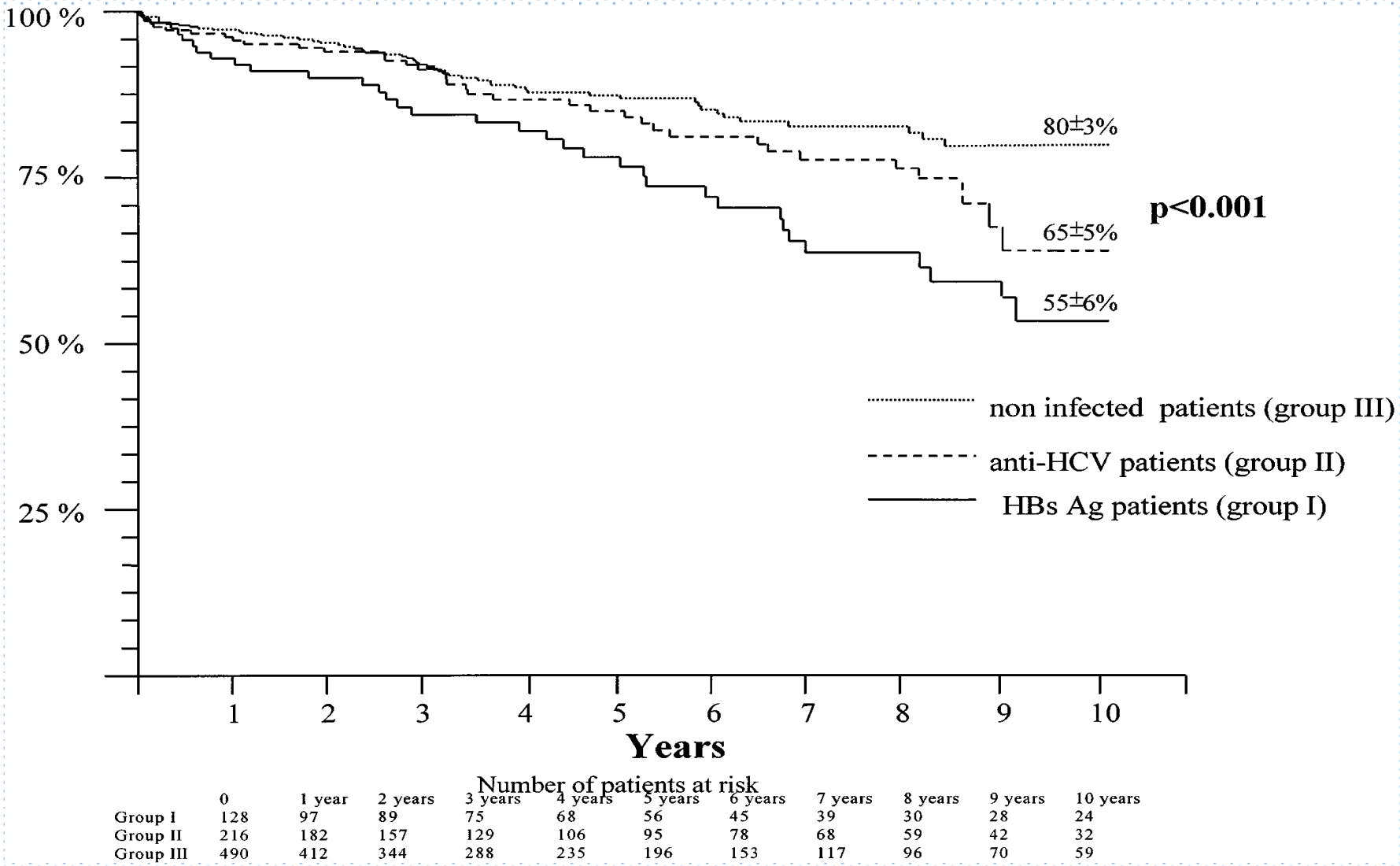




Gentil MA et al. Nephrol Dial Transplant. 1999;14:2455-2460.

The detrimental role of HCV upon patient and graft survival was confirmed by multivariate analysis in order to exclude the role of confounding factors (i.e., age, diabetes, time on dialysis, time after RT, etc)

Mathurin P, et al. Impact of Hepatitis B and C Virus on Kidney Transplantation Outcome. Hepatology 1999



	0	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Group I	128	97	89	75	68	56	45	39	30	28	24
Group II	216	182	157	129	106	95	78	68	59	42	32
Group III	490	412	344	288	235	196	153	117	96	70	59

Mathurin P, et al. Impact of Hepatitis B and C Virus on Kidney Transplantation Outcome. Hepatology 1999

Systematic review and meta-analysis of observational studies (*n*=18; 133,530 unique RT recipients)

Fabrizi F, Messa P. Meta-analysis of observational studies: Hepatitis C and survival after renal transplant
J Viral Hepat 2014

Summary estimate for adjusted Relative Risk of all-cause mortality after RT:

1.85 (95% CI, 1.49; 2.31)

Fabrizi F, Messa P. Meta-analysis of observational studies: Hepatitis C and survival after renal transplant. J Viral Hepat 2014

Summary estimate for adjusted Relative Risk of all-cause graft loss after RT:

1.76 (95% CI, 1.46; 2.11)

Fabrizi F, Messa P. Meta-analysis of observational studies: Hepatitis C and survival after renal transplant. J Viral Hepat 2014

NDT Plus (2010) 3 [Suppl 2]: ii41–ii46
doi: 10.1093/ndtplus/sfq070

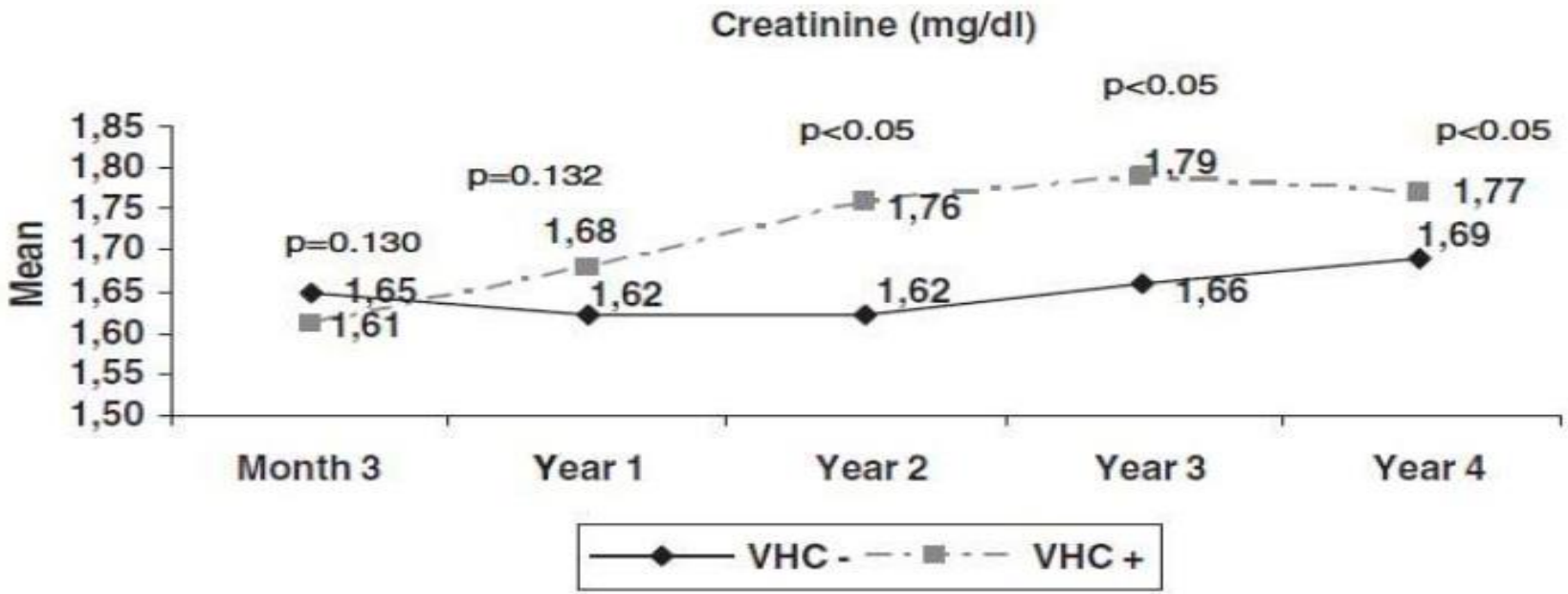
NDT PLUS
Nephrology Dialysis Transplantation

Renal transplantation in patients with hepatitis C virus antibody. A long national experience

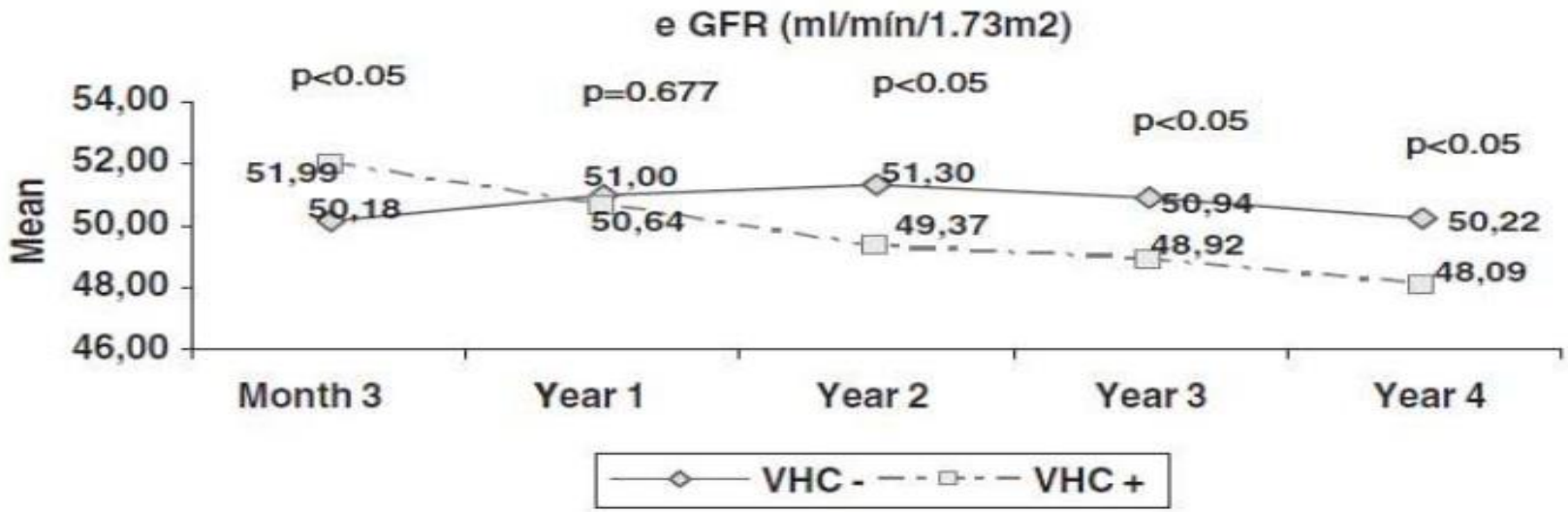
Jose María Morales[1], Roberto Marcén[2], Amado Andres[1], Beatriz Domínguez-Gil[3], Josep María Campistol[4], Roberto Gallego[5], Alex Gutierrez[6], Miguel Angel Gentil[7], Federico Oppenheimer[4], María Luz Samaniego[8], Jorge Muñoz-Robles[9] and Daniel Serón[10]

Results. Among recipients alive with graft function 1 year post-transplant, the 4-year graft survival was 92.8% in the whole group; this was significantly better in HCV-negative *vs* HCV-positive patients (94.4% *vs* 89.5%, $P < 0.005$). Notably, HCV patients showed more acute rejection, a higher degree of proteinuria accompanied by a diminution of renal function, more graft biopsies and lesions of *de novo* glomerulonephritis and transplant glomerulopathy. Serum creatinine and proteinuria at 1 year, acute rejection, HCV positivity and systolic blood pressure were independent risk factors for graft loss. Patient survival was 96.3% in the whole group, showing a significant difference between HCV-negative *vs* HCV-positive patients (96.6% *vs* 94.5%, $P < 0.05$). Serum creatinine and diastolic blood pressure at 1 year, HCV positivity and recipient age were independent risk factors for patient death.

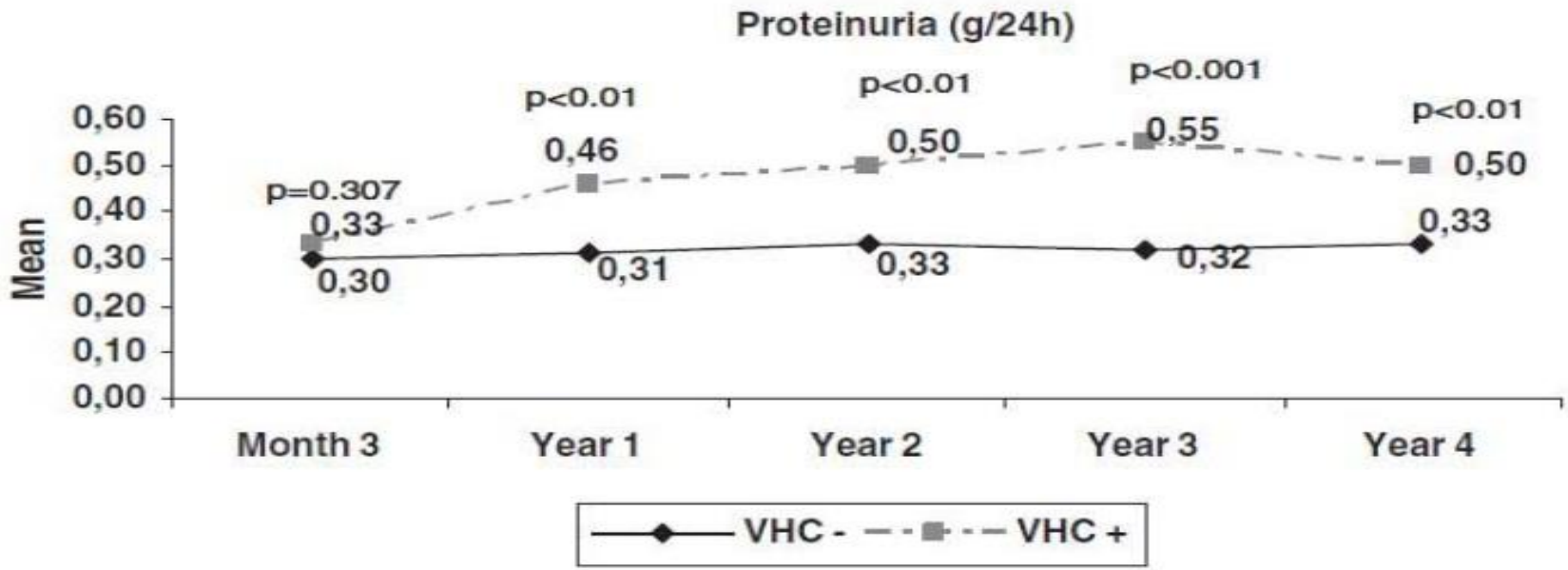
Serum creatinine showed higher mean values in HCV+ vs HCV– patients from the second year



Mean values of eGFR were lower in HCV+ vs HCV– patients from the second year post-transplant



Mean values of proteinuria were higher from the first year in HCV+ vs HCV– patients



Survival is better compared to dialysis

Renal Transplant in HCV cases

- Renal transplantation is associated with a 68% reduction in long-term mortality compared to remaining on the waiting list

J Am Soc Nephrol 22: 1152–1160, 2011

Effect on the liver

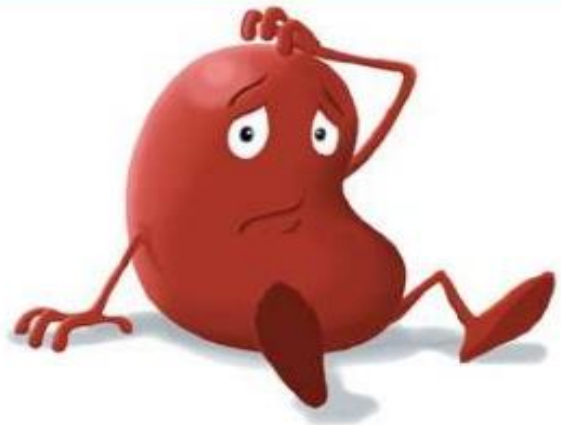
Hepatoma and cirrhosis in HBV, HCV infection or co-infection among renal transplantation patients

477 cases were followed-up from 1984 to 1999

	Prevalence(N)	Hepatoma	Cirrhosis
HBV-/HCV-	58.5%(279)	1.4%	3.2%
HBV-/HCV+	9.9%(47)	4.4%	6.6%
HBV+/HCV-	28.5%(136)	6.4%	21.3%
HBV+/HCV+	3.1%(15)	6.7%	20%

Lee WC, et al. Am J Nephrol. 2001,21:300-6

Should we accept HCV positive donor ?



HCV-infected donors to HCV negative Recipients

NO

KDIGO guidelines 2008

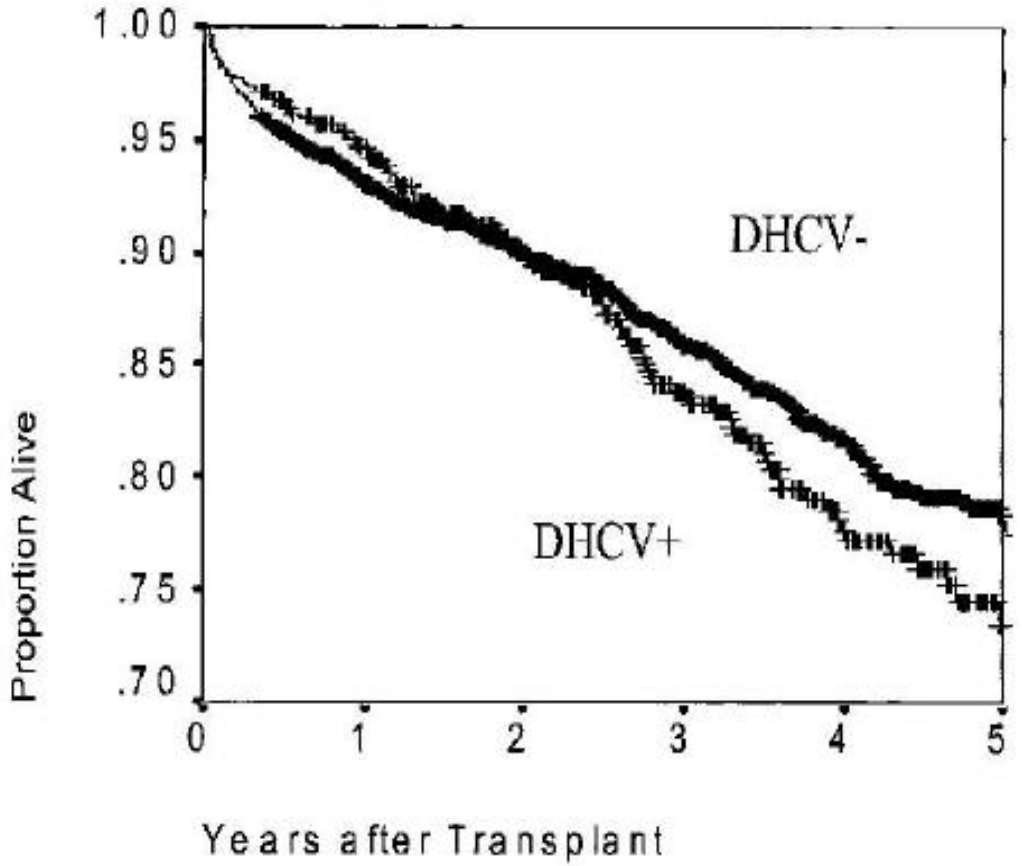
- kidneys from anti-HCV-positive deceased donors should be given to only HCV RNA-positive recipients. (Lead to shorter waiting list)
- In cases of HCV-positive living donors for HCV-positive recipients, the risks of delaying transplantation for the antiviral treatment should be weighed against the benefits.

Use of Increased Risk Donors

What is the Risk of HCV Transmission to the Transplant Recipient?

- Very small chance for transmission (<0.5%) of HCV to an HCV-negative recipient with transplantation of a kidney from a treated or cleared HCV-positive donor

Worse Outcomes in HCV-Infected Recipients of HCV+ Kidneys

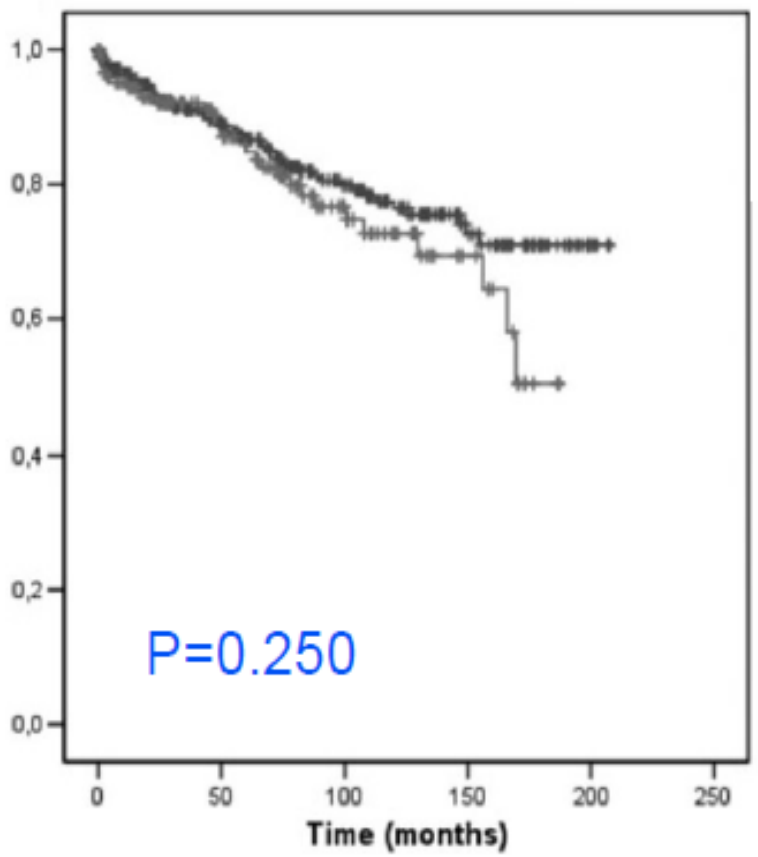


- USRDS, 1996-2001, n=36,956
- Recipient level data limited
  - Liver disease severity
  - NAT vs serological testing
  - Reasons for use of HCV+ donor
- Donor level data limited
  - No NAT
  - Clinical information

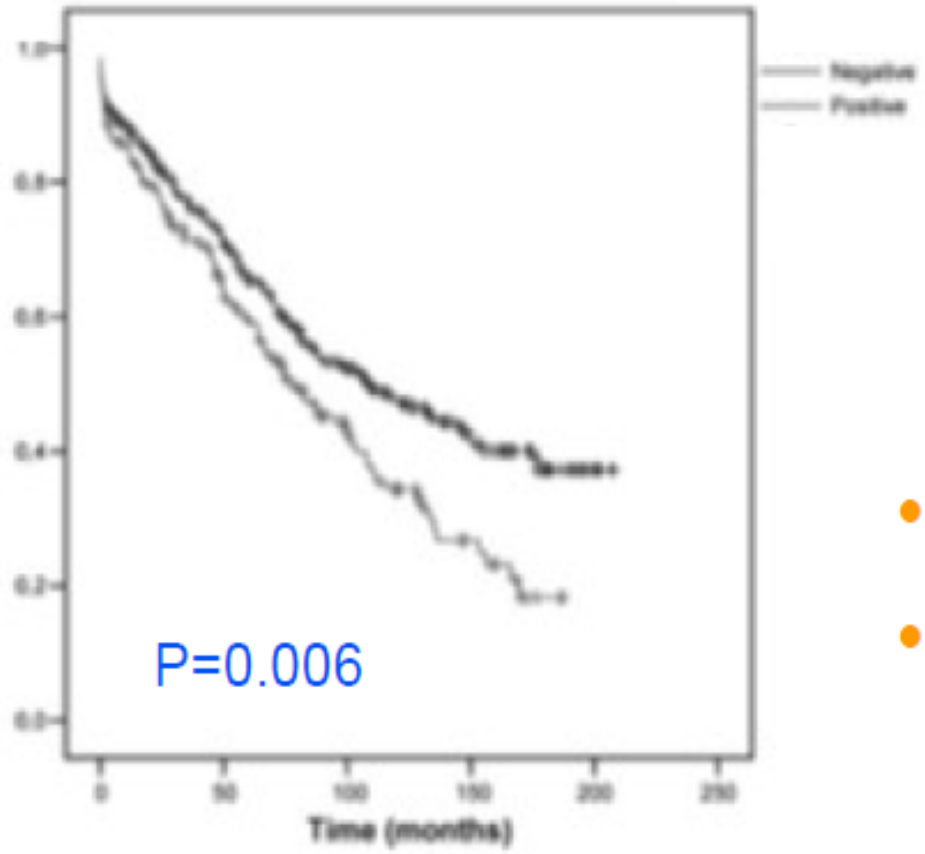
Abbott et al. J Am Soc Nephrol 2003

Worse Outcomes in HCV-Infected Recipients of HCV+ Kidneys

Patient survival



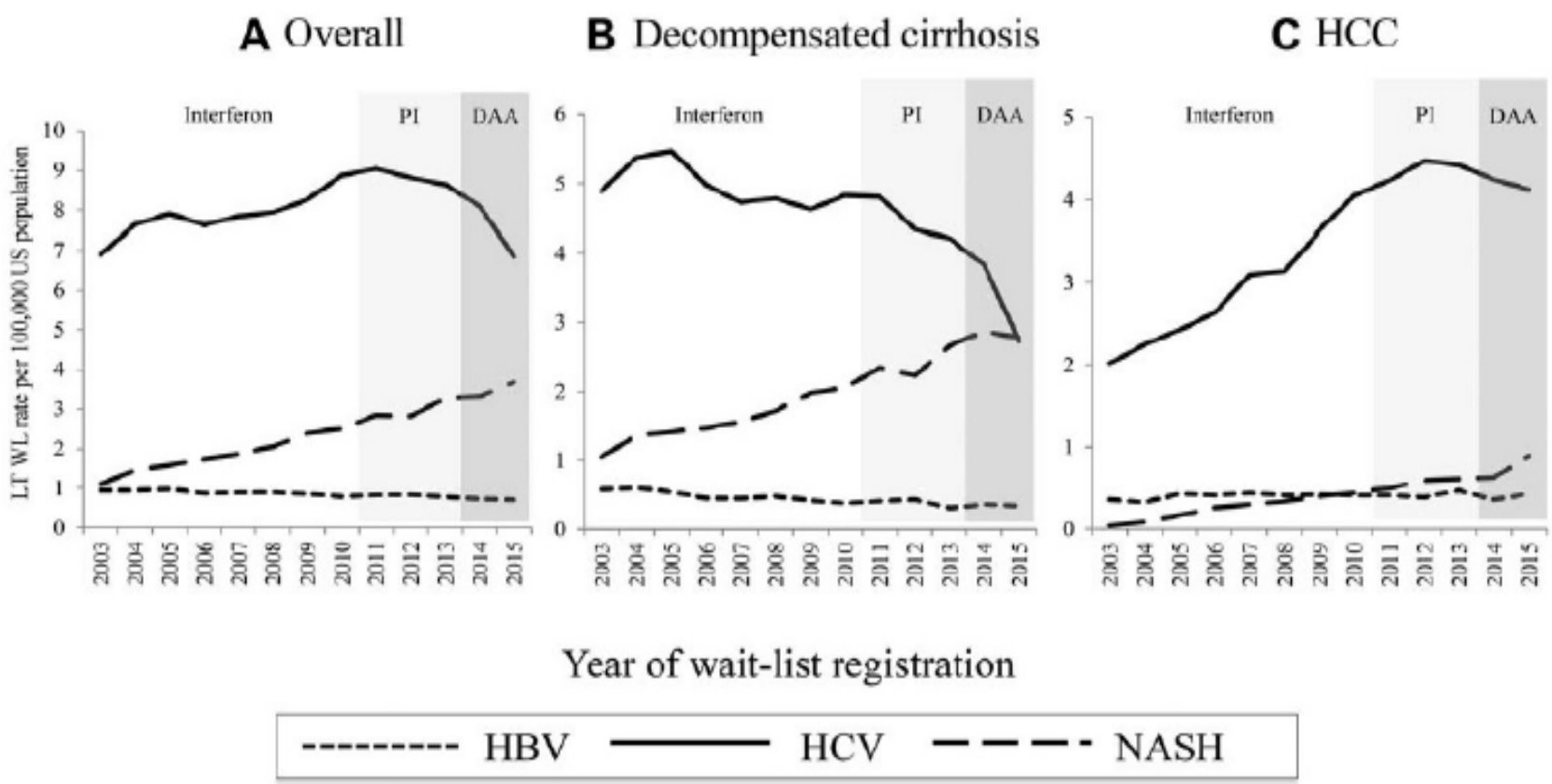
Graft survival

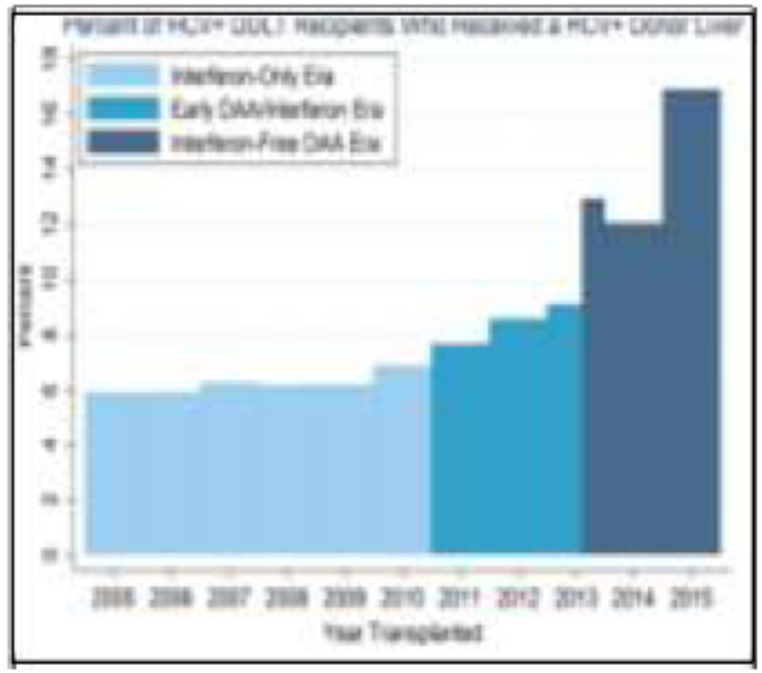


- 162 HCV+ donors
- 306 HCV- donors

Morales et al, Am J. Transplantation 2010

Shorter Wait Times for Organs From HCV-Infected Donors





Bowring *et al*, Am J Transplant 2017

Flemming *et al*, Hepatology, 2016

Opportunity for Increased Organ Utilization with Procured HCV+ Donors

Disposition of 6546 Kidneys fr … y between 2005 and 2014.*

Disposition of Kidney Pairs	No Dono…	…mated Additional Graft-Years Obtainable by Transplanting Both Kidneys		
		…Survival	3-Yr Survival	5-Yr Survival
Both kidneys discarded	1718	…000	7637	10,301
1 kidney transplanted, 1 discarded	708	636	1675	2,361
Both kidneys transplanted	847	—	—	—

Acceptance of HCV+ kidneys decreases wait time by 395 days

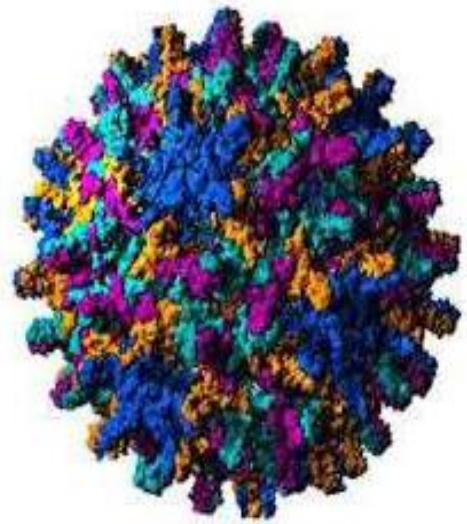
Kucirka *et al*, Am J Transplant, 2010

Reese *et al*, NEJM, 2015

Comorbidities Associated with HCV Infection

Hepatic

- Hepatitis
- Fibrosis
- Cirrhosis
- ESLD
- HCC



Extrahepatic

- Kidney disease
- Diabetes
- CVD/metabolic syndrome
- NODAT
- Infection
- PTLD
- AMR/Transplant GN
- Glomerular disease

HCV-associated renal disease post-transplantation

- ✓ Posttransplant proteinuria
- ✓ Membranoproliferative glomerulonephritis
- ✓ Membranous nephropathy
- ✓ Renal thrombotic microangiopathy
- ✓ Acute transplant glomerulopathy
- ✓ Chronic transplant glomerulopathy
- ✓ Mixed cryoglobulinemia (rare)
- ✓ PTDM or worsening of diabetic nephropathy
- ✓ Increased incidence of PTLD
- ✓ TB

- **Greater all-cause patient/graft loss in RT-recipients with HCV related to** (in addition to chronic liver disease):

-Higher rate of post-transplant diabetes (PTDM)
-de novo or recurrent HCV-GN
-chronic allograft nephropathy
-exposure to calcineurin inhibitors

Fabrizi F, Messa P. **Meta-analysis of observational studies: Hepatitis C and survival after renal transplant. J Viral Hepat 2014**

American Journal of Transplantation 2005; 5: 2433–2440
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01040.x

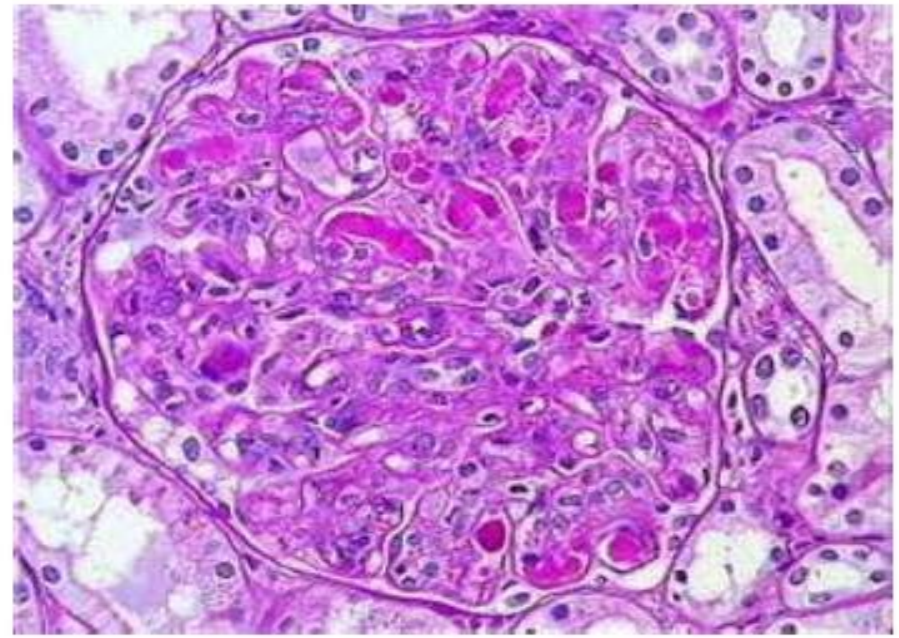
Post-Transplant Diabetes Mellitus and HCV Seropositive Status After Renal Transplantation: Meta-Analysis of Clinical Studies

Table 6: Anti-HCV seropositive status and diabetes mellitus after RT: multivariate analysis adjusted odds ratio (aOR) and 95% CI.

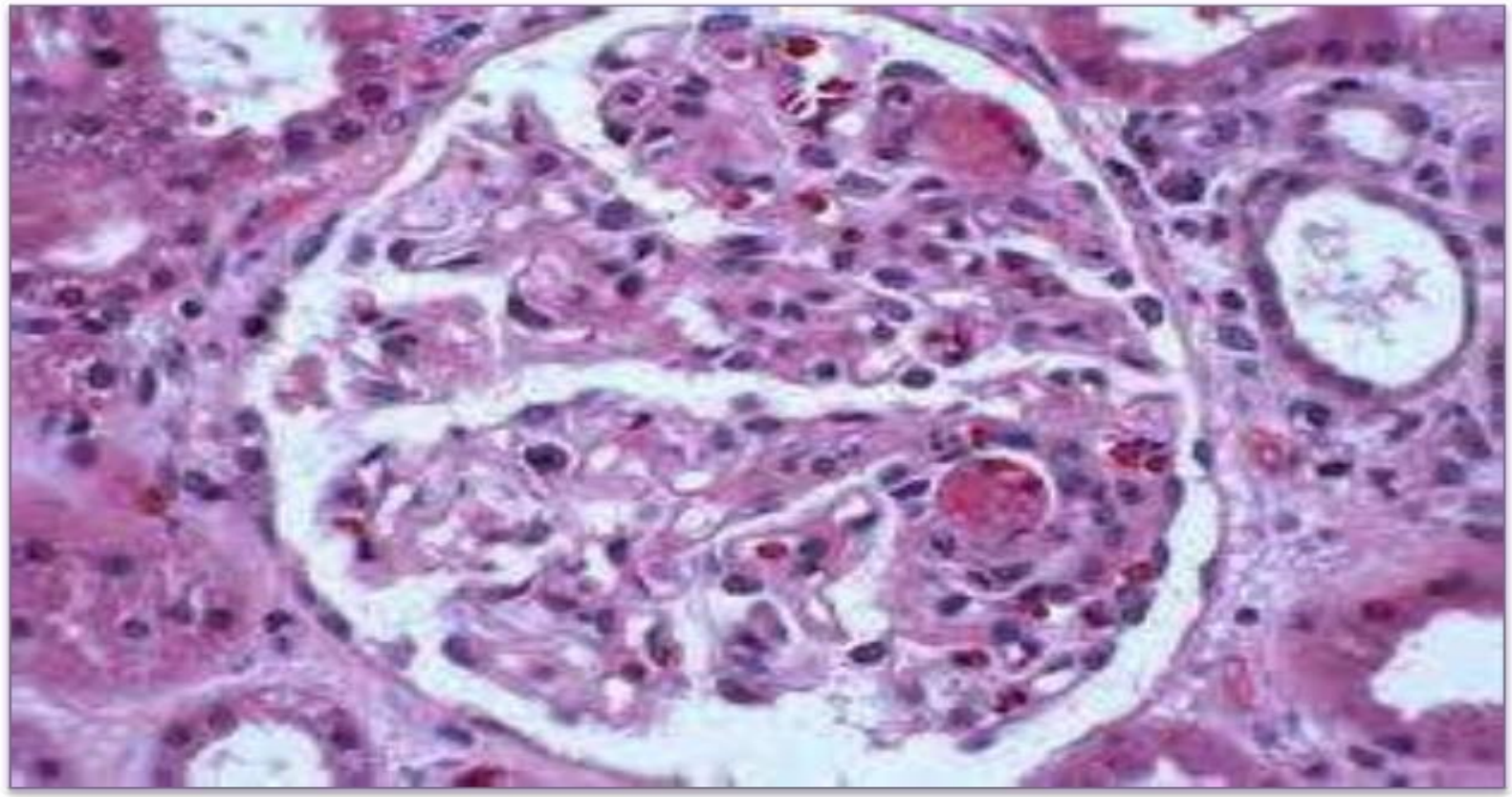
Authors	aORs	95% CI	*P*
Yildiz A et al.	17.44	2.48–122.6	0.004
Bloom RD et al.	6.76	2.36–19.38	0.0001
Gentil MA et al.	1.778	0.768–4.125	NS
Gentil MA et al. (1)	5.65	2.6–12.0	0.0001
Gentil MA et al. (2)	1.232	0.255–5.964	NS
Gourishankar S et al.	3.4	1.02–11.2	0.047
Overall random effect model estimate	3.97	1.83–8.61	

Kidney diseases associated with HCV infection

- **Membranoproliferative GN (Cryo+ve /-ve)**
- **Membranous GN**
- **Mesangioproliferative GN**

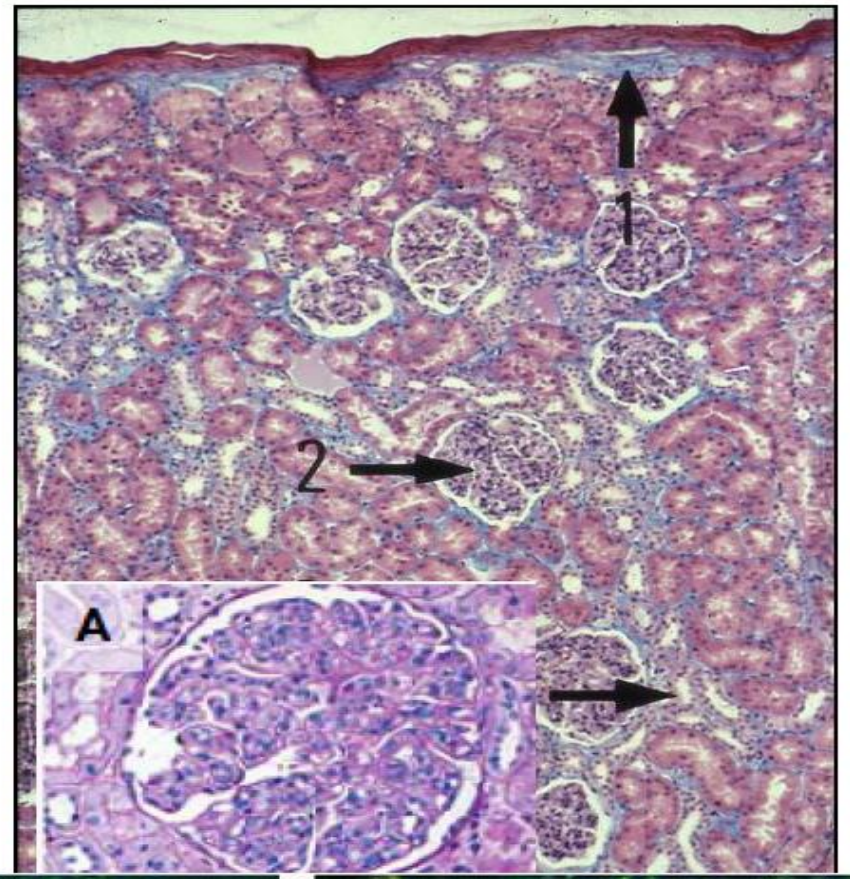


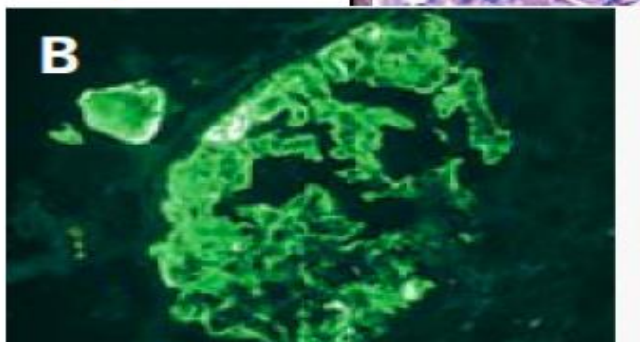
Thrombotic Microangiopathy

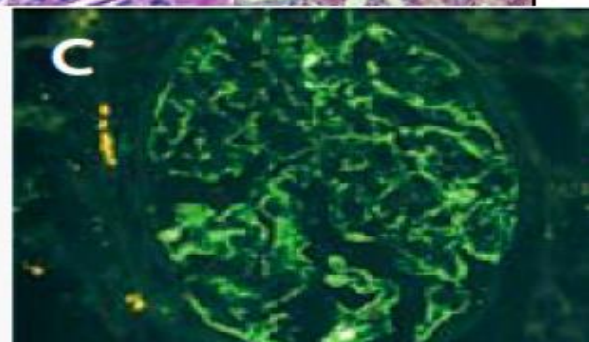


HCV infection may be associated with any kidney disease

- Glomerulus :
  - Type II Cryoglobulinemia (MPGN)
  - GN with mesangial IgA deposits
  - Membranous GN
  - Hyalinosis
  - Fibrillar GN
  - Immunotactoïd GN
- Interstitium
  - Sjogren Syndrom
  - B Lymphoproliferation
- Vascular : thrombotic microangiopathy
- Rejection nephropathy







Extrahepatic Manifestations of HCV

Hematological and Lymphoid Disorders *

- **Mixed cryoglobulinemia**
- **Non-Hodgkin B-cell lymphoma (NHL)**
- **Aplastic anemia (association ????)**
- **Idiopathic thrombocytopenic purpura**

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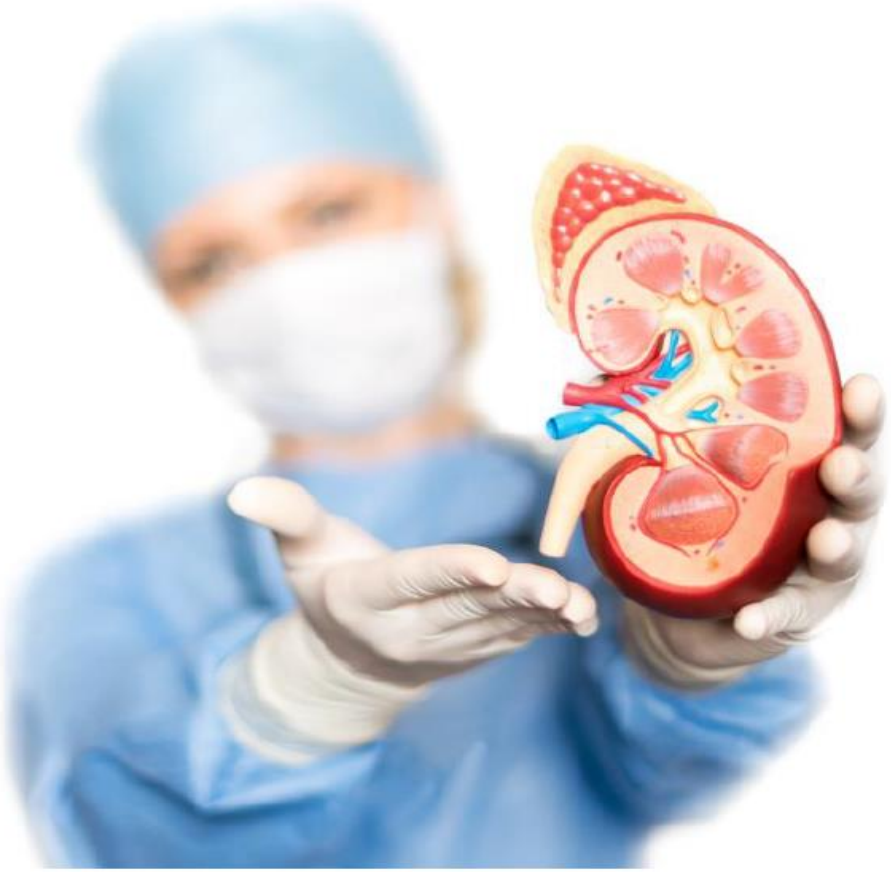
*Linked to lymphotropism of HCV to PBLs, dendritic cells, BM,megacariocyte,vascular endothelium and/or chronic antigenic stimulation

Treatment options for hepatitis C in kidney transplant candidates

Should we treat HCV (+) kidney transplant candidates?

- **Yes,**
  - Every HCV (+)/RNA (+) patient
  - Liver biopsy is not mandatory (we can rely on liver elastometry)
  - Genotyping, viral load at D0
  - During therapy, the patient is not a transplant candidate

Candidate for living donor transplant



- Treat hepatitis C in patients with living donors prior to kidney transplantation

Pre vs. post transplant treatment

Pre-transplant treatment

- HCV-associated liver damage may be accelerated by immunosuppression.

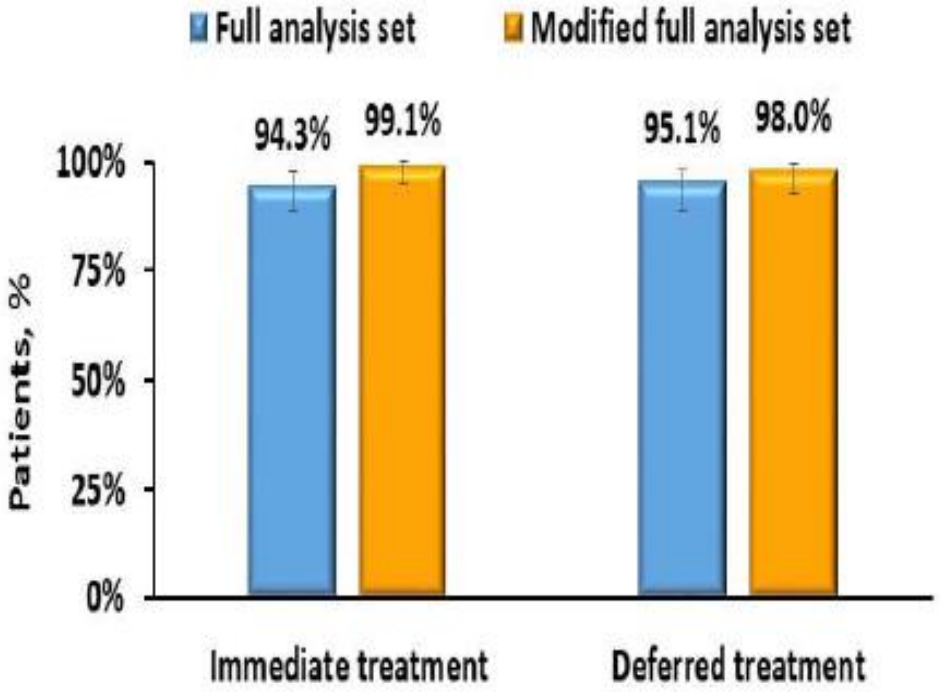
- For this reason, antiviral therapy should be considered for all haemodialysis patients who will be candidates for renal transplantation

EASL Recommendations on Treatment of Hepatitis C 2015

Treating Pre-transplant: The Pros

- Mostly curable

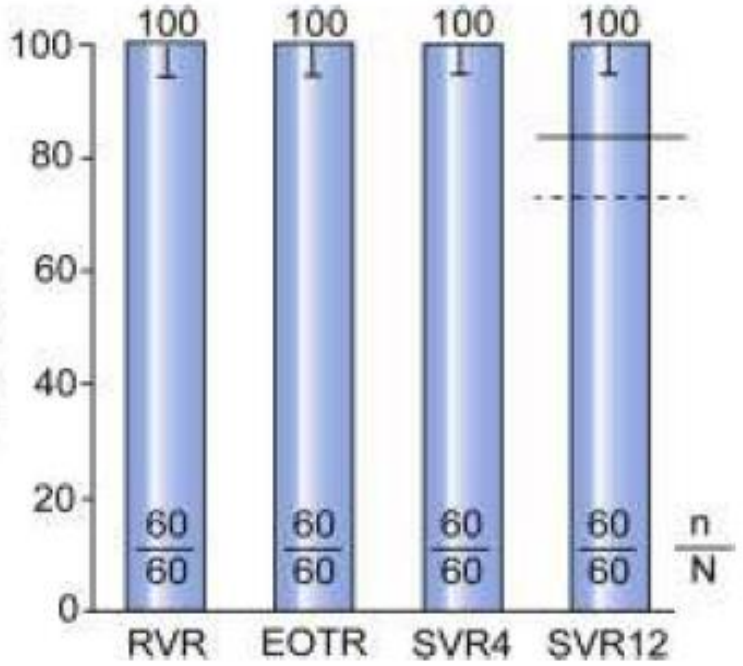
CKD Stage 4 and 5d



Roth *et al*, Lancet 2015

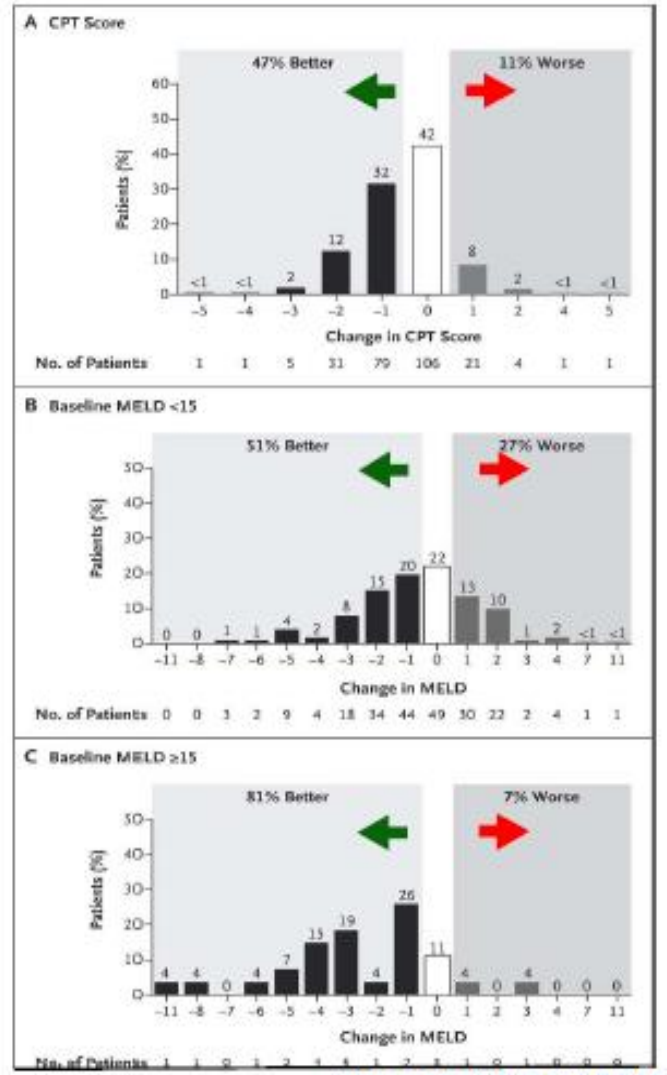
Compensated cirrhosis

- SVR 75-100%



Feld *et al*, J. Hepatol, 2016

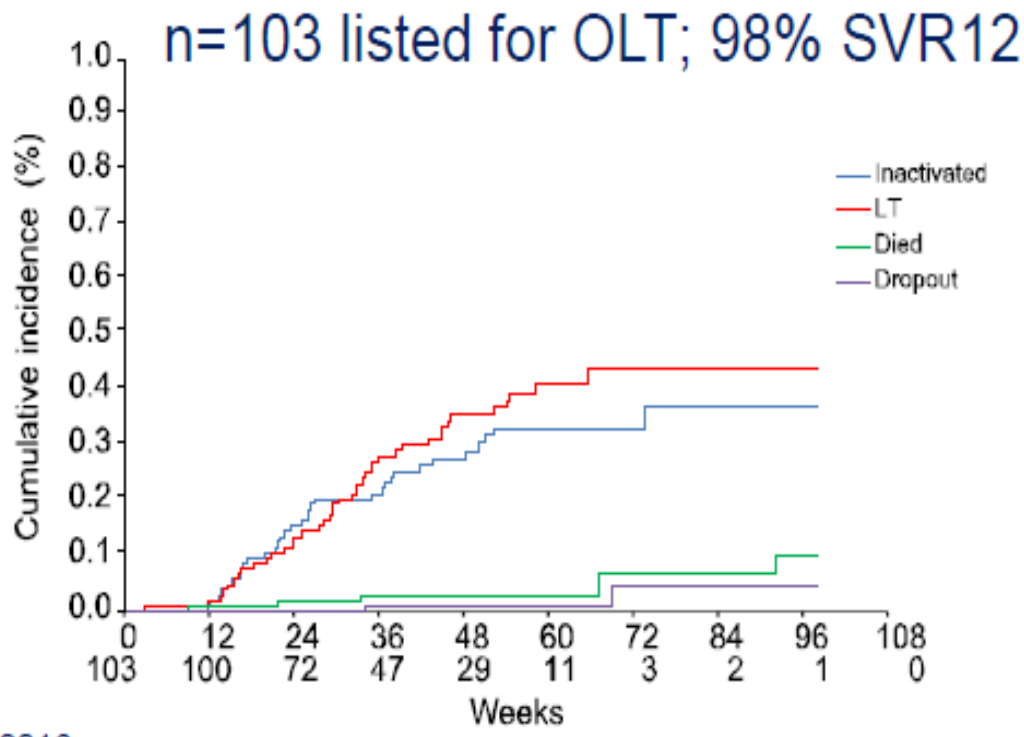
Decompensated cirrhosis



Curry *et al*. NEJM 2015

Treating Pre-transplant: The Pros

- Mostly curable
- Slow liver disease progression



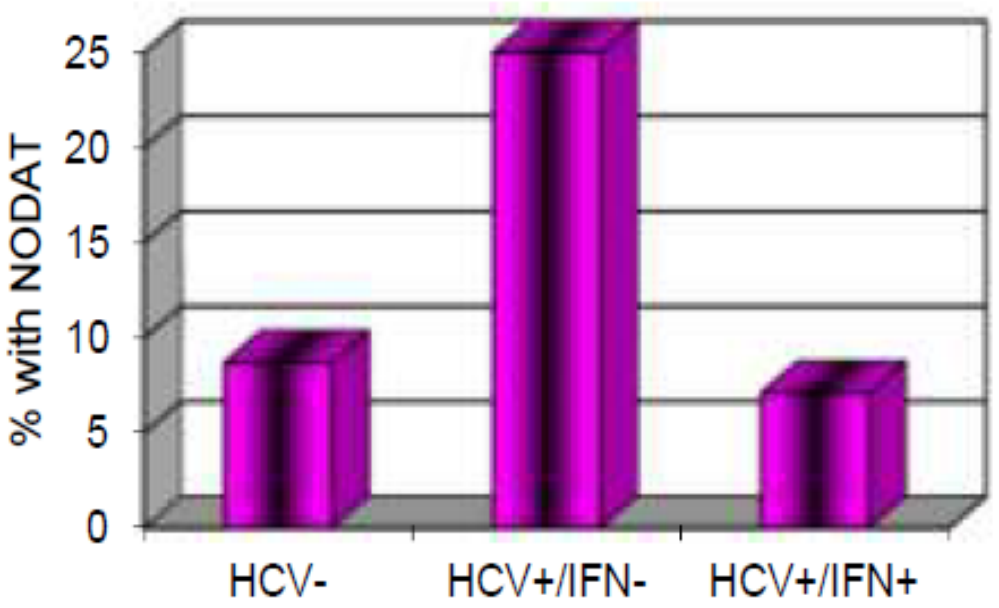
Belli *et al*, J. Hepatol 2016

- Sufficiently sick to benefit
- Low MELD regions
- Low HCV prevalence

Treating Pre-transplant: The Pros

- Mostly curable
- Slow liver disease progression
- Reduce transplant complications: NODAT

Author	Organ	NODM (%) HCV-	HCV+
Baid, 2001	L	28	64
Khalil, 2004	L	7	15
Bloom, 2002	K	10	39
Fabrizi, 2005	K	OR 3.97	

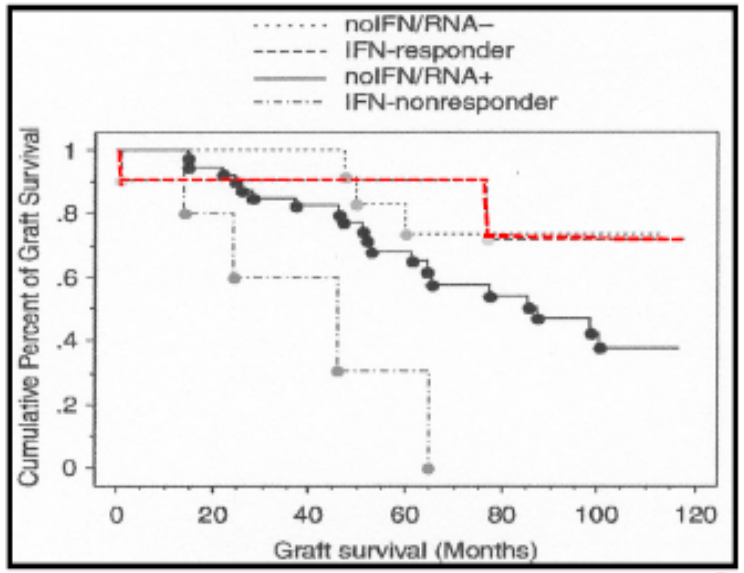


Gursoy, Transplant Proc, 20

Treating Pre-transplant: The Pros

- Mostly curable
- Slow liver disease progression
- Reduce transplant complications: Recurrent disease

Glomerular disease



Cruzado et al, Am J. Transplantation 2003

Treating Pre-transplant: The Pros

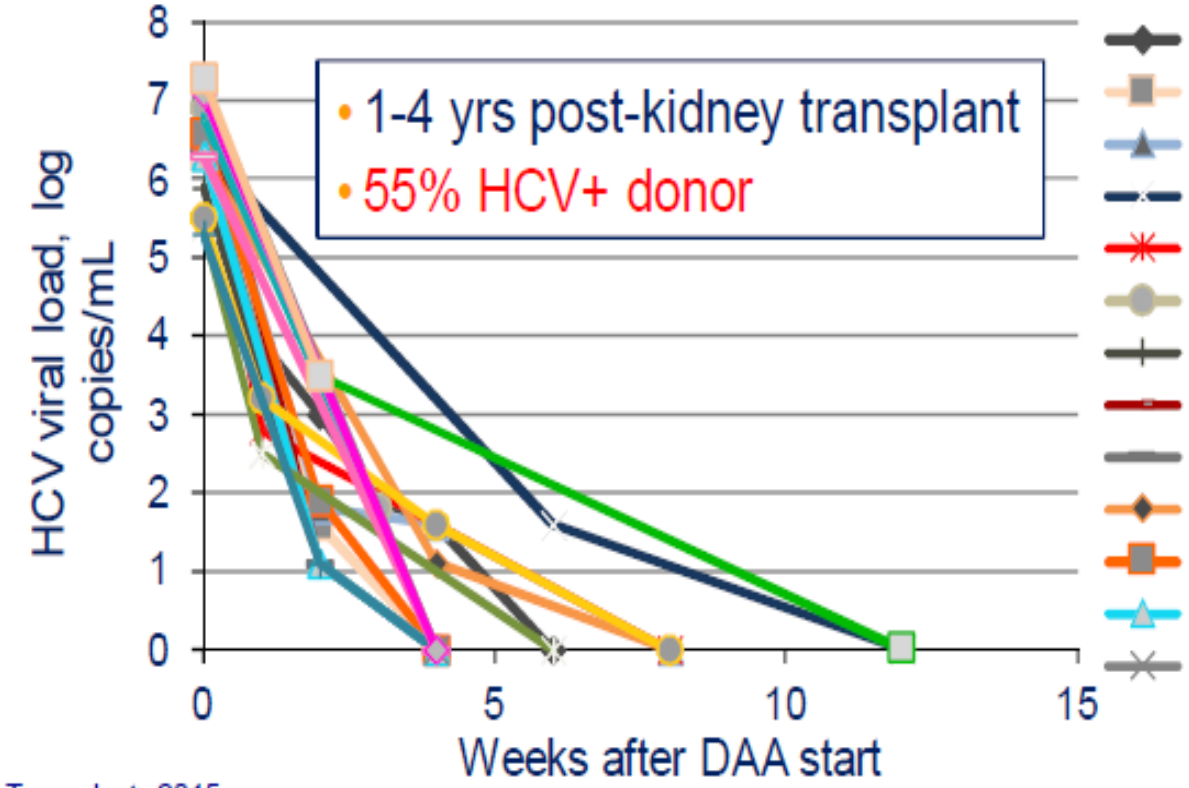
- Mostly curable
- Slow liver disease progression
- Reduce transplant complications: Recurrent disease
- Avoid post-transplant drug-drug interactions
- Public health concerns e.g. HD unit transmission

Immunosuppressive treatment with concurrent hep C treatment

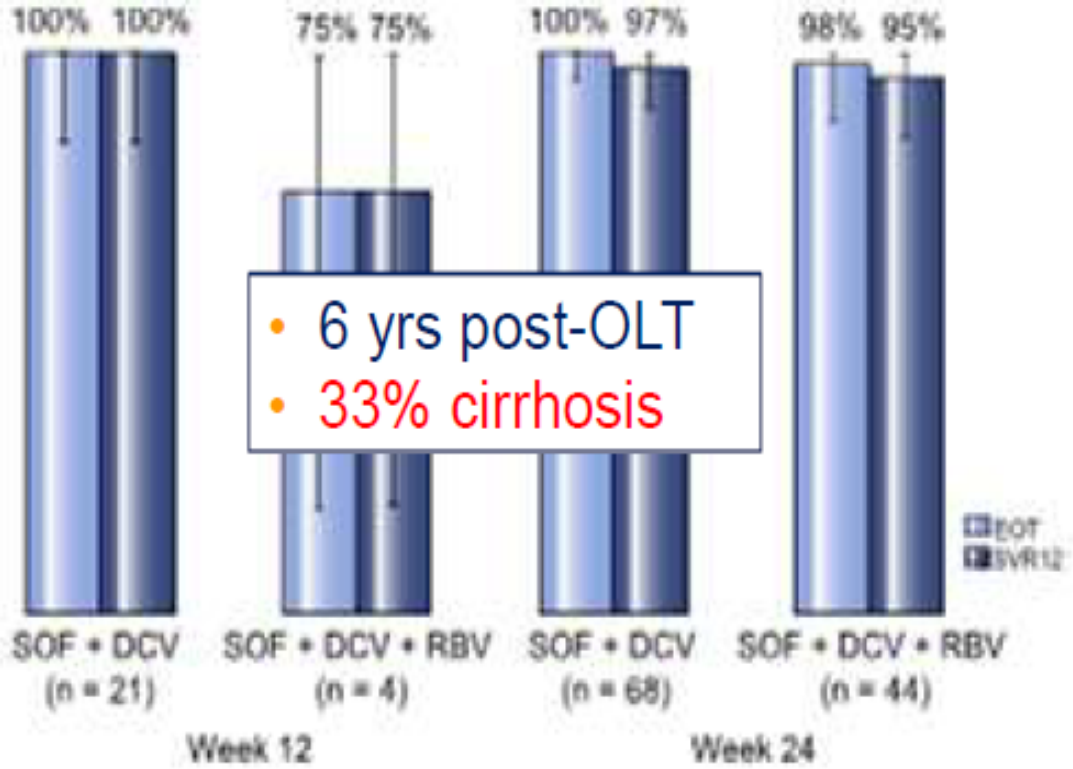
- Beware of cyclosporine and hepatitis medication interactions
- Some regimens have worse drug interactions than others

Why Treat Post-transplant with DAAs

- Highly efficacious
- Not contraindicated (unlike IFN)



Am J Transplant, 2015



Coilly *et al*, J. Hepatology 2016

Treatment after transplant

- All patients with HCV infection should receive antiviral therapy after kidney transplant ideally while the eGFR is greater than 30
  - Should wait until immunosuppressive regimen is stable
- No dose adjustment for renal function is required in patients with eGFR greater than 30 for the direct-acting antiviral agents

Why Treat Post-transplant with DAAs

- Highly efficacious
- Not contraindicated (unlike IFN)
- Can use kidney from HCV-infected donor
  - Increase organ utilization
  - Shorter waiting time
  - Longer life
  - Lower cost

Recipient HCV: Treat Early vs Late

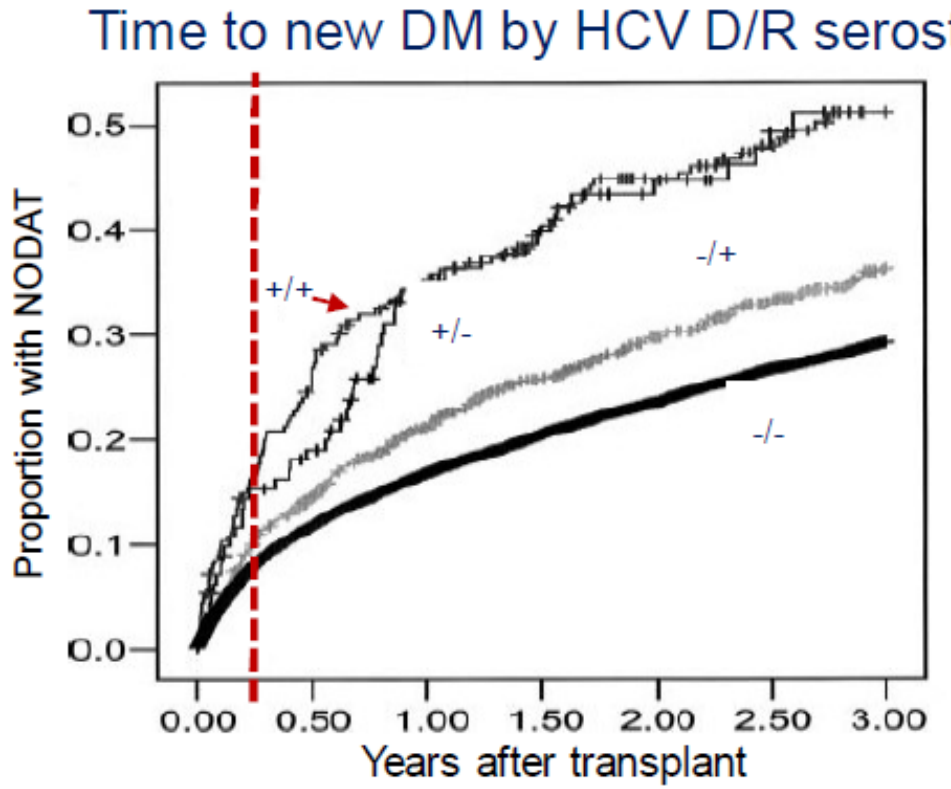
Early

Pros

- Prevent complications of HCV?
  - New DM
  - AMR
  - Recurrent disease (GN or liver)

Cons

- Early drug-drug interactions



Abbott et al, J Am Soc Nephrol, 2004

Recipient HCV: Treat Early vs Late

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Drug Interaction Charts

Do Not Coadminister | Potential Interaction | No Interaction Expected | No Clear Data

Do Not Coadminister | Potential Interaction | No Interaction Expected | No Clear Data

Results Key

	Daclatasvir	Elbasvir/Grazoprevir	Ledipasvir/Sofosbuvir	OBV/PTV/r + DSV	Velpatasvir/Sofosbuvir
Azathioprine	◆	◆	◆	◆	◆
Ciclosporin	◆	●	◆	■	◆
Daclatasvir		●	◆	●	●
Eculizumab	◆	◆	◆	◆	◆
Elbasvir/Grazoprevir	●		●	●	●
Ledipasvir/Sofosbuvir	◆	●		●	●
Mycophenolate	◆	◆	◆	■	◆
OBV/PTV/r + DSV	●	●	●		●
Sirolimus	◆	■	◆	■	◆
Tacrolimus	◆	■	◆	■	◆
Velpatasvir/Sofosbuvir	●	●	●	●	

Recipient HCV: Treat Early vs Late

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Pros

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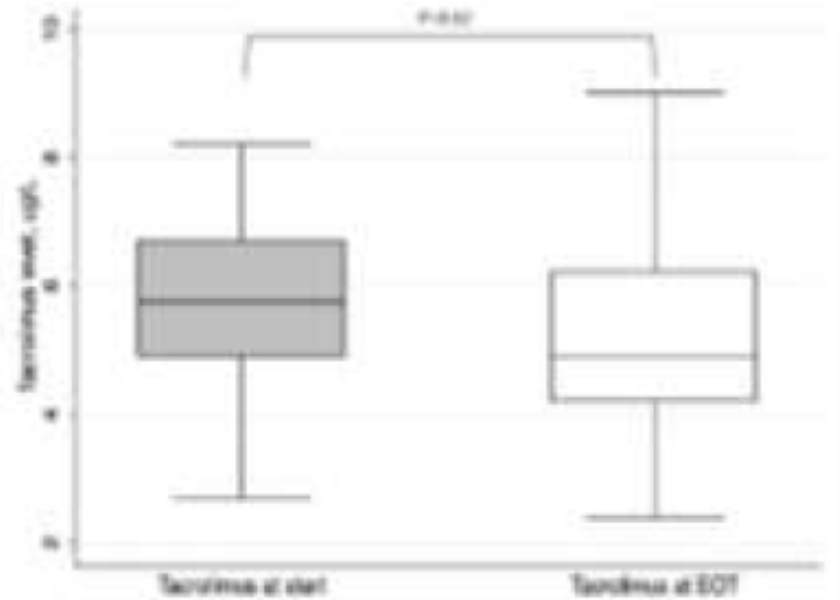
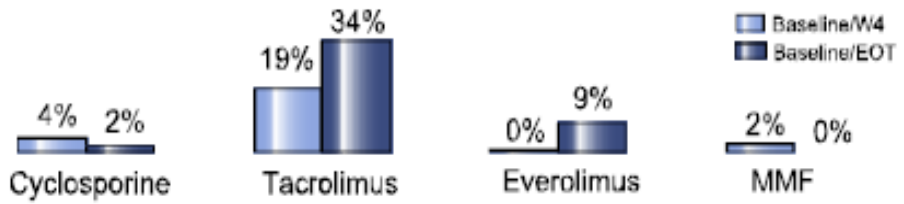
  - Recurrent disease (GN or liver)

Cons

- Early drug-drug interactions
- Effect on drug levels
- Impaired kidney function





Sawinski *et al*, Am J Transplant, 2016; Coilly *et al*, J. Hepatology 2016

Recipient HCV: Treat Early vs Late

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Cons

- Early drug-drug interactions
- Effect on drug levels
- Impaired kidney function
- Genotype superinfection

Drug	Metabolized	Renal dosing
Sofosbuvir	Renal	CrCl > 30 ml/min
Ledipasvir	Hepatic	Unknown
Grazoprevir	Hepatic	No restrictions
Elbasvir	Hepatic	No restrictions
Daclatasvir	Hepatic	No restrictions
Simeprevir	Hepatic	CrCl > 30 ml/min
Paritaprevir	Hepatic	No dose adjustment
Ombitasvir	Hepatic	
Dasabuvir	Hepatic	

Recipient HCV: Treat Early vs Late

Early

Pros

- Prevent complications of HCV?
  - New DM
  - AMR
  - Recurrent disease (GN or liver)

Cons

- Early drug-drug interactions
- Effect on drug levels
- Impaired kidney function
- Genotype superinfection

Later

Pros

- Wait until stable
  - Superinfection detected by 3-4 mos
  - Improved kidney function
  - Ventilator issues resolved
- Drug levels may be less critical

Cons

- Too late to prevent complications

Recipient HCV: Treat Early vs Late

- Who will treat
  - Hepatologists
  - Nephrologists
  - Transplant IDs
- Emergence of pan-genotypic agents
- Re-treatment?
  - Pre/Post-transplant
  - Post/Post-transplant
- Insurance barriers

Direct acting antiviral(DAAs)

SOFOSBUVIR

- 80% of sofosbuvir is renally excreted
- Can not be used in GFR < 30 ml/min

ledipasvir

- Biliary excretion is the major route of excretion

Simeprevir

- Eliminated by biliary excretion
- No dose reduction in kidney disease

Daclatasvir

- Eliminated in faeces (90%)
- No dose reduction in kidney disease

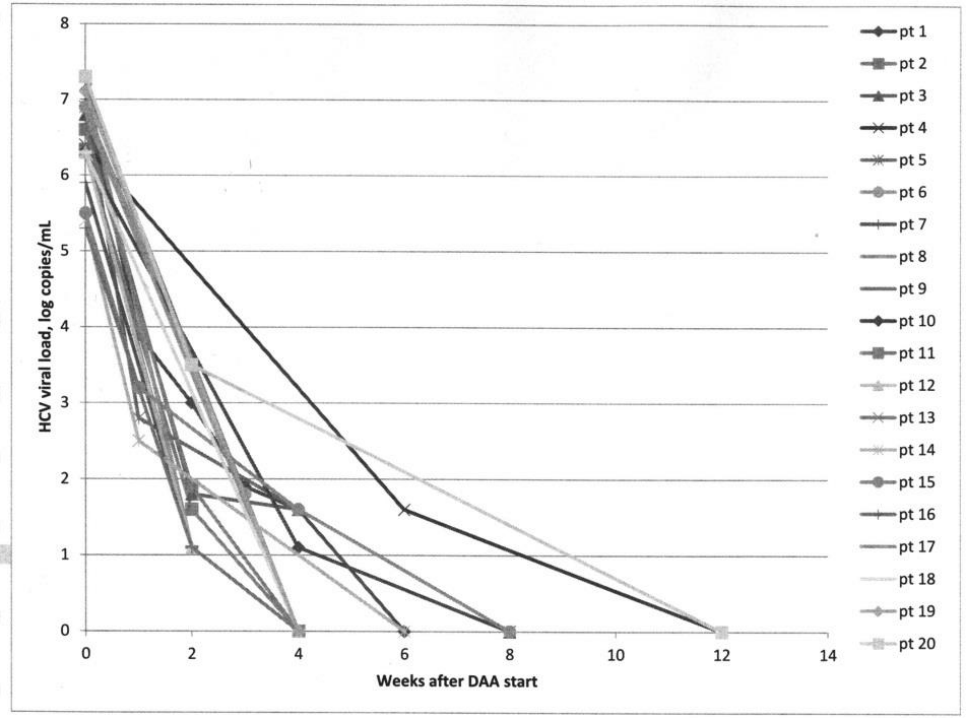
Treatment of Patients with Post organ Transplantation

SOF/DCV ± RBV for 24 weeks

Successful treatment of Hepatitis C in renal transplant recipients with direct-acting antiviral agents

- **20 HCV (+) / RNA (+) KT patients treated with interferon-α- free therapy**
  - **88% were infected with genotype 1**
  - **50% had biospsy-proven advanced hepatic fibrosis (Metavir F3 or F4)**
  - **DAA treatment was initiatied 888 days post-KTx ; the most commonly used regimen was sofosbuvir 400 mg/d in combination with simeprevir150 mg/d**
  - **All patients cleared the virus while on therapy**
  - **100% achieved a sustained virological response at 12 weeks after completion of DAA therapy**

Kinetics of HCV viral load clearance on DAA therapy.



Sawinski D et al, AJT nov 2015

Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection AfterKidney Transplantation

- 29 HCV (+) / RNA (+) KTx patients were given for 12 (n=19) or 24 weeks (n=6) sofosbuvir + another antivral drug.
  - 88% of patients had no detectable HCV/RNA 4 weeks after starting DAA therapy
  - 100% of viral clearance at end of viral therapy
  - 100% sustained virological response 12 weeks after completing DAA therapy.

Kamar N et al. AJT 2015

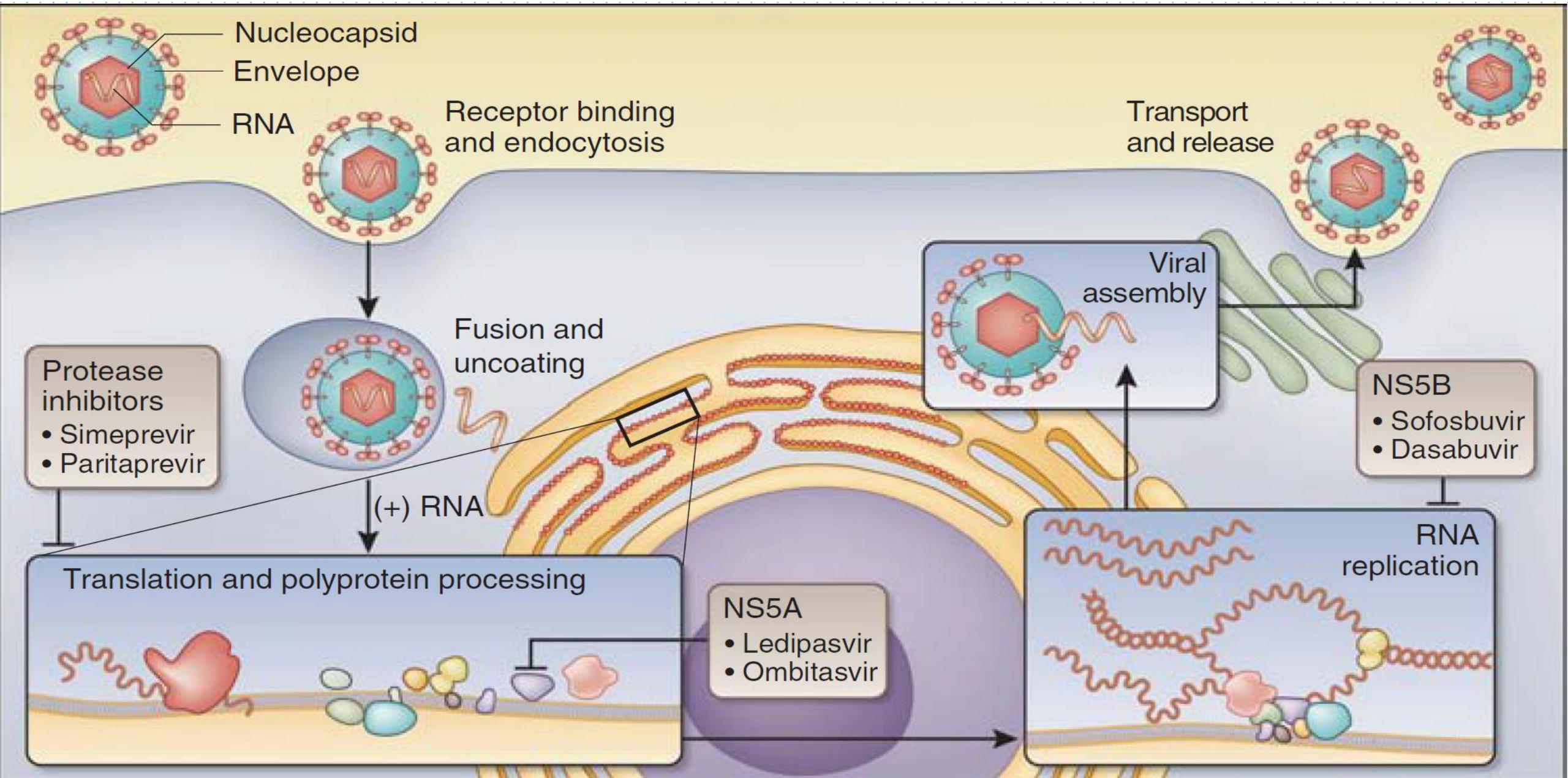
Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection AfterKidney Transplantation

Combinations of DAAs and treatments

HCV genotype	N	DAA combination	Duration (wk)
1a	2	Sofosbuvir + ledipasvir	12
	1	Pegylated interferon + ribavirin + sofosbuvir	24
	1	Sofosbuvir + simeprevir	12
1b	5	Sofosbuvir + simeprevir	12
	5	Sofosbuvir + ledipasvir	12
	3	Sofosbuvir + daclatasvir	24
	1	Sofosbuvir + ledipasvir + ribavirin	24
	1	Sofosbuvir + simeprevir + ribavirin	12
2	2	Sofosbuvir + ribavirin	12
3	1	Sofosbuvir + ribavirin	24
4	2	Sofosbuvir + ledipasvir	12
	1	Sofosbuvir + daclatasvir	12

Kamar N et al. AJT 2015

Hepatitis C virus life cycle and mechanisms of action of direct-acting antivirals




Thank you
all for your
attention