HBV, HCV, HIV and Kidney Transplantation

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Objectives

- Prevalence of hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) in ESRD population
- Transplant evaluation of patients with these viral infections
- Kidney transplantation in patients with HBV, HCV or HIV
  - Immunosuppression
  - Outcomes
  - New developments

HBV, HCV, HIV Infections

- Chronic HBV, HCV or HIV infections: were relative contraindications to kidney transplant in the past
- Concerns:
  - Effects of immunosuppressive drugs on viral replication-acceleration of liver injury and progression to hepatocellular failure/death
  - Development of *de novo* glomerulonephritis in the graft
  - Serious opportunistic infections/malignancy

Case #1 (HBV)

- 33 year old Asian male, on dialysis since 2014, blood group B
- Has IgA nehropathy and he is **hepatitis B surface antigen positive**
- Came in for kidney transplant evaluation
- No potential living donors
- Has been on Entecavir
- HBsAg positive, HBsAb negative, HBcAb positive, HBV viral load 0

Case #2 (HCV)

- 56 yo AA male; on dialysis since 1/2017; blood group B
- Has history of diabetes, hypertension, and **hepatitis c**
- Came in for kidney transplant evaluation
- No potential living donors

Case #2-(HCV)

- HCV viral load 6.3 log-never been treated
- s/p liver biopsy: stage 2 fibrosis, no evidence of cirrhosis; no varices
- Liver enzymes, serum albumin and platelets are normal
- Waiting time for a DD kidney in the region: **average 5 years**

Case #3 (HIV)

- 35 yo female with ESRD due to lupus- on dialysis since 2015
- Has history of HIV-diagnosed in 2006; has history of HSV infection; PRA 20%; HIV viral load undetectable
- Would like to be evaluated for a kidney transplant

Hepatitis B (HBV)

- The prevalence of chronic HBV infection: differs between regions
  - Low rates (≤2%) in Western Europe and the U.S
  - Intermediate rates (2–8%) in Mediterranean countries and Japan
  - High rates (8–20%) in Southeast Asia and Sub-Saharan Africa
- In 2017, approximately 257 million people with chronic hepatitis B virus infection
- Successful vaccination in CKD/ESRD patients, improved infection control in dialysis units, and widespread use of EPO rather than blood transfusions for anemia

HBV Serologic Markers
Consensus Guidelines

- Positive HbsAg/HBV DNA/HbeAg: active infection
- Positive HbcAb IgM: a marker of acute or reactivated infection
- Positive HbsAb: immunity (anti-Hbs>10 IU/mL protective)
- Positive HbcAb: in the absence of HBsAg, could be a false positive result, past exposure with resolved infection, or rarely chronic HBV infection with detectable HBV DNA

Huprikar S, et al. AJT 2015

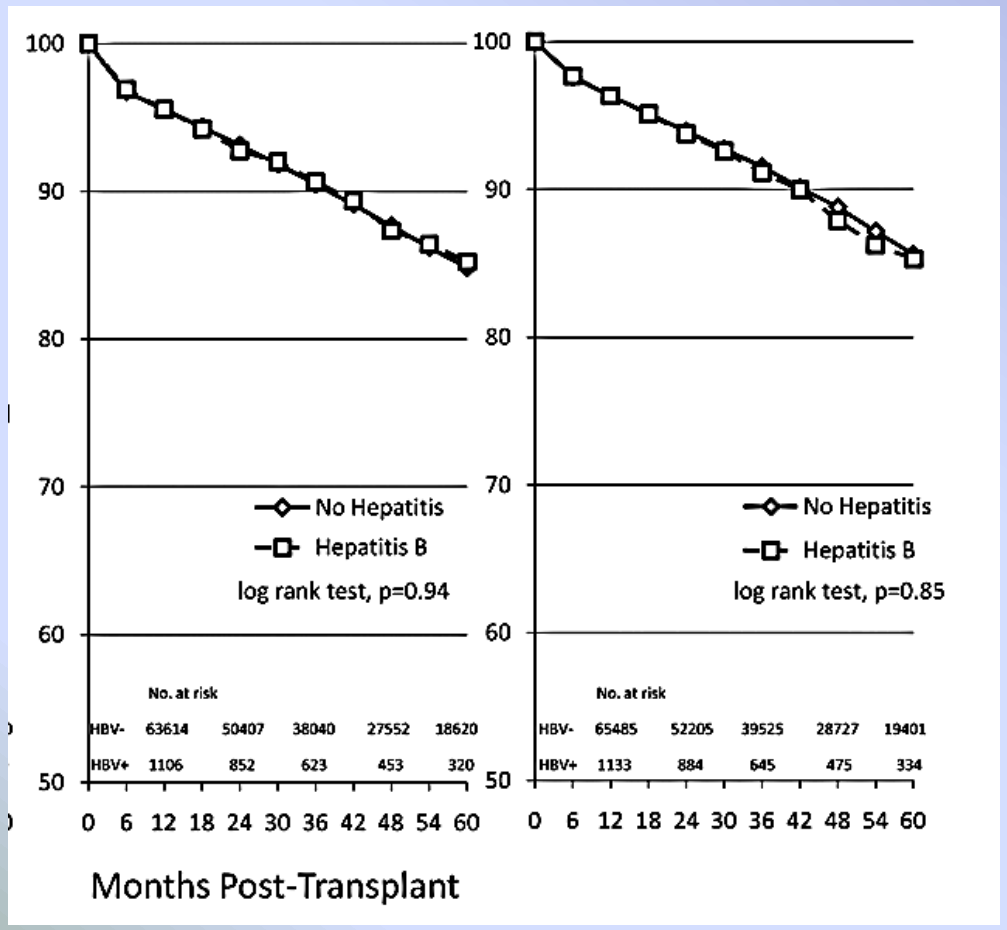
Complications after Transplantation

- HBV reactivation/chronic hepatitis
- Massive liver necrosis due to fulminant hepatitis
- Severe cholestatic hepatitis
- HBV-related membranous nephropathy
- Hepatocellular carcinoma

Transplant Evaluation of Patients with HBV

- All candidates should be screened
- Obtain serologies and HBV viral load
- All candidates who are HbsAg positive: must be referred to Hepatology
  - Most patients require a liver biopsy-to make sure that they do not have cirrhosis or portal hypertension
  - Assess the need for treatment

Impact of Pre-existing HBV Infection on Outcomes



- 1346 HBsAg+ recipients from UNOS database 2001-2007
- 5 yr death-censored **graft survival** 85.2% and **patient survival** 85.3% in HbsAg+; **no significant difference from HBV- patients**
- 5-yr cumulative incidence of **hepatic failure higher in HBV+ recipients** (1.3% *vs* 0.2%; $P < 0.001$)-still low, 5x risk of severe liver disease in HBV+ recipients

Reddy P, et al. CJASN 2011

Outcomes-Meta-analysis

- Ten observational studies with a total of 87,623 kidney transplant patients
- HBsAg-positive status was significantly associated with increased risk of mortality (2.5-fold) after kidney transplantation and also with increased risk of renal allograft failure (1.5-fold)
- Significant negative correlations between the risks of mortality and allograft failure and year of study, representing potential improvements in patient and graft survivals overtime

Thongprayoon C, et al. World J Hepatol 2018

HBV Therapies
Consensus Guidelines

- Effective HBV therapies have improved outcomes significantly
  - **Lamivudine** was the primary antiviral agent used for the treatment of chronic HBV both before and after transplantation
  - **New agents**: potent oral nucleoside analogs with a high genetic barrier to resistance such as **entecavir and tenofovir** (very low resistance rates (<1%) in treatment naive patients)

Huprikar S, et al. AJT 2015

Antiviral Treatments for HBV Infection

Drug	Anti-viral potency	Barrier to resistance	Side effects
Adefovir	+	++	Nephrotoxicity, diabetes insipidus, Fanconi syndrome
Lamivudine	++	+	Lactic acidosis, pancreatitis
Emtricitabine	++	+	Lactic acidosis, anemia, leukopenia
Telbivudine	+++	+	Neuropathy, myopathy, elevated creatinine kinase
Entecavir	+++	+++	Lactic acidosis, transaminitis
Tenofovir	+++	+++	Nephrotoxicity, Fanconi syndrome, lactic acidosis, osteomalacia

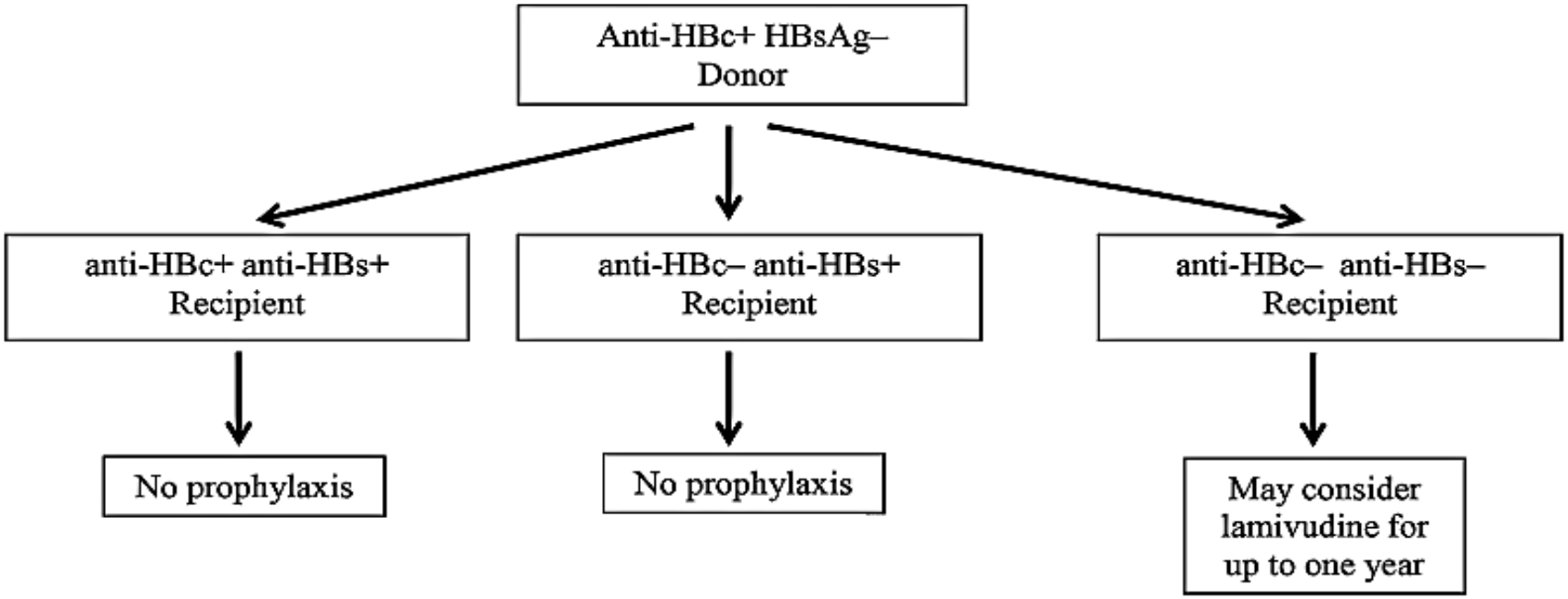
Use of HBV-positive Donors (HbsAg negative and anti-HbcAb positive)

- UNOS database from 1994-1999: multivariate regression analyses-neither donor nor recipient anti-HbcAb status influenced the risk of graft failure or patient death
- Anti-HbcAb positive kidneys resulted in a higher incidence of anti-Hbc antibody seroconversion; was not associated with a higher incidence of HbsAg detection

Fong TL, et al. Transplantation 2002

HBV-positive Donors

- The risk of HBV transmission from HBcAb-positive kidney donors is extremely low *Mahboobi N, et al. Tranpl Infect Dis 2012*
- Organs from HBsAg+ donors are not routinely transplanted in the U.S., but consideration should be made in endemic regions-potential donors are frequently HBsAg+; indefinite prophylaxis with ETV or tenofovir is recommended for all recipients



Algorithm for use of non-liver grafts from anti-HBc+ donors in recipients without chronic HBV.

- HBV vaccination is recommended for all non-immune (anti-Hbs antibody negative) transplant candidates and recipients
- HBV DNA with or without HbsAg should be monitored every 3 months for 1 year posttransplant
- HBIG is not recommended

Huprikar S, et al. AJT 2015

Recommendations

- All dialysis and renal transplant recipients should be screened for HBV markers
- All HBsAg-positive renal transplant recipients should receive ETV or TAF as prophylaxis or treatment
- HBsAg-negative, anti-HBc positive subjects should be monitored for HBV infection posttransplant
- HBsAg-negative, anti-HBc positive renal transplant recipients do not require prophylaxis or treatment
- All patients should be monitored for risk of disease progression and HCC

EASL 2017 Clinical Practice Guidelines, J Hepatol 2017

Hepatitis C (HCV)

- Estimated to affect approximately 170 million individuals worldwide
- Prevalence of HCV in patients with ESRD (worldwide 5% to 60%) far exceeds that of the general population (5-10% in the US)
- HCV-infected patients with CKD has an **increased mortality** and an **accelerated rate of progression** to ESRD
- Liver failure and hepatocellular carcinoma are the major long-term complications in chronic HCV-infected patients
- **Patients co-infected with HIV**-have an **increased mortality** and **overall worse prognosis**

Ladino M, et al. JASN 2016

Belga S, et al. World J Gastroenterol 2016

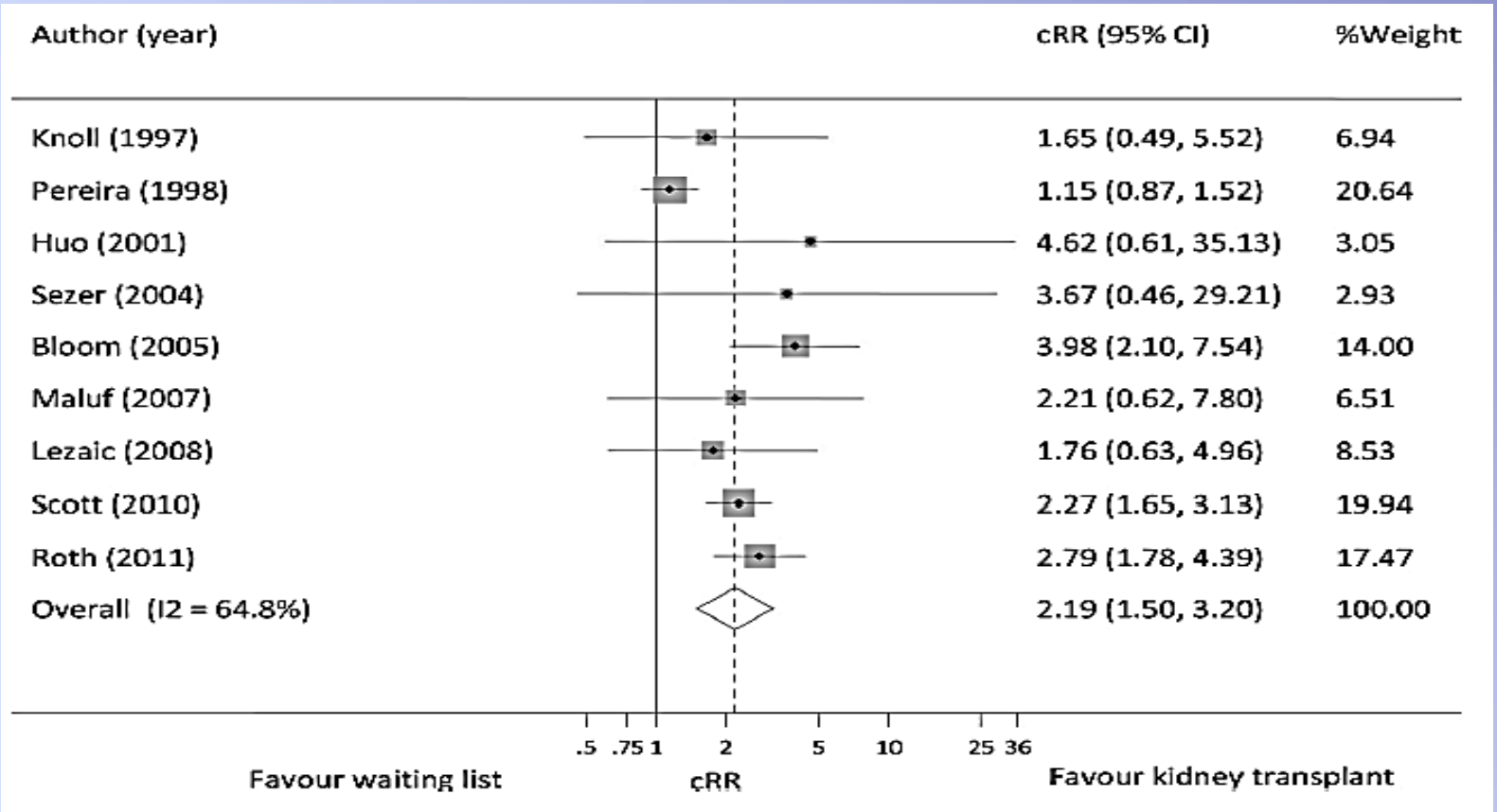
HCV and Kidney Transplant

- KDIGO (2008): all kidney transplant candidates should be tested for HCV infection-via antibody screening or nucleic acid testing (NAT)
- All patients who are HCV NAT positive should be referred to Hepatology for liver biopsy to assess the degree of hepatic disease severity prior to transplantation
- Updated recommendations from 2017-ongoing

KDIGO guidelines. Kidney Int 2008

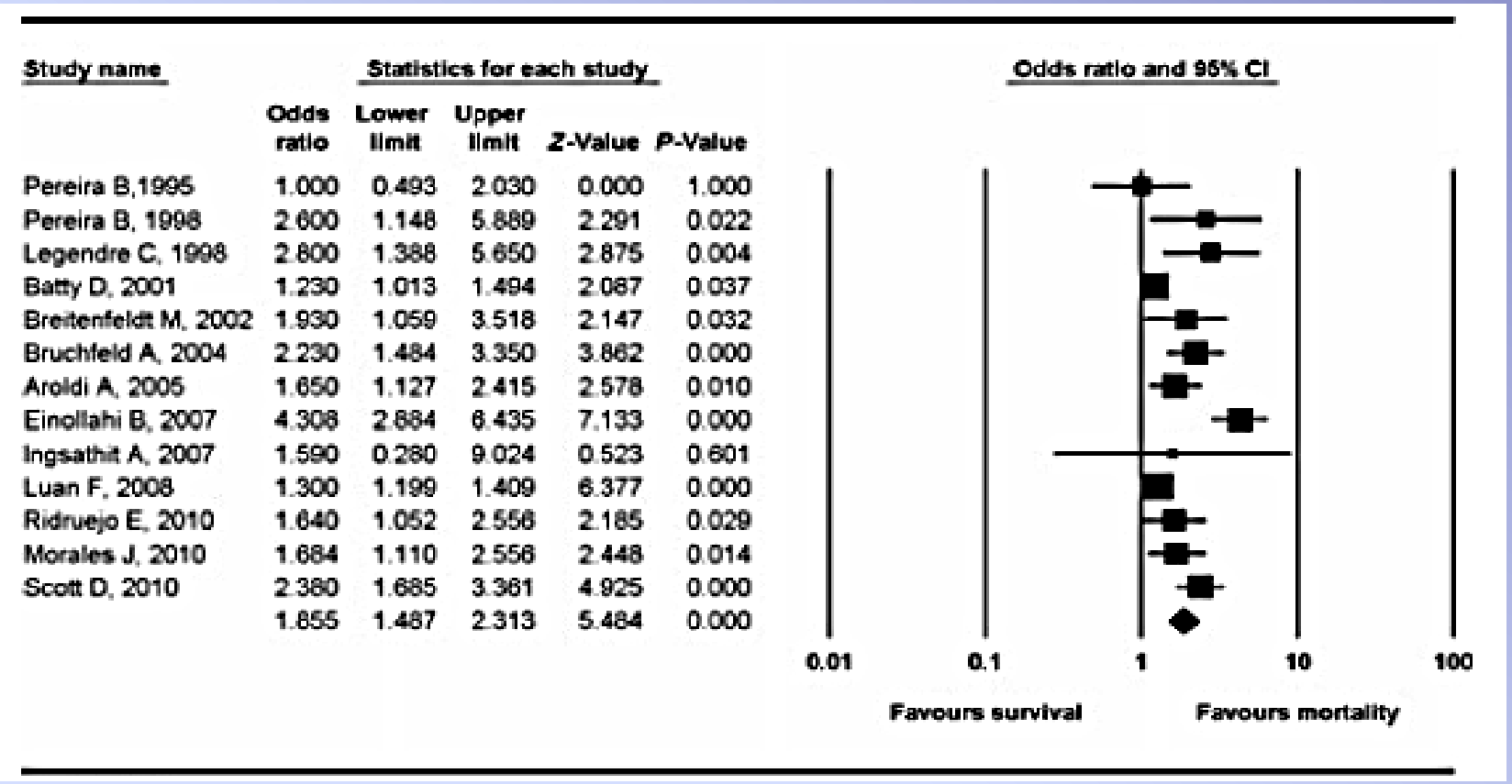
Transplant Evaluation of Patients with HCV

- Liver enzymes and HCV viral load correlate poorly with disease activity and liver fibrosis in advanced CKD
- Liver biopsy remains the “gold standard”
- Transient elastography (FibroScan) is emerging as a highly reproducible noninvasive technique-but liver stiffness is affected by central venous pressure



- Meta-analysis (overall mortality): Patients with HCV infection on waiting list had **2.19 times higher** risk for death than patients who had kidney transplantation
- **Transplant provides a survival benefit for HCV+ patients**
- Benefit of kidney transplantation-approx **55% lower risk of death at 5 years**
- Waiting list group had **higher risk of cardiovascular diseases**
- Survival advantage particularly in HCV patients **aged 45 years or older**

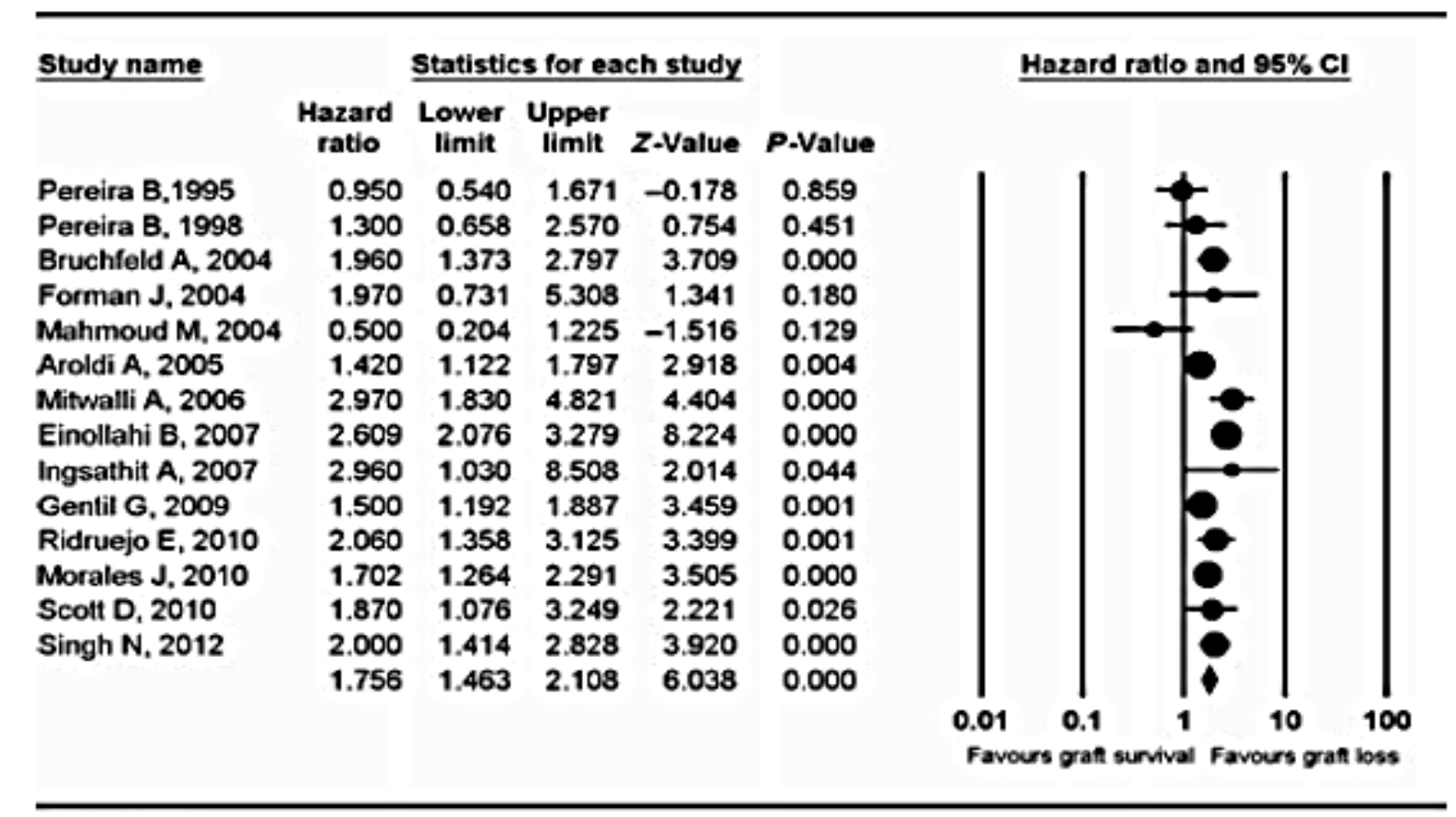
Ingsathit A, et al. Transplantation 2013



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	P-Value
Pereira B,1995	1.000	0.493	2.030	0.000	1.000
Pereira B, 1998	2.600	1.148	5.889	2.291	0.022
Legendre C, 1998	2.800	1.388	5.650	2.875	0.004
Batty D, 2001	1.230	1.013	1.494	2.087	0.037
Breitenfeldt M, 2002	1.930	1.059	3.518	2.147	0.032
Bruchfeld A, 2004	2.230	1.484	3.350	3.862	0.000
Aroldi A, 2005	1.650	1.127	2.415	2.578	0.010
Einollahi B, 2007	4.308	2.884	6.435	7.133	0.000
Ingsathit A, 2007	1.590	0.280	9.024	0.523	0.601
Luan F, 2008	1.300	1.199	1.409	6.377	0.000
Ridruejo E, 2010	1.640	1.052	2.556	2.185	0.029
Morales J, 2010	1.684	1.110	2.556	2.448	0.014
Scott D, 2010	2.380	1.685	3.361	4.925	0.000
	1.855	1.487	2.313	5.484	0.000

- Meta-analysis: 18 observational studies; 133,530 renal transplant récipients
- **Increased all-cause mortality in HCV+ patients**-due to cardiovascular dz
- **HCV+ patient outcomes are inferior to HCV-**
- Meta-regression showed that living donor rate had a favorable influence on patient (P = 0.031) and graft survival (P = 0.01), **diabetes** had a detrimental role **on patient survival** (P = 0.001)

Fabrizi F, et al. J Viral Hepatitis 2014



•The link between HCV and **lower graft survival after kidney transplant** was demonstrated irrespective of reference year, country of origin or size of the study group

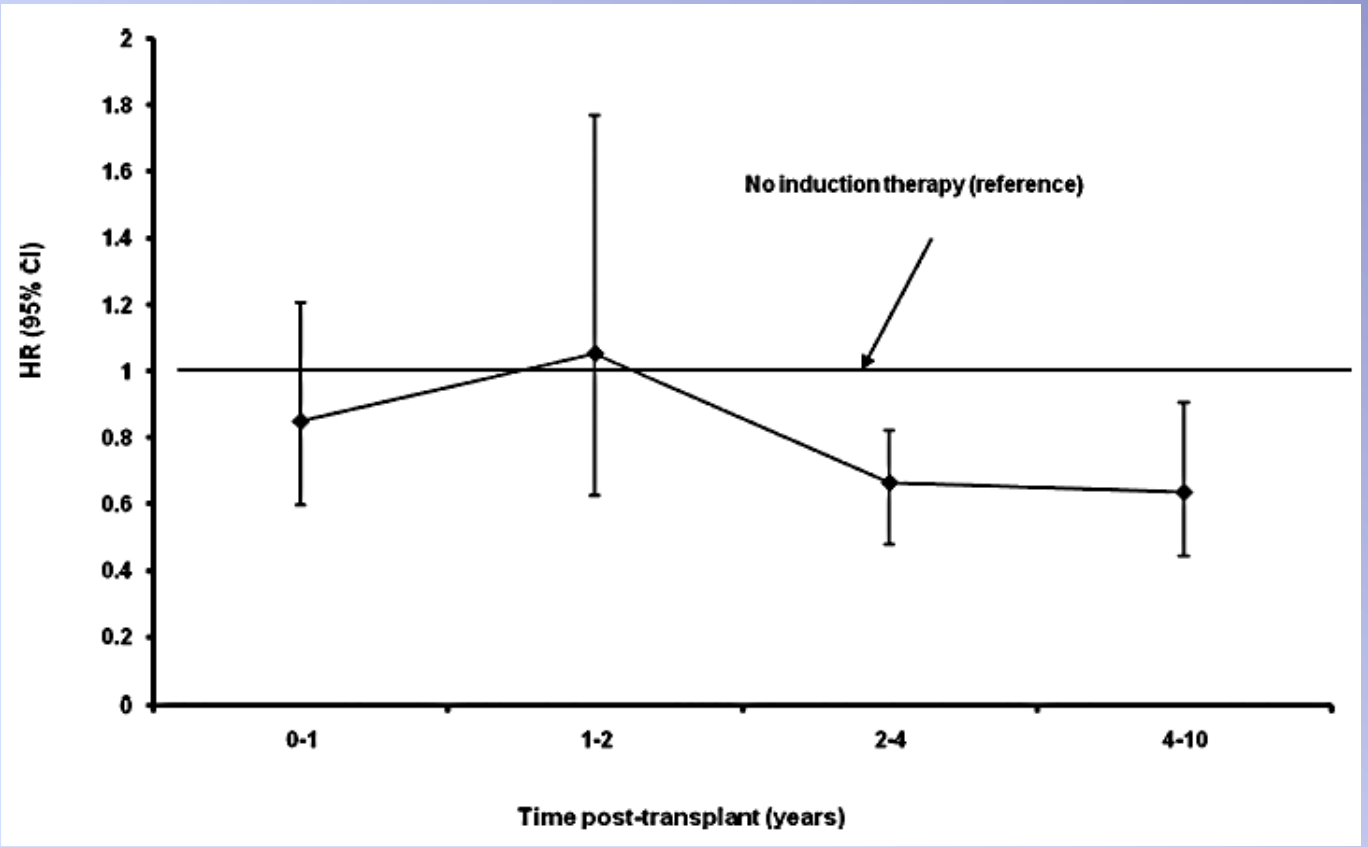
•**Causes of graft loss**: increased risk of new onset diabetes after transplant, recurrence of HCV-associated glomerulonephritis and chronic rejection/transplant glomerulopathy/TMA

Fabrizi F, et al. J Viral Hepatitis 2014

Immunosuppression in Patients with HCV

- UNOS database; 3708 HCV+ and 75,629 HCV- kidney transplant recipients
- Increased mortality risk for HCV+ kidney transplant recipients compared with HCV- recipients, particularly among younger age groups
- With HCV positive serology, the **use of induction therapy was not associated with an increased mortality risk**

Luan FL, et al. Transplantation 2008



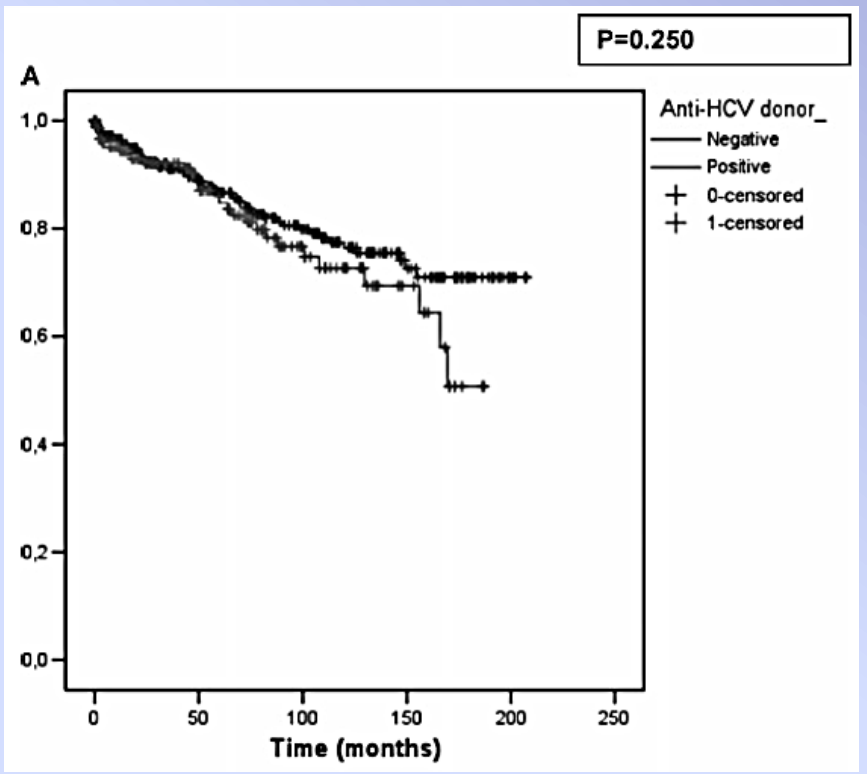
	HR (use vs. no use)	95% CI	*P*
Tacrolimus	1.03	0.79–1.35	0.83
Cyclosporin A	1.12	0.88–1.44	0.37
Mycophenolate mofetil	0.77	0.64–0.92	0.005
Sirolimus/everolimus	1.13	0.83–1.55	0.43
Steroid	1.16	0.79–1.71	0.44

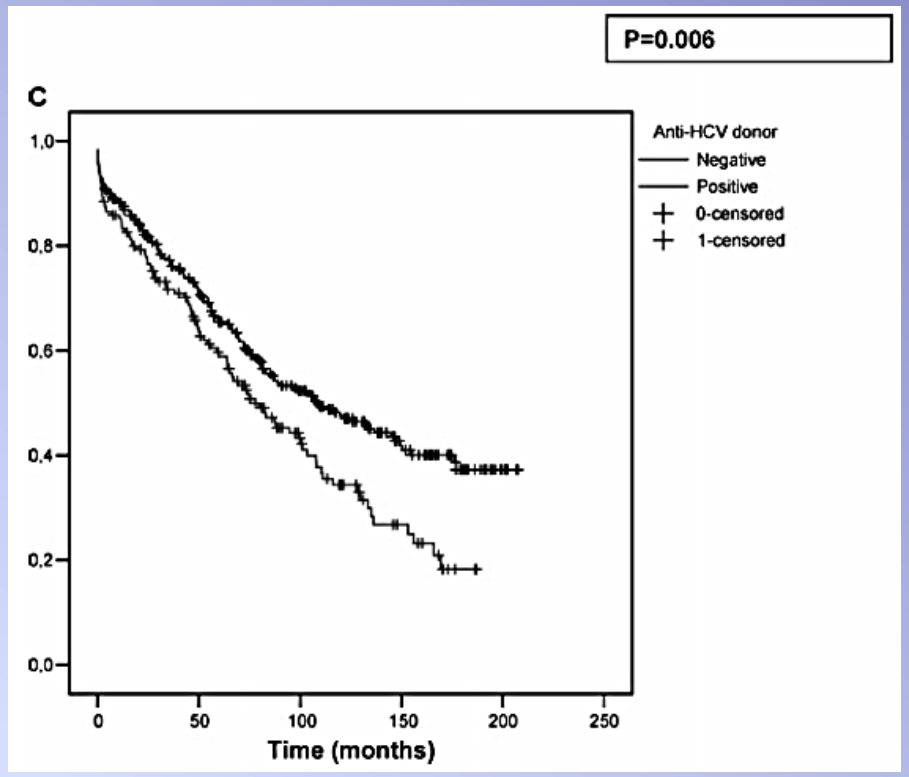
Luan FL, et al. Transplantation 2008

- A **lower mortality risk with induction** was observed beyond the first 2 years after tx
- The **choice of CNI (CsA or Tac)** and use vs nonuse of steroids had **no effect on patient mortality**
- The **use of MMF** (yes vs no) was associated with a significantly **reduced mortality rate**

Use of HCV-positive Kidneys

- HCV+ organs to HCV+ recipients
- Overall shortage of suitable donor kidneys/long waiting times; not every center accepts these kidneys
- Usually limited to recipients who are viremic with genotype 1
- Risk of superinfection with other HCV genotypes
- With new direct-acting antivirals to cure HCV, no need to limit to genotype 1 recipients





•162 **HCVR+** received a kidney from **HCVD+** (group 1) and 306 from HCVD− (group 2)

•**Similar patient survival:** Five-and 10-year patient survival was 84.8% and 72.7% in group 1 *vs.* 86.6% and 76.5% in group 2 (p = 0.250)

•**Decreased graft survival**: Five- and 10-year graft survival was 58.9% and 34.4% versus 65.5% and 47.6% respectively (p = 0.006)

•Decompensated chronic liver disease was similar: 10.3% versus 6.2%.

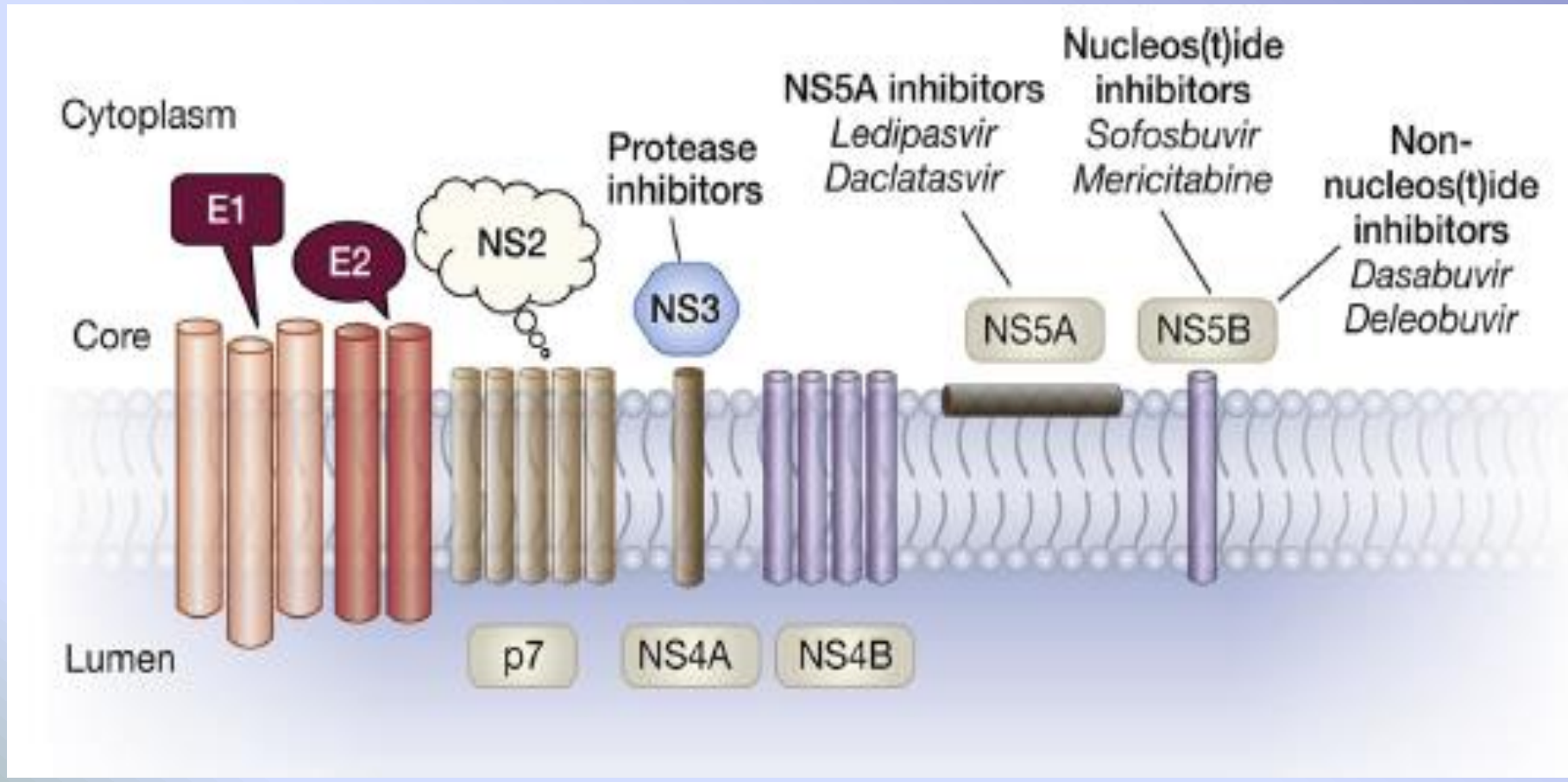
Morales JM, et al. AJT 2010

Treatment of HCV

- KDIGO guidelines: treatment of HCV in all kidney transplant candidates-interferon based; low response rate and poor tolerability
- Treatment with interferon after transplant is not recommended-increased rejection risk
- New interferon-free direct acting antiviral (DAA) regimens-cure rates up to 90% and efficacious posttransplant as well-new treatment recommendations are underway

KDIGO guidelines. Kidney Int 2008

DAA Agents for Treatment of HCV-Targeting the Essential Proteins for HCV Replication



•The HCV genome and target sites of action

Fabrizi F, et al. Kidney Int 2016

DAA-Based Regimens in HCV

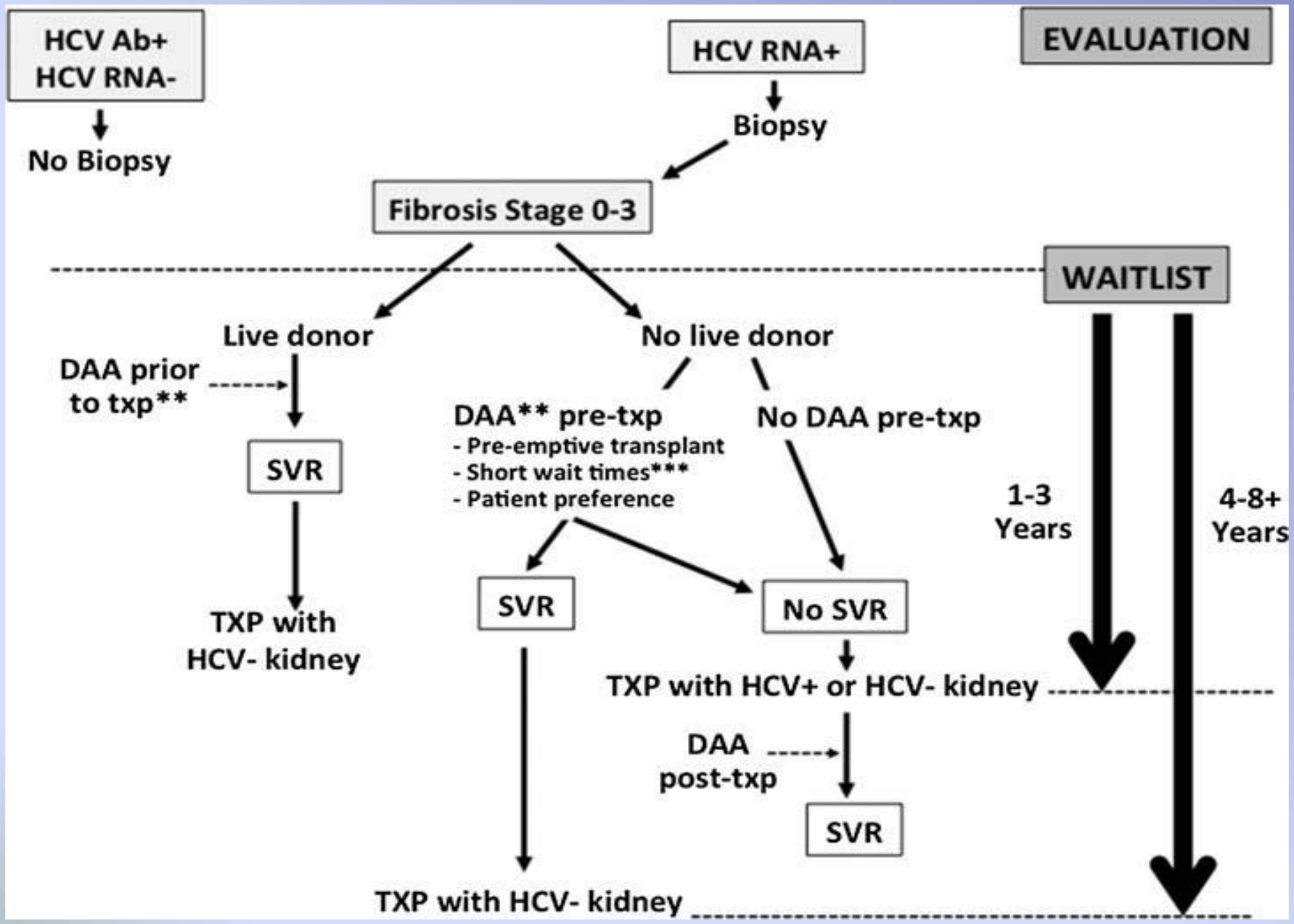
Treat pretransplant

- Can remain active on the waitlist during therapy
- Cure of HCV is likely
- Prevent disease transmission
- Avoids drug-drug interactions with immunos
- Possible decreased risk:
  - Progressive liver disease
  - Posttransplant GN
  - New onset diabetes posttransplant

Do not treat pretransplant

- Efficacious and safe posttransplant
- Potential drug-drug interactions
- Cure eliminates HCV+ organ
  - Longer waiting time
  - Increased kidney discard rate

Sawinski et al. Transplantation 2015



Sawinski et al. Transplantation 2015

Treatment of HCV

- Reactivation of **hepatitis B** infection following successful therapy of HCV infection with DAA-based therapy
- In patients with HCV and CKD, serum markers of HBV infection (HBsAg, HBV DNA) should be obtained prior to antiviral therapy

HCV Treatment

- The optimal timing of antiviral treatment: depends on the availability of a living donor or of an HCV+ kidney graft- shorter time to transplantation
- Issues: the extent of liver disease (severe disease calls for urgent DAA tx to halt worsening of liver disease+avoid the need for a liver transplant) and the HCV genotype (complexity of treatment in late CKD and dialysis)
- Awaiting the update of the KDIGO recommendations on HCV in CKD/posttransplant
- Patients might need to be treated if they have symptomatic vasculitis or if they are kidney recipients
- Patients with no significant fibrosis treatment may be postponed to the posttransplantation period

Jaoul M, et al. Semin Dial 2017

Pol S, et al. NDT 2017

Table 3 Indications to treat HCV infection before or after transplantation

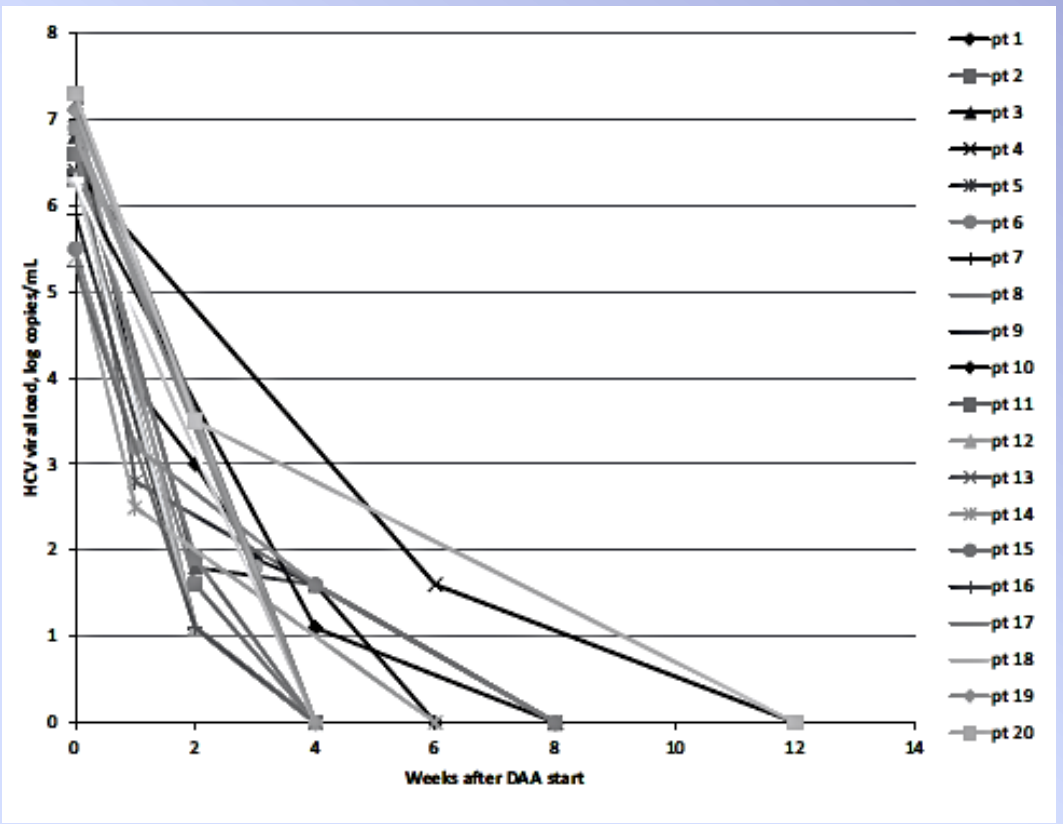
HCV treatment indicated *before* transplantation	HCV treatment indicated *after* transplantation
Transplant to be performed in a region where there is no difference in waiting time by accepting an HCV(+) kidney	Transplant to be performed in an area where wait time is expected to be shorter by accepting an HCV(+) kidney
Transplant candidates with live donor available only after 24 wk	Transplant candidates with live donor available in less than 24 wk
Compensated cirrhosis in patients with significant risk of liver disease progression	Decompensated cirrhosis or portal hypertension in simultaneous liver/kidney transplant (SLK) candidates
Increases organ discard rates	Improves organ utilization by increasing the donor pool
DAAs not available and only available treatment is interferon-based	Only sofosbuvir-based DAA regimens available
Severe HCV extrahepatic manifestations • Vasculitis (Mixed cryoglobulinemia syndrome) • Lymphoproliferative disorder	
Transplant center does not use HCV(+) kidneys	
Patient does not consent for HCV(+) kidney	
Decreases HCV transmission in dialysis centers	

CKD = chronic kidney disease; DAA = direct acting antiviral; HCV = hepatitis C virus.

Cohen-Bucay A, et al. Hemodial Int 2018

FDA Approval in 8/2017 (Glecaprevir and Pibrentasvir)

- (HCV) genotypes 1-6 without cirrhosis (liver disease) or with mild cirrhosis, including patients with **moderate to severe CKD or on dialysis**
- Adult patients with HCV genotype 1 infection who have been previously treated with a regimen either containing an NS5A inhibitor or an NS3/4A protease inhibitor but not both
- Total of 8 weeks; headache, fatigue and nausea
- Contraindicated in patients taking the drugs atazanavir and rifampin



DAAs Clear HCV Viremia Posttransplant

- 20 consecutive kidney recipients
- 88% were infected with genotype 1; 50% had biopsy-proven advanced hepatic fibrosis on most recent liver biopsy
- 60% had failed treatment pretransplant with interferon-based therapy

- All patients cleared the virus quickly while on therapy, and 100% have achieved a sustained virologic response at 12 weeks after completion of DAA therapy
- Most commonly used regimen: sofosbuvir 400 mg+simeprevir 150 mg daily

Sawinski, et al. AJT 2016

Use of DAAs Posttransplant

DAA	CYP3A4 Inhibition	Adjust Dose for eGFR < 30 mL/min
NS3 Protease Inhibitors		
Boceprevir	++	–
Telaprevir	+++	–
Simeprevir	+	–
Paritaprevir (ritonavir boosted)	+++	–
NS5A		
Ledipasvir	–	–
Ombitasvir	–	–
NS5B Nucleoside Inhibitor		
Sofosbuvir	–	++
NS5B N006Fn-Nucleoside Inhibitor		
Dasabuvir	+	–

- DAA-immunosuppressive drug-drug interactions are very important
- CNI levels have been shown to fluctuate during and even after DAA treatment is completed
- Need for careful monitoring of kidney function and CNI drug levels both during and after therapy
- Combined efforts by hepatologists and transplant nephrologists

Sawinski D, et al. Transplantation 2015

HCV-positive Donors and HCV-negative Recipients

- Limited data across all organ transplants
- Wait time for transplant might be shorter by accepting an organ from an HCV-infected donor
- People injecting drugs to be the main source of HCV-viremic donors in next decade
- US data suggest that currently there are 300–500 additional (unrealized) opportunities for donation among HCV-viremic deaths and the trend increasing

Levitsky J, et al. AJT 2017

Transplanting Hepatitis C Kidneys into Negative Kidney Recipients (THINKER)

- Open-label, single-group, pilot trial at the University of Pennsylvania; (ClinicalTrials.gov number, NCT02743897)
- 10 patients received HCV-infected kidneys (median age: 59 years; half were men and 2 were black; median time from eligibility to transplantation was 58 days)
- Patient had detectable HCV RNA on day 3 posttransplant

Goldberg DS, et al. NEJM 2017

THINKER STUDY

- Nine had HCV genotype 1a infection; none had identifiable NS5A resistance
- Patients were treated with elbasvir–grazoprevir posttransplant
- All recipients were cured of HCV (sustained virologic response 12 weeks after the end of treatment)
- Proteinuria (at an estimated level of 2 g per day of urinary protein excretion) in one patient (FSGS on biopsy)

Goldberg DS, et al. NEJM 2017

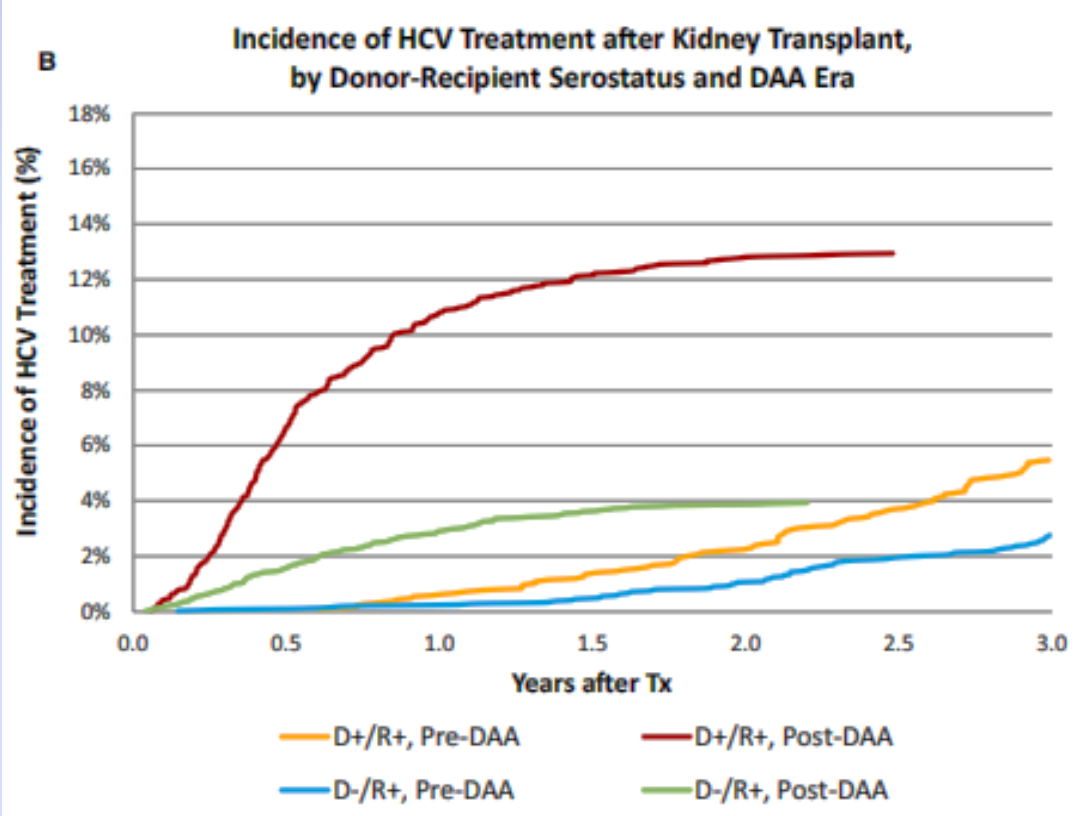
12-Month Outcomes of THINKER Study

- 20 HCV-negative transplant candidates-kidneys infected with genotype 1 HCV and received elbasvir–grazoprevir on posttransplant day 3
- Mean age: 56.3 years; 70% were male, and 40% were black
- All 20 participants achieved HCV cure
- Hepatic and renal complications were transient or were successfully managed.

Reese PP, et al. Ann Intern Med 2018

Impact of DAAs on Transplant Cost and Outcomes

- Data from the Scientific Registry of Transplant Recipients (SRTR)
- Integrated with national pharmaceutical claims (2007-2016) to identify HCV treatments before January 2014 (pre-DAA) and after (post-DAA)
- Treatment increased in D+R+ KT recipients (5.5% pre-DAA vs 12.9% post-DAA)
- DAAs reduced the risk of death after D+/R+ KT by 57% and graft loss by 46%



Axelrod DA, et al. Am J Transplant 2018

New Studies-HCV

- In the DAA era, candidates were 2.2-times more likely to list as willing to accept HCV+ kidneys and HCV+ recipients were 1.95-times more likely to have received an HCV+ kidney: **HCV+ kidneys were 3.7-times more likely to be discarded** than HCV- kidneys in the DAA era; the number of **centers performing HCV+ kidney transplants remains low**

  Bowring MG, et al. Transplantation 2018

- MAGELLAN-2, a phase 3, open-label trial: once-daily **glecaprevir/ pibrentasvir for 12 weeks**: well-tolerated and efficacious, ribavirin-free treatment for patients with chronic HCV GT1-6 infection who have received a liver or kidney transplant; Patients **without cirrhosis who were HCV treatment-naive (GT1-6)** or treatment-experienced (GT1, 2, 4-6; with interferon-based therapy with or without sofosbuvir, or sofosbuvir plus ribavirin)

  Reau N, et al. Hepatology 2018

AST Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation

- The efficacy, safety, and tolerability of DAA therapy make transplantation of HCV-viremic donors into HCV-negative recipients feasible to study
- The transplantation of organs from HCV-viremic donors into nonviremic recipients should only be conducted under IRB-approved protocols with multistep informed consent processes.
- Individuals likely to suffer clinical deterioration while waiting for an organ offer should be considered first, as the risk of remaining on the waitlist may outweigh the risk of donor-derived HCV infection

Levitsky J, et al. AJT 2017

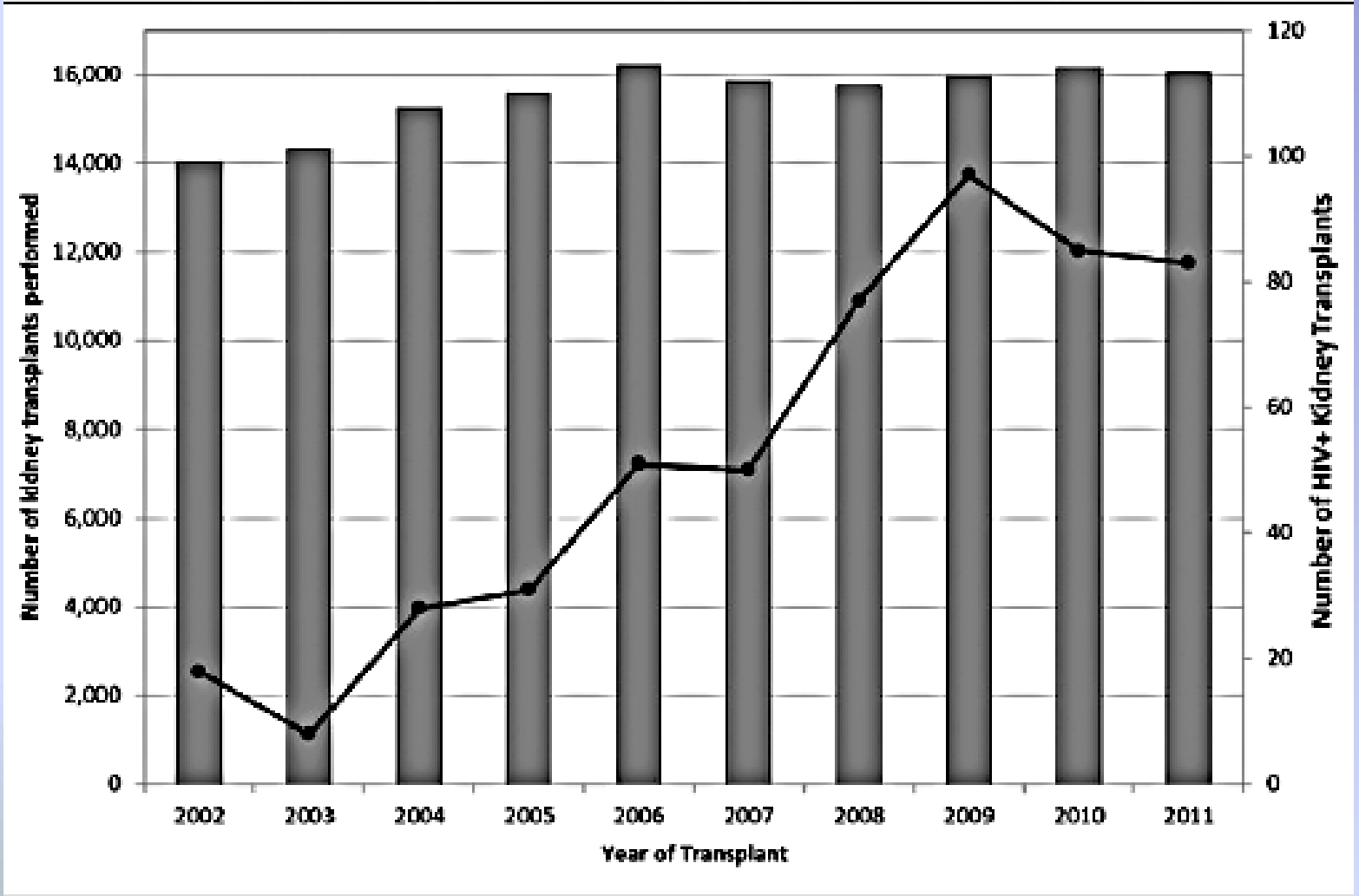
HIV and Kidney Transplantation

- With HAART use-decline in HIV-related deaths; number of patients living with HIV increased
- HIV is the third-leading cause of ESRD in African Americans after diabetes and hypertension
- Kidney transplantation is now offered as an acceptable treatment option for HIV+ ESRD patients
- High incidence of acute rejection
- Increased risk of delayed graft function

Evaluation of HIV Positive Candidates

- All patients are required to have:
  - CD4 count >200/mm^3
  - An undetectable HIV viral load on stable antiviral therapy for at least 6 months prior to transplant
  - No significant opportunistic infections
  - Evaluation by Transplant Infectious Diseases

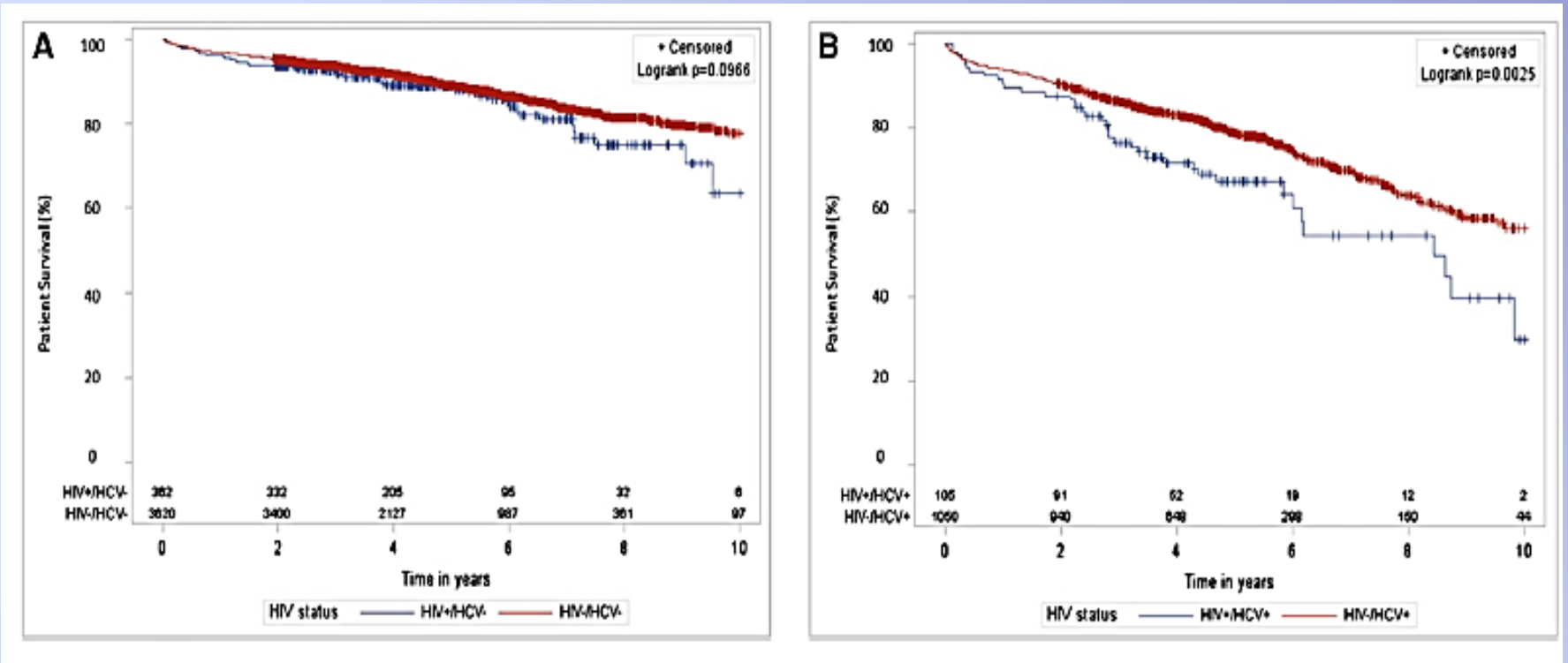
HIV and Kidney Transplantation



Locke J, et al. JASN 2015

Patient Survival-HIV+ Patients

(SRTR; 2002–2011; 510 adults, median follow-up:3.8 years)

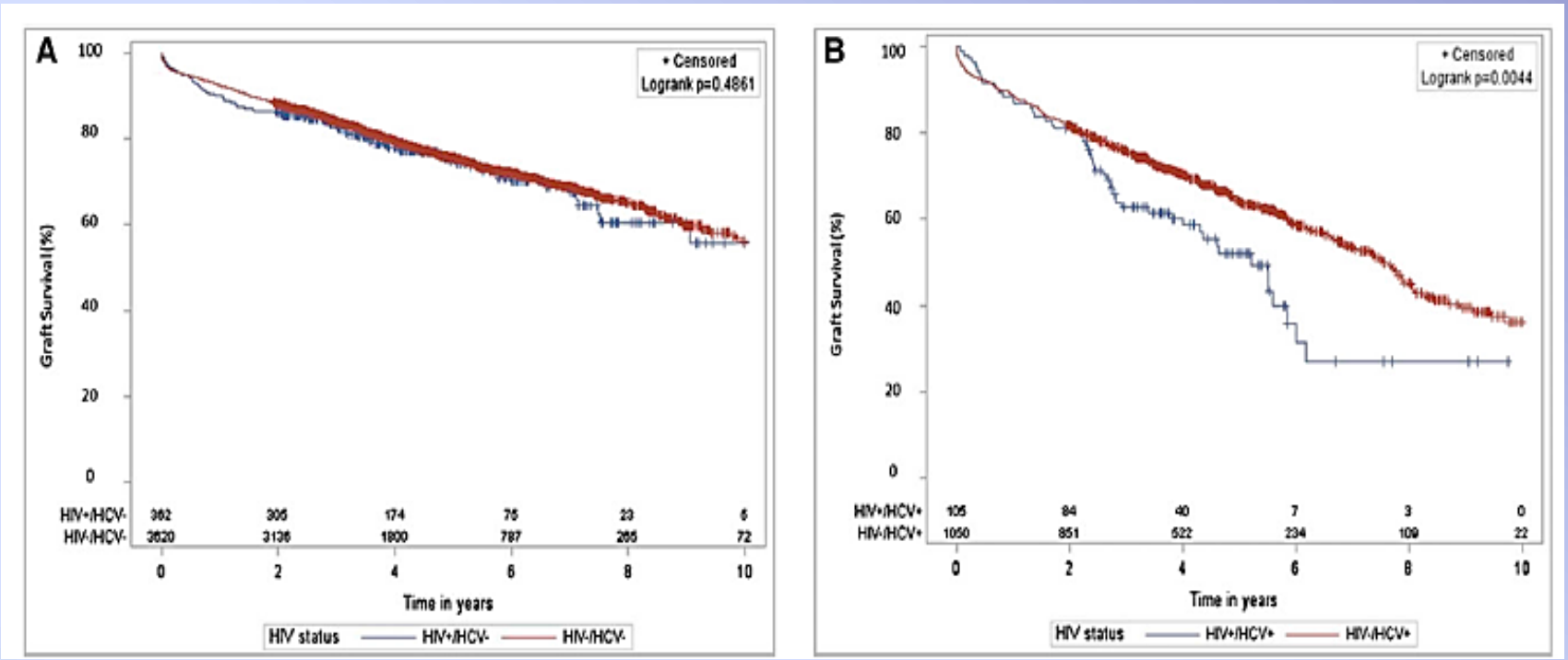


- **PS: similar for HIV-monoinfected recipients** and HIV negative/HCV negative controls both at 5 years and 10 years
- **HIV/HCV coinfected recipients had worse PS** compared with HIV-negative/HCV positive controls

Locke J, et al. JASN 2015

Graft Survival-HIV+ Patients

(SRTR; 2002–2011; 510 adults, median follow-up:3.8 years)



- **GS: similar for HIV-monoinfected recipients** and HIV negative/HCV negative controls both at 5 years and 10 years
- **HIV/HCV coinfected recipients had worse GS** compared with HIV-negative/HCV positive controls

Locke J, et al. JASN 2015

HIV-Choice of Immunosuppression

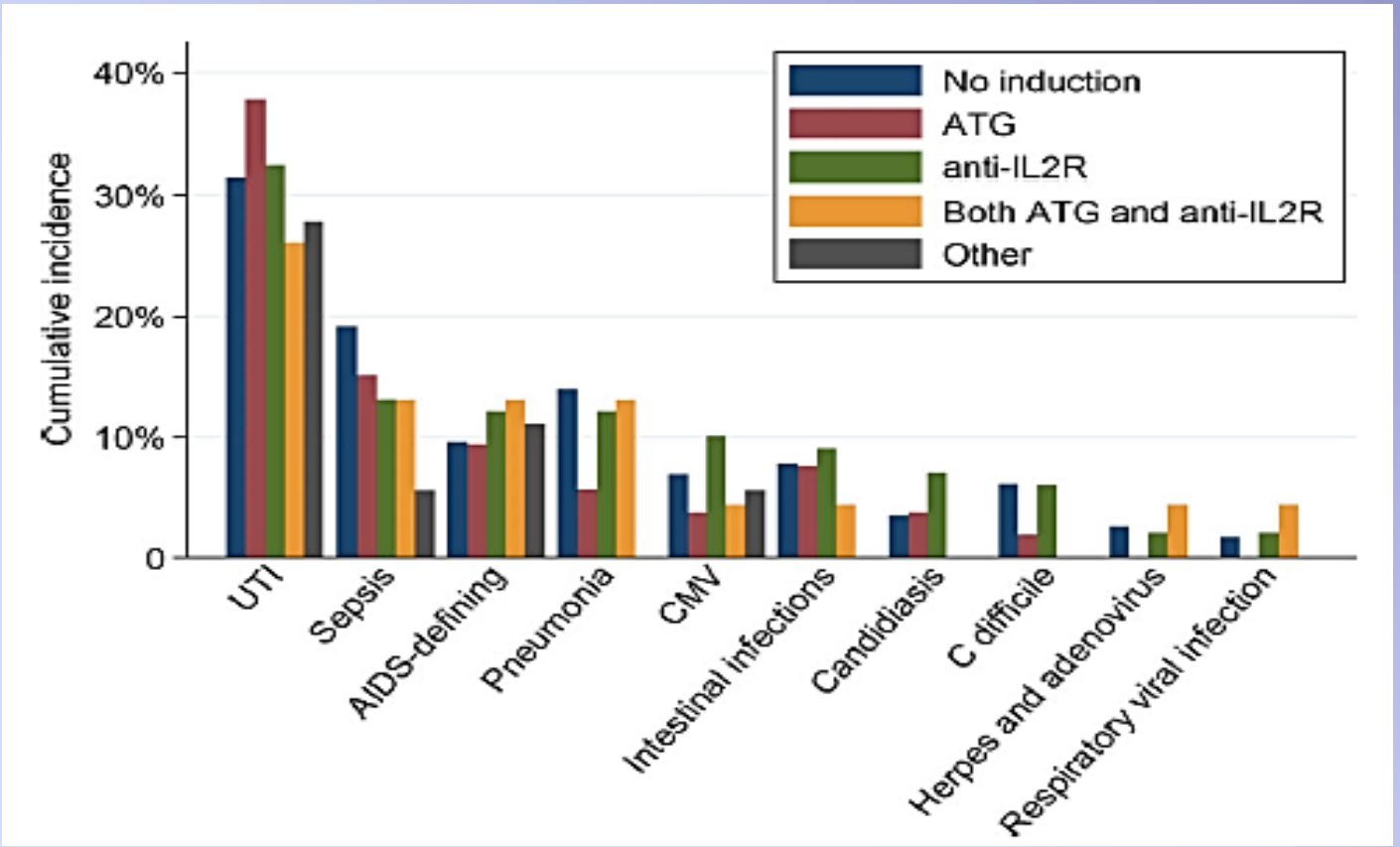
(SRTR: 2003-2011 data, 516 adults)

	HIV-negative (n=93,027)	HIV-positive (n=516)	*P*
Induction therapy			<0.001
None	21.4	35.1	
ATG	43.5	25.8	
IL-2 inhibitor	23.1	33.5	
Alemtuzumab	12.0	5.6	
Maintenance therapy			<0.001
Neither	5.0	9.3	
CNI-based	89.0	83.7	
Sirolimus-based	6.1	7.0	

	Rejection (1 year, RR)	95% CI	*P*
Induction therapy			
None	Reference		
ATG	0.39	0.18–0.87	0.02
IL-2 inhibitor	1.11	0.66–1.86	0.7
Alemtuzumab	1.6	0.8–3.2	0.2
Maintenance therapy			
CNI-based	Reference		
Sirolimus-based	2.15	1.2–3.87	0.01
Neither CNI or sirolimus-based	1.21	0.58–2.54	0.6

- HIV-positive patients had a **1.77-fold higher risk of AR** at 1 year compared with their HIV-negative counterparts (15% vs 8%)
- Among HIV-positive and HIV-negative patients receiving ATG induction therapy, the risk of AR was 1.16 and was not statistically different
- HIV-positive patients that received **ATG induction had a 2.6-fold or 61% lower risk of AR at 1 year** compared with no induction therapy
- Sirolimus-based therapy had a 2.2-fold higher risk of AR at 1 year

Locke J, et al. Transplantation 2014



- 830 HIV+ kidney transplant recipients (from 2000-2014, SRTR)
- HIV+ recipients who received induction spent fewer days in the hospital, had lower rates of DGF, less graft loss, lower rates of AR (with ATG induction), and a trend toward lower mortality
- **Induction therapy was not associated with increased infections**

Kucirka LM, et al. AJT 2016

Impact of Antiretroviral Therapies on Outcomes

- 332 HIV+ kidney transplant recipients
- Protease inhibitor (PI)-based regimens; associated with 1.8-fold increased risk of allograft loss (greatest risk observed in the first post-transplant year); 1.9-fold increased risk of death as compared to non-PI regimens
- Suggests-whenever possible recipients **should be converted to a non-PI regimen prior to transplant**

Sawinski D, et al. AJT 2017

HIV Medications and Immunosuppression

- Profound **drug-drug interactions**, especially with protease inhibitors
- Frequent drug level monitoring of CNIs
- New integrase inhibitors, CCR5-antagonists and fusion inhibitors cause significantly less pharmacokinetic interactions
- Must work closely with a Transplant Infectious Diseases expert

HIV and Kidney Transplantation

- Prospective, nonrandomized study of kidney transplantation in **27 HIV-infected patients** (CD4 count>200 and undetectable HIV RNA level)-all on antivirals; **received HIV positive kidneys**-results at 5 years
- Patient survival: 84% at 1 year, 84% at 3 years, and 74% at 5 years; graft survival: 93%, 84%, and 84%
- Rejection rates were 8% at 1 year and 22% at 3 years.
- HIV infection remained well controlled, with undetectable virus in blood after the transplantation

Muller E, et al. NEJM 2015

Kidney as a Reservoir for HIV after Transplantation

- Protocol biopsies from 19 recipients with HIV-1 who did not have detectable levels of plasma HIV-1 RNA at transplantation
- HIV-1 infected the kidney allograft in 68% of these patients; HIV-1 infection was detected in either podocytes predominately (38% of recipients) or tubular cells only (62% of recipients)
- **HIV-1 can re-infect kidney allografts after transplantation despite undetectable viremia**, and this infection might influence graft outcome
- Close monitoring of proteinuria is needed after transplantation

Canaud G, et al. JASN 2014

HIV Organ Policy Equity Act (HOPE Act)

- Enacted on November 21, 2013; reversed the federal ban on HIV-to-HIV transplantation
- Allows for the development and publication of criteria for research relating to transplantation of organs from donors with HIV into individuals who HIV positive
- The first HIV-to-HIV kidney and liver transplants were performed at Johns Hopkins in March of 2016
- As of November 2017, 22 transplant centers approved to perform HIV-to-HIV transplants in 10 UNOS regions
- Organ transplantation from suspected HIV false-positive donors is an unexpected benefit of the HOPE Act

HIV-Infected Waitlist Candidates

- 1636 HIV+ and 72,297 HIV- kidney transplantation candidates
- HIV+ waiting list candidates: more often **young** (<50 years old: 62.7% vs 37.6%), **men** (75.2% vs 59.3%, **black** (73.6% vs 27.9%), had **longer time on dialysis** (2.5 yrs vs 0.8), **coinfected with HCV** (9.0% vs 3.9%), and were **less likely to remain active** on the waiting list (37.7% vs 49.4%)

Locke JE, et al. Clin J Am Soc Nephrol 2017

HIV-Infected Waitlist Candidates

- Waitlist mortality among HIV+ candidates was similar compared with HIV- candidates
- Likelihood of living donor kidney transplantation was 47% lower
- A trend toward lower likelihood of deceased donor kidney transplantation
- Disparities in access to transplantation among HIV+ kidney waitlist candidates

Locke JE, et al. Clin J Am Soc Nephrol 2017

Retransplantation (re-KT) in HIV+ Recipients

- SRTR data (2004-2013); 22 HIV+ vs. 4127 HIV- negative adult re-KT
- HIV+ re-KT recipients: more commonly AA (63.6% vs. 26.7%, $p < 0.001$), infected with hepatitis C (31.8% vs. 5.0%, $p < 0.001$) and had longer median time on dialysis (4.8 years vs. 2.1 years, $p = 0.02$)
- HIV+ re-KT recipients: had **3.11-fold** increased **risk of death** and 1.96-fold increased risk of graft loss compared to HIV- re-KT recipients

Shelton BA, et al. AJT 2017

Case #1 (HBV)

- 33 year old Asian male, on dialysis since 2014, blood group B
- Has IgA nehropathy and he is **hepatitis B surface antigen positive**
- Came in for kidney transplant evaluation
- No potential living donors
- Has been on Entecavir
- HBsAg positive, HBsAb negative, HBcAb positive, HBV viral load 0

Case #1

-What would be your recommendation?

- A-Transplant is contraindicated in this setting; no listing
- B-Advise to accept only a living donor kidney
- C-List for DD kidney transplant if no cirrhosis on liver biopsy; lifelong entecavir use
- D-List for DD kidney transplant-no need for a liver biopsy; no need for prophylaxis after transplant

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Case #2 (HCV)

- 56 yo AA male; on dialysis since 1/2017; blood group B
- Has history of diabetes, hypertension, and **hepatitis c**
- Came in for kidney transplant evaluation
- No potential living donors

Case #2-(HCV)

- HCV viral load 6.3 log-never been treated
- s/p liver biopsy: stage 2 fibrosis, no evidence of cirrhosis; no varices
- Liver enzymes, serum albumin and platelets are normal
- Waiting time for a DD kidney in the region: **average 5 years**

Case #2-Hepatitis C

What would you recommend for this patient to do?

- A-List for DD kidney transplant and start treatment with interferon and ribavirin
- B-List for DD kidney transplant and start treatment with DAAs
- C-List for DD kidney transplant; no HCV treatment now; advise to accept HCV positive kidneys and offer HCV treatment with DAAs posttransplant
- D-Kidney transplant is contraindicated in this setting; no listing

Case #2-Hepatitis C

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- A-List for DD kidney transplant and start treatment with interferon and ribavirin
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- C-List for DD kidney transplant; no HCV treatment now; advise to accept HCV positive kidneys and offer HCV treatment with DAAs posttransplant
- D-Kidney transplant is contraindicated in this setting; no listing

Case #3 (HIV)

- 35 yo female with ESRD due to lupus- on dialysis since 2015
- Has history of HIV-diagnosed in 2006; has history of HSV infection; PRA 20%; HIV viral load undetectable
- Would like to be evaluated for a kidney transplant

Case #3 (HIV)

What is the correct statement in this setting?

- A-Transplant is contraindicated; no listing
- B-Advise to accept a kidney only from an HIV positive living donor
- C-List for DD kidney transplant if patient is stable on antiretrovirals
- D-List for DD kidney transplant-no need for her to be on any HIV medications

Case #3 (HIV)

What is the correct statement in this setting?

- A-Transplant is contraindicated; no listing
- B-Advise to accept a kidney only from an HIV positive living donor
- C-List for DD kidney transplant if patient is stable on antiretrovirals
- D-List for DD kidney transplant-no need for her to be on any HIV medications

Summary

- HBV positive recipient outcomes have improved significantly with vaccination and antiviral therapy
- HbcAb positive organs can be used safely in most patients
- Treatment of HCV with interferon-free regimens is now possible; long-term studies needed
- HIV+ kidney transplant recipients have excellent patient and allograft survival