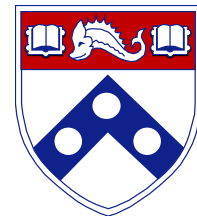


HEPATITIS C AND KIDNEY TRANSPLANTATION

EVALUATION AND RECIPIENT MANAGEMENT

Roy D. Bloom MD

Department of Medicine
University of Pennsylvania



Hepatitis C Infection in Kidney Transplantation

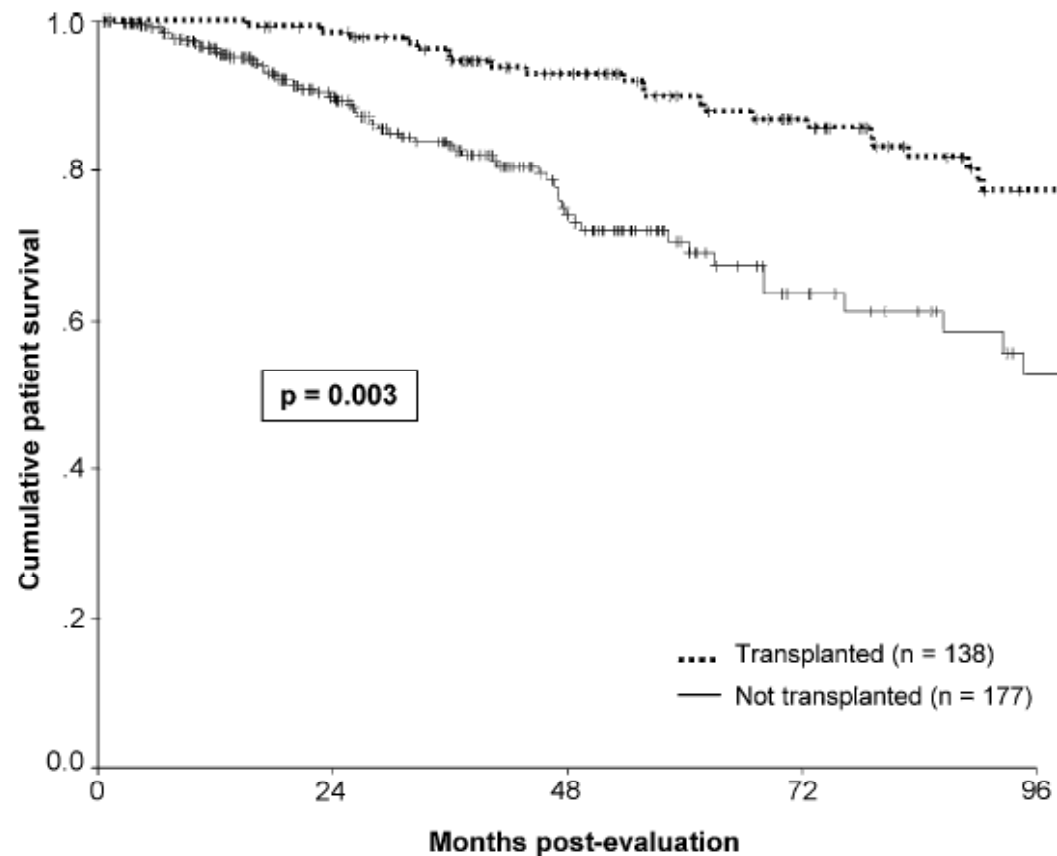
- **DIAGNOSIS AND SCREENING**
- **OUTCOMES**
 - **Waitlist**
 - **Post-transplant**
- **MANAGEMENT APPROACH**

Characteristics of Hepatitis C Infected Kidney Candidates

- Longer dialysis duration
- Prior transplants
- Drug/EtOH use
- Co-infection with HBV/HIV
- Ethnic minorities

Impact of Transplantation on Survival in HCV-infected ESRD Patients

- n=315 HCV+ pts listed 1992-2001



Screening for Hepatitis C in Kidney Transplant Candidates

- ALT
 - Not elevated in HD pts
 - Peaks & troughs
- Anti-HCV Ab
 - False negative
 - Poor humoral response
 - Prior vs active infection
- HCV RNA
- Liver biopsy
 - Gold standard

Spectrum of Liver Disease in HCV+ Kidney Transplant Candidates

Refs	# pts	Normal ALT (%)	Bridging Fibrosis (%)	Cirrhosis (%)
<i>Glicklich et al</i>	22	59	5	0
<i>Roth et al*</i>	152		5	5
<i>Caramelo et al</i>	33	21	3	9
<i>Pol et al</i>	17	69	-	12
<i>Sterling et al</i>	50	96	11	11
<i>Cotler et al</i>	46	74	5	9
<i>Martin et al</i>	37		8	24

*abstract

Waitlist Mortality Among HCV+ Kidney Patients

n=177 waitlisted HCV-infected pts

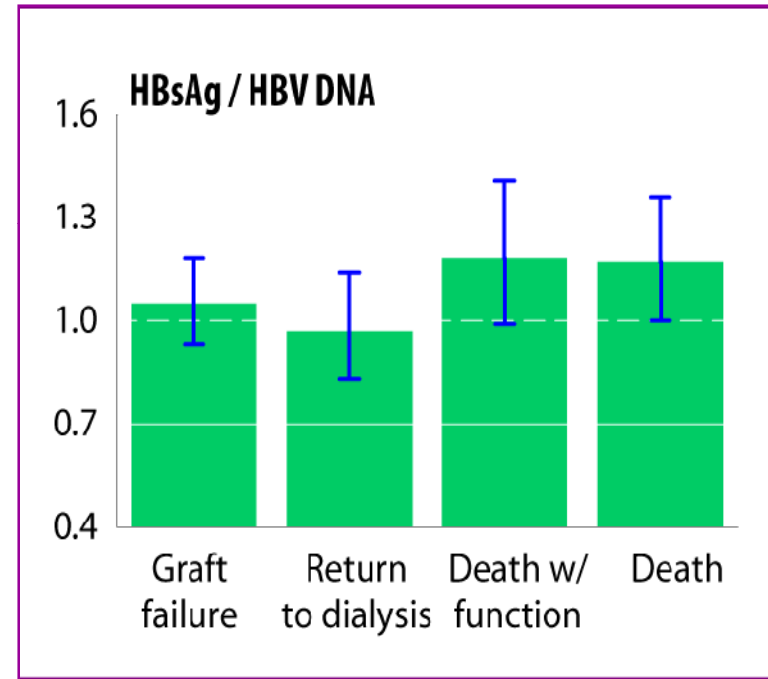
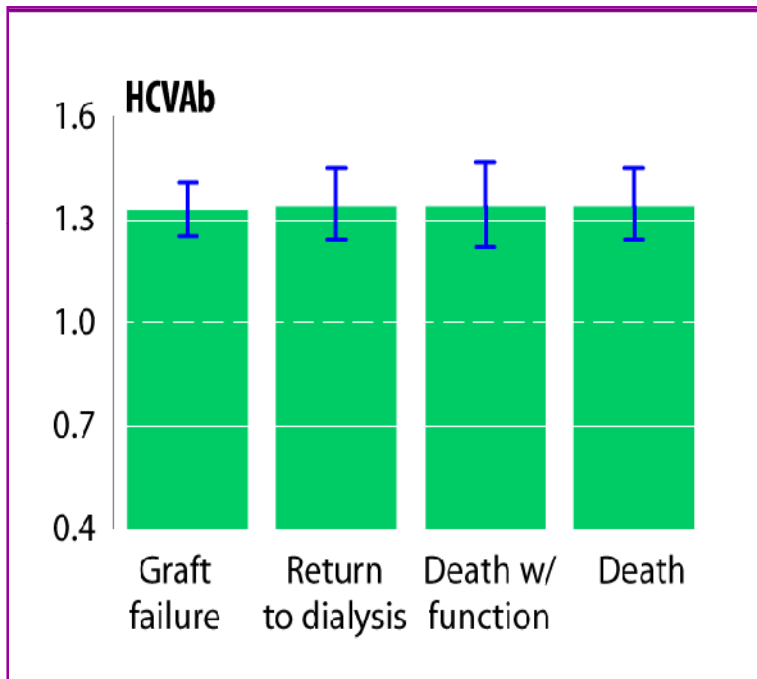
Variable	Hazard Ratio	P value
ESRD duration	1.17	0.716
Any liver disease*	0.83	0.547
Prior transplant	1.22	0.657
Age at evaluation	1.02	0.109
Diabetes	2.17	0.020

*Pts with decompensated cirrhosis not listed for kidney alone

Hepatitis C Infection and Outcomes After Kidney Transplantation

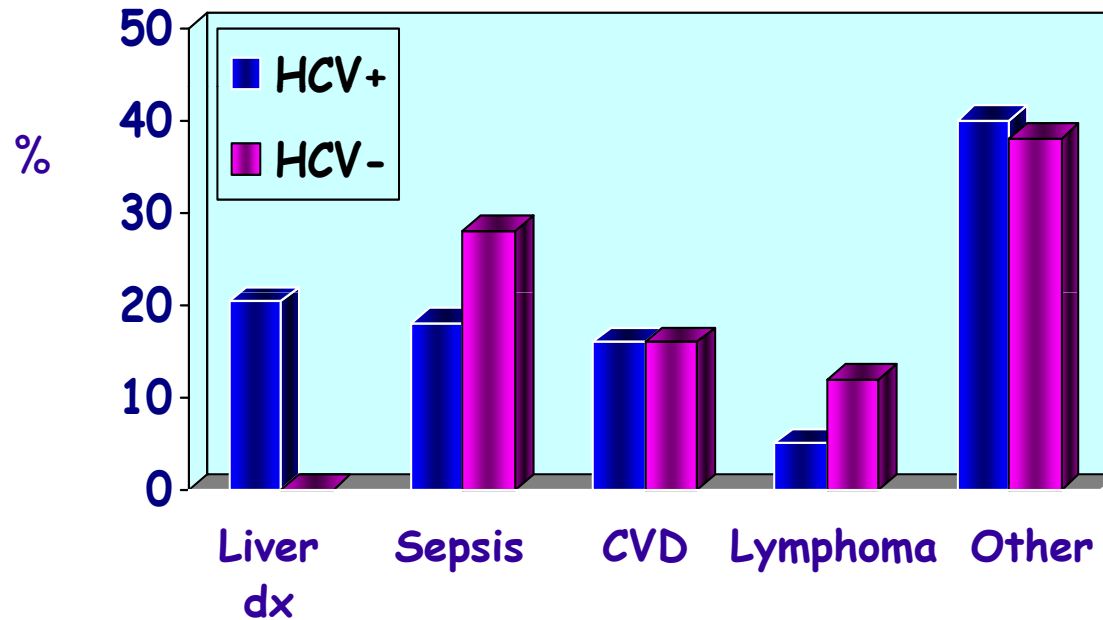
- Survival
 - Patient
 - Graft
- Hepatic complications
 - Progressive liver disease
- Extrahepatic complications
 - New onset diabetes (NODAT)
 - Glomerulonephritis
 - Infection

Adverse Outcome for HCV+ Kidney Recipients



Adjusted for donor HCV, txp year, age, gender, ethnicity, dialysis duration, primary diagnosis, PRA, CMV, education level, employment status, BMI, number of previous transfusions

Increased Death due to Liver Disease in HCV+ Kidney Recipients

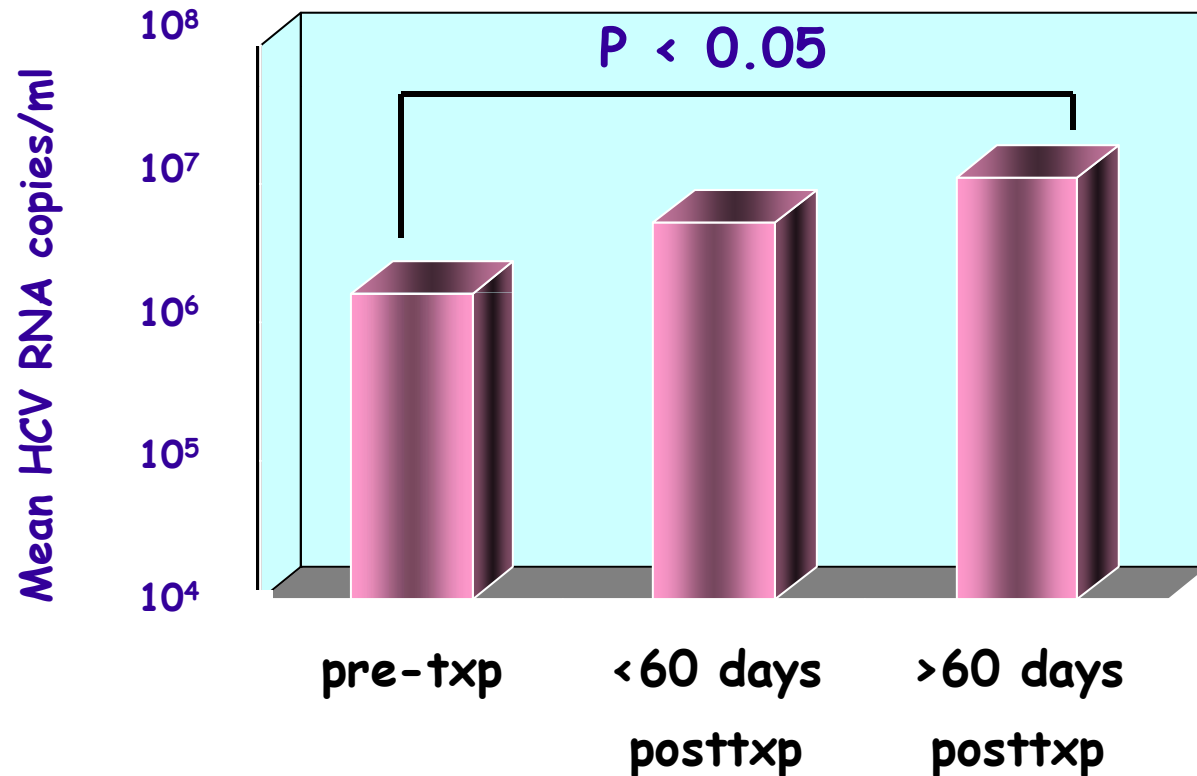


Liver Disease After Kidney Transplantation Problems with Most Studies

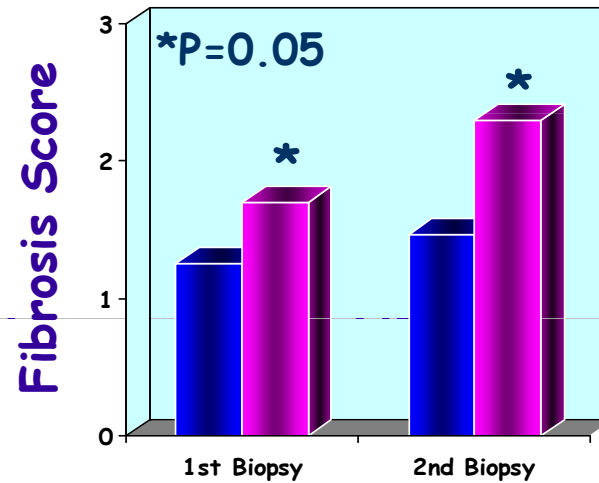
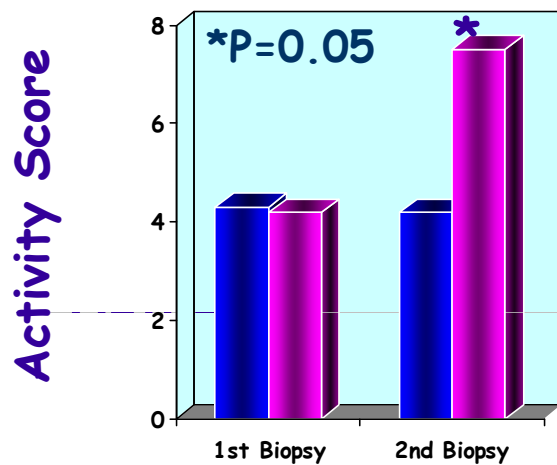
- Retrospective
- Historic serum samples
- No pre-txp liver biopsies
- No selection criteria
- High steroid dosing
- High rejection rates

Immunosuppression and Viral Replication in HCV+ Kidney Recipients

- 14 HCV+ pts, Ab induction-CNI-Aza-pred

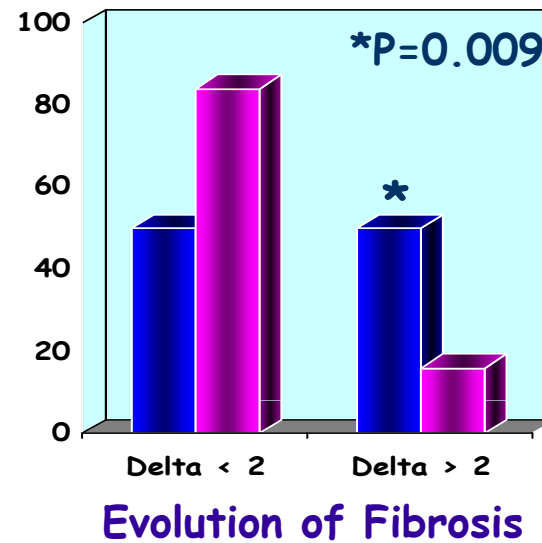
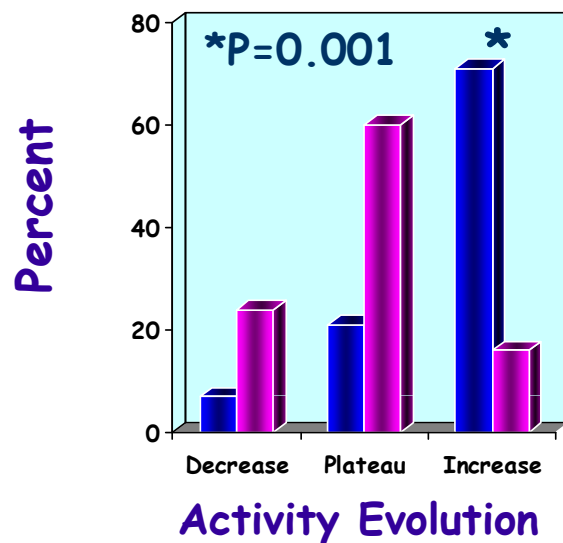


Effect of Kidney Transplantation on Liver Histology



■ Transplant
■ No kidney dx

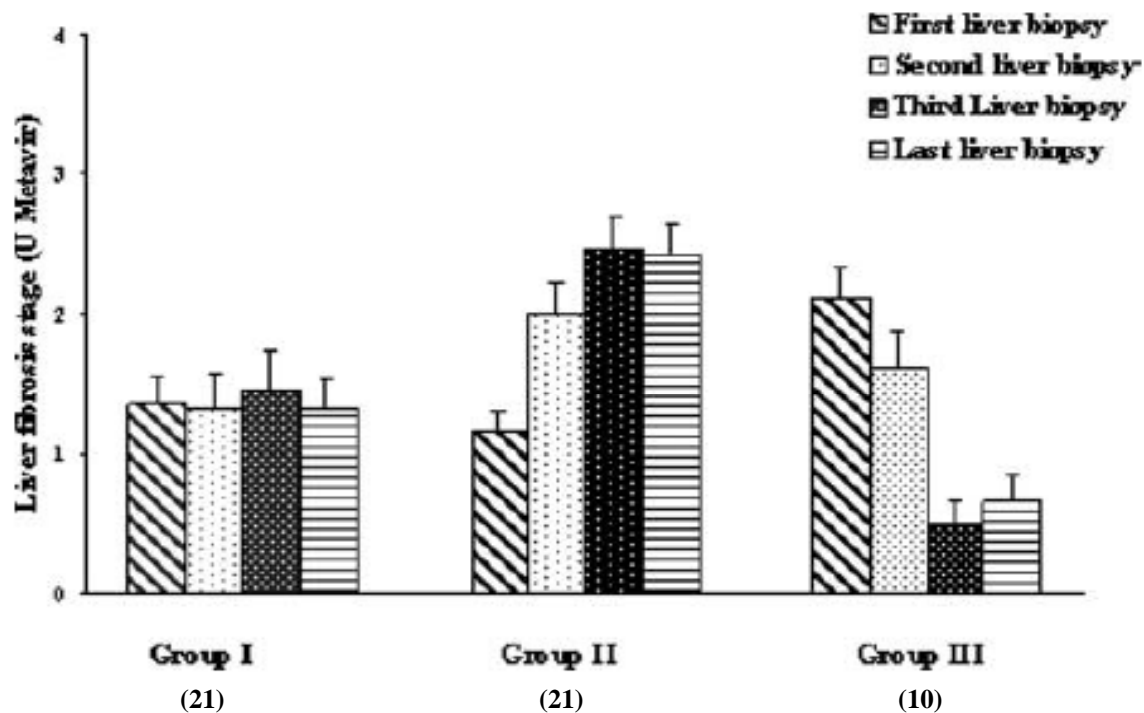
(Alric, Gastroenterology 2002)



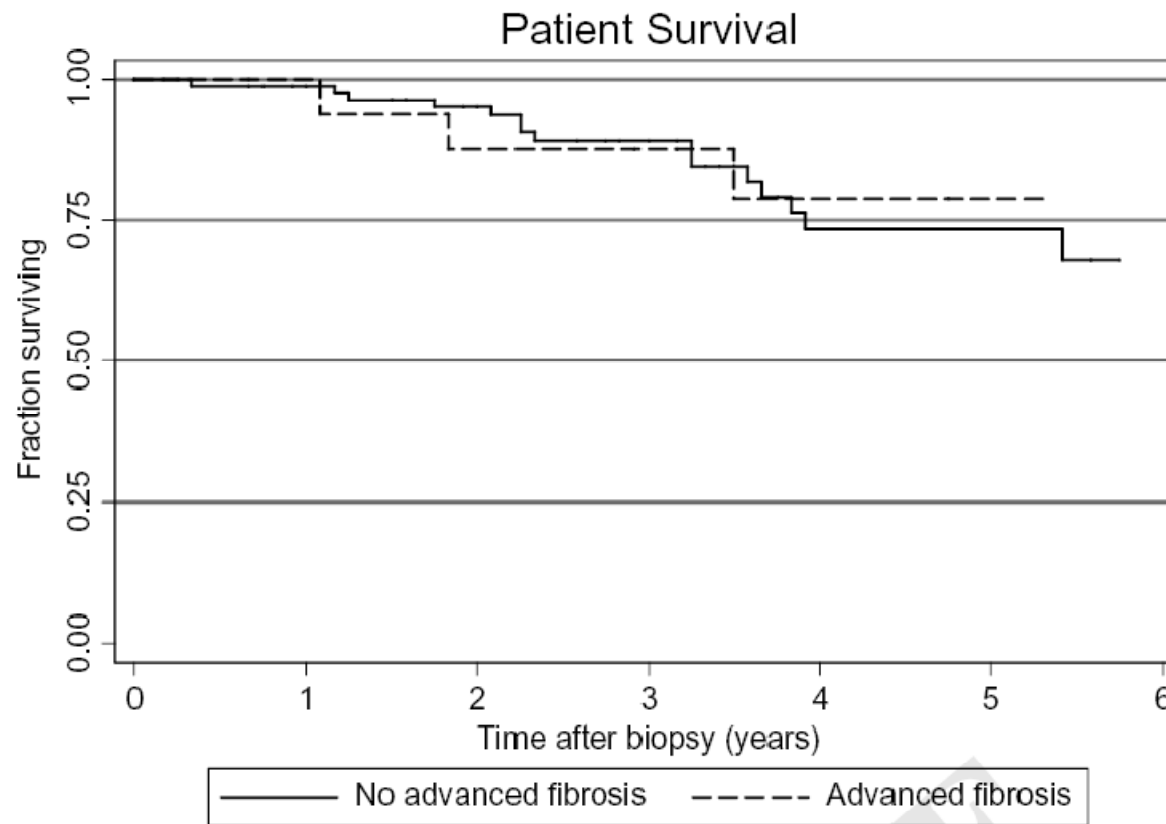
(Zylberberg, NDT 2002)

Natural History of HCV-Related Liver Fibrosis

- n=52, sequential post-txp bx, >10 yrs f/u , no IFN
- 60% pts stable or improved
- 3 pts developed cirrhosis



Patient Survival According to Liver Fibrosis on Pre-transplant Liver Biopsy



n=58 pts, 10 with advanced fibrosis (stage 3 or 4)

Predictors of Patient Survival in HCV-Infected Kidney Recipients

HCV+KTx n=43	Hazard ratio	P value
Previous kidney tx	9.3	0.007
Pre-tx diabetes	4.7	0.053
deceased donor	17.9	0.02
Knodell score	1.358	0.012

72% of deaths 2^o to infectious complications

Progression of Liver Disease After Kidney Transplantation

- Not well established, likely slow
- Risk factors
 - advanced histology?
 - Immunosuppression?
 - Ab induction
 - coinfection (HBV or HIV)
- Role for Interferon

Interferon- α Therapy in Kidney Transplant Recipients

Study	# pts	IFN-2 α Dose (MU)	Response (%)	ARF (%)
Thervet	13	3-5	N/A	15.4
Magnone	11	1.5-5	N/A	63.6
Rostaing	16	3	25	37.5
Ozgur	3	4.5	N/A	40

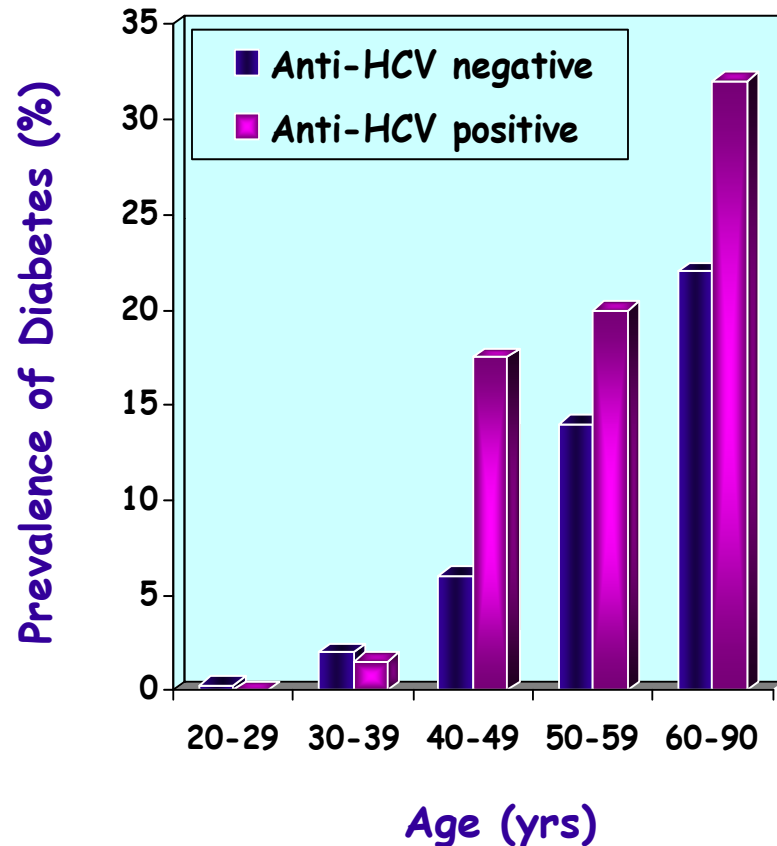
Pre-Txp Interferon in HCV+ Kidney Transplant Candidates

Study	n	Duration of IFN (mo)	Pre-txp SVR (%)	Post-txp SVR (%)	Post-txp f/u (mo)
Casanovas-Taltavull, 2001	29	6-12	64	7/9	41
Kamar, 2003	55	6-12	38	16/16	22.5

SVR = sustained virological response (6 consecutive mos viremia-free after stopping Rx)

HCV Infection and Type II Diabetes

- 3rd National Health and Nutrition Examination Survey (NHANES III)
- 9841 pts > 20 yrs old



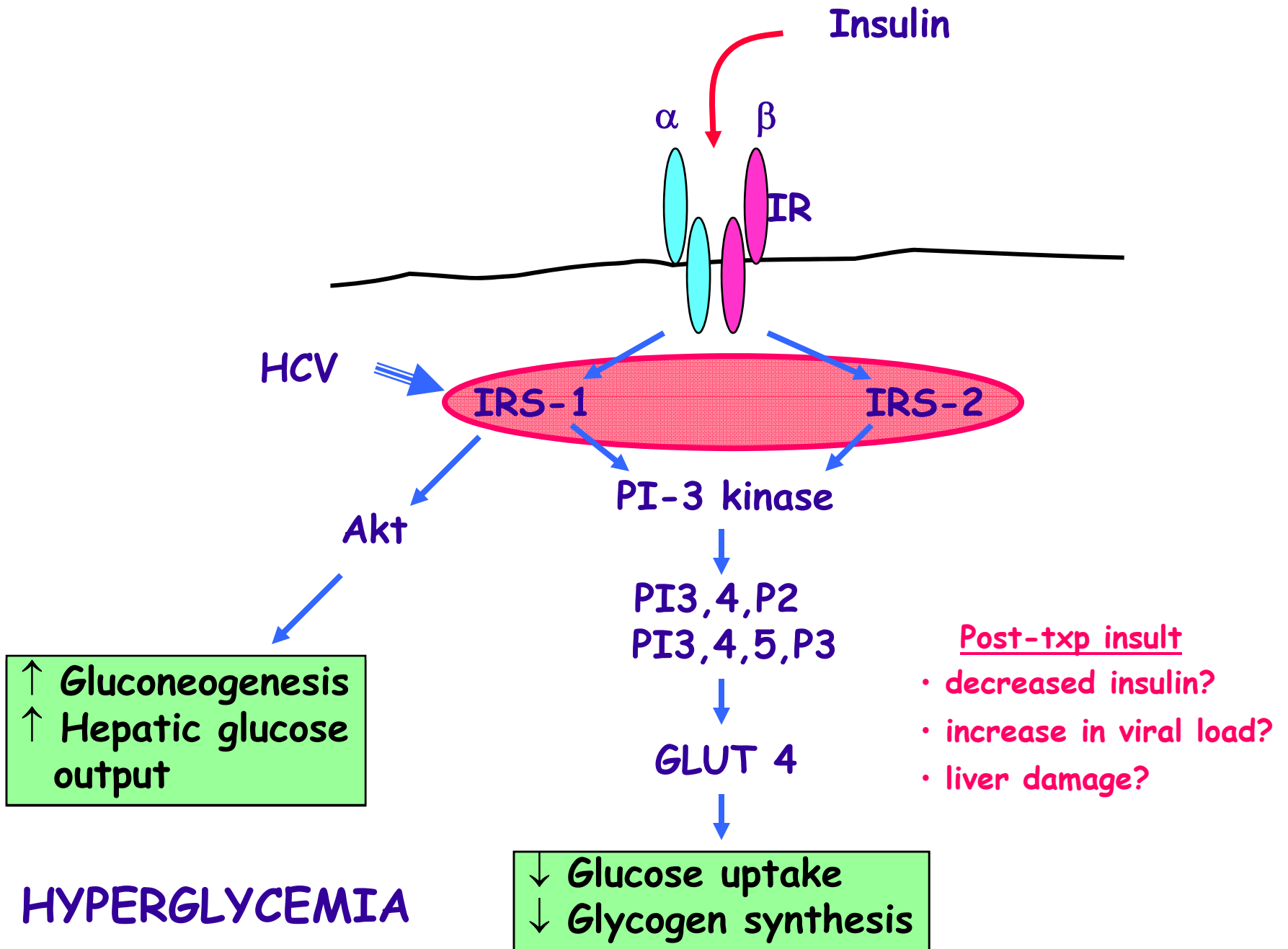
Adjusted OR for Type 2 DM 3.77 (HCV+ vs HCV- pts > 40 yrs)

HCV Infection and NODAT in Organ Recipients

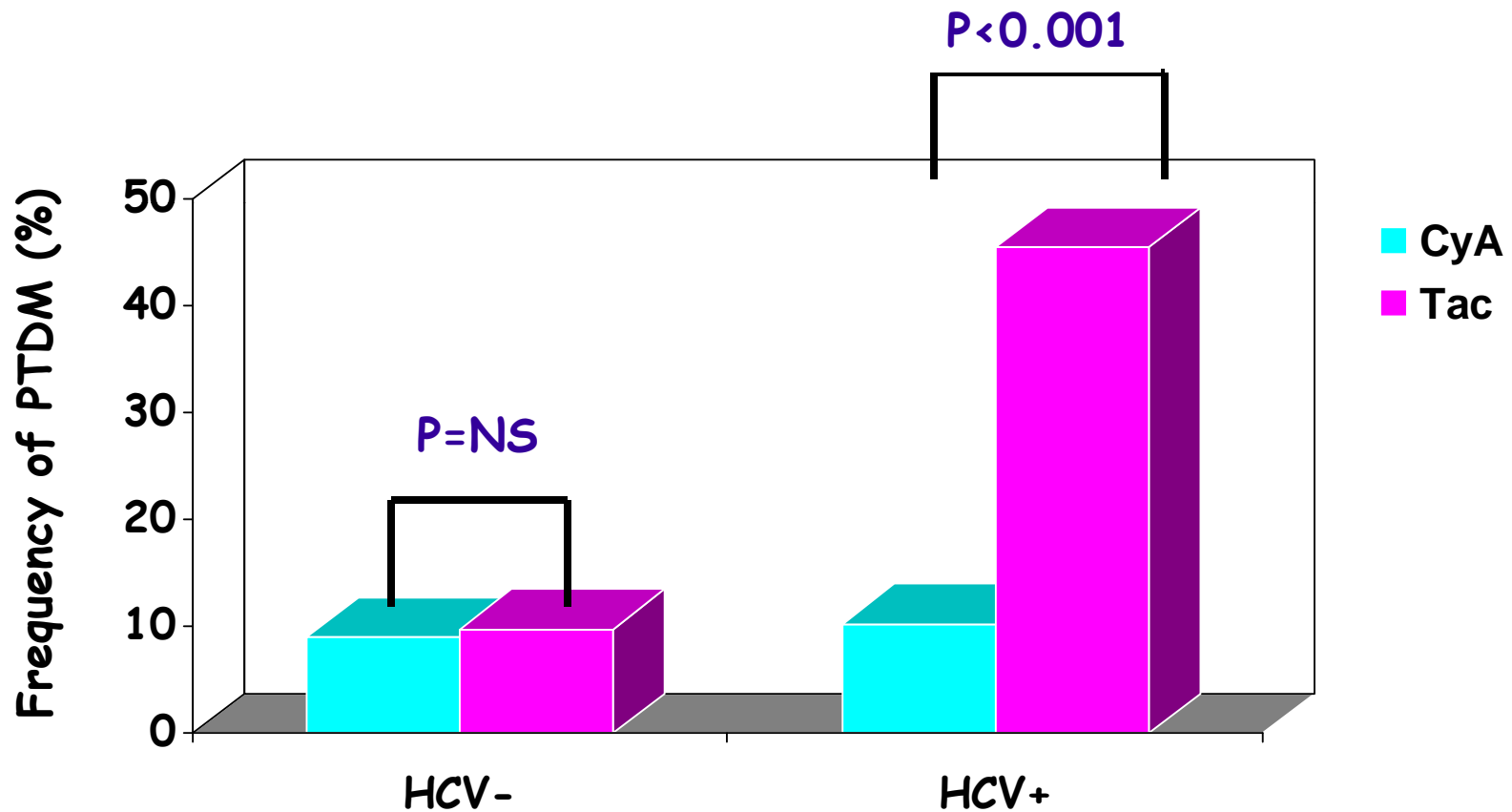
Author	Organ*	Cohort size (n)	HCV+ (n)	NODM (%)	
				HCV-	HCV+
Baid, 2001	L	158	47	28	64
Khalil, 2004	L	555	156	7	15
Bloom, 2002	K	427	71	10	39
Kasiske, 2003	K	11,659	658	HR 1.33	
Fabrizi, 2005	K	2,502	606	OR 3.97	

*L=liver, K=kidney

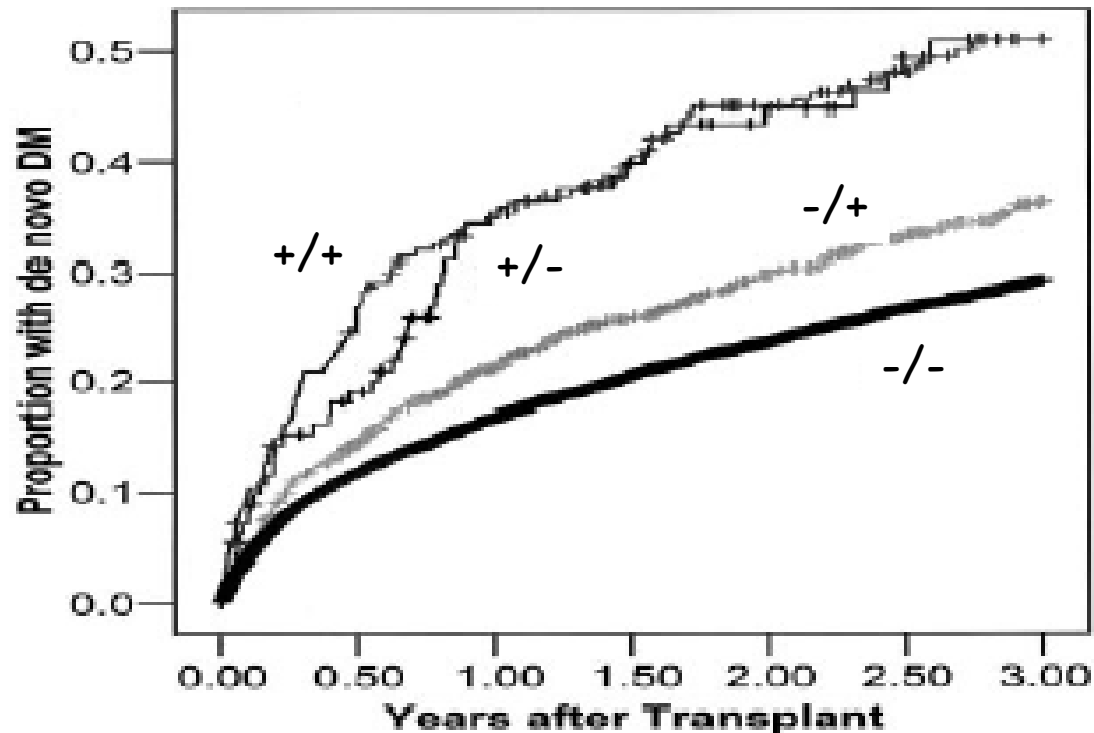
Adapted from Bloom RD, Am J. Trans 2006



Association of HCV Infection with New Onset Diabetes Under Tacrolimus



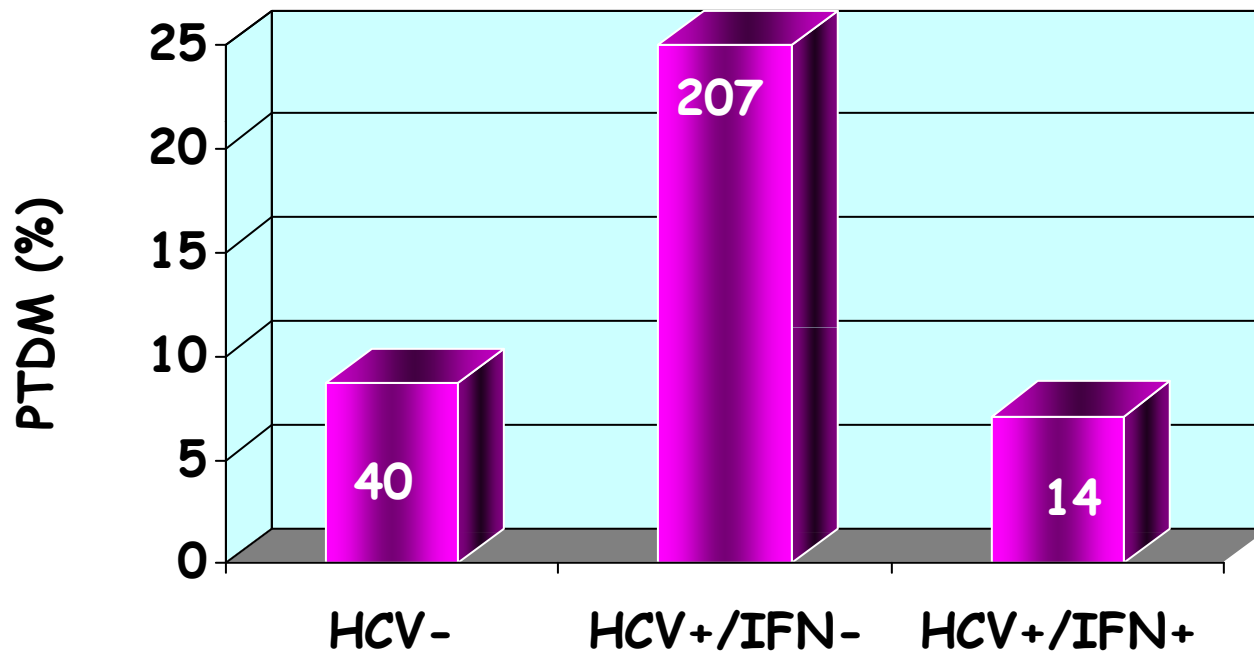
Increased NODAT in Recipients of Kidneys from HCV+ Donors



Impact of NODAT on Life Expectancy in Hepatitis C Kidney Recipients

Donor-Recip Sero-pairing	Overall Life-Years	Life-Years lost from PTHCV	Life-Years lost from PTDM
D+/R-	11.1	-0.08	5.5
D+/R+	11.5	0.82	5.4
D-/R+	15.9	0	6.2
D-/R-	19.8	0.03	5.4

Pre-transplant Interferon and NODAT in Kidney Recipients



n=261, CyA-treated

HCV Infection and Proteinuria in Kidney Transplant Patients

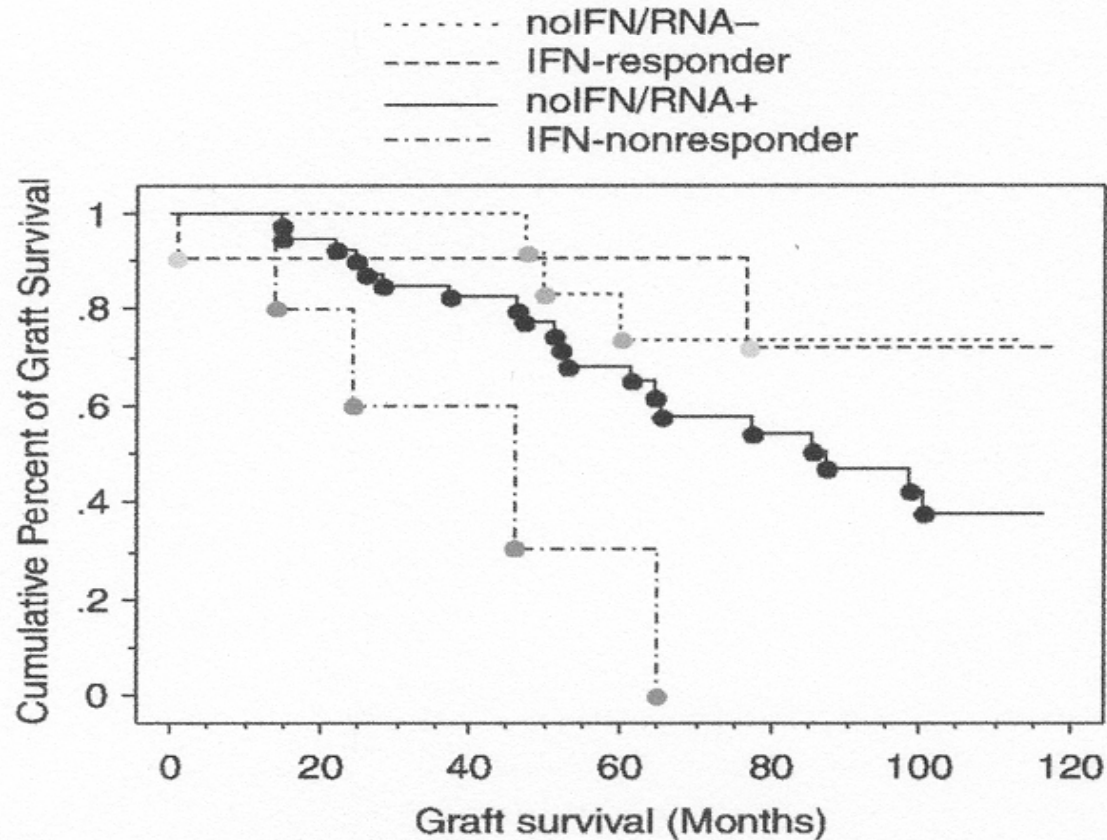
Study	n	Proteinuria (%)	
		HCV+	HCV-
Hestin, 1998	378	45	13
Nampoory, 2001	498	43	12
Virgilio, 2001	187	20	9
Ozdemir, 2006	165	34	7

Spectrum of Glomerular Disease in HCV+ Kidney Recipients

• 5-6 yrs post-txp

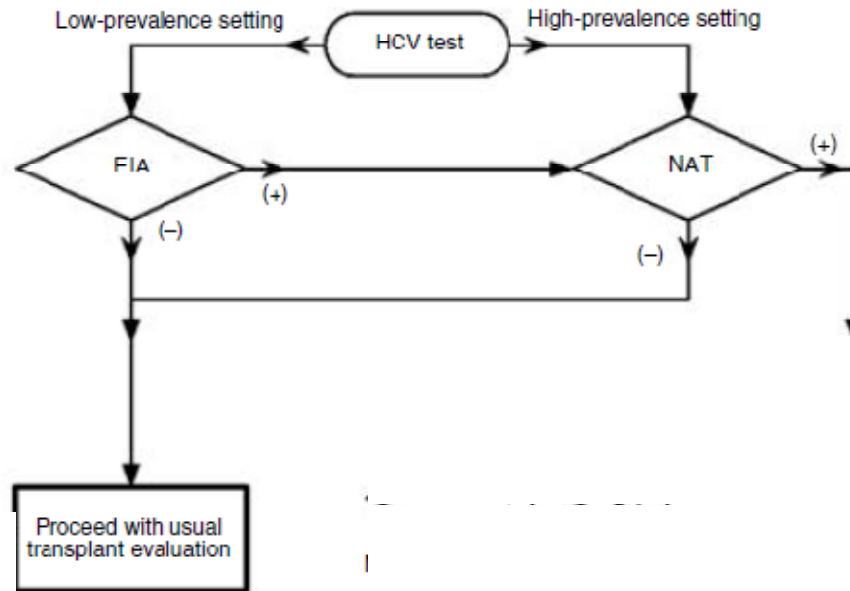
	HCV+ (n=44)	HCV- (n=52)
CAN (%)	20.5	59.6
Chronic txp glomerulopathy (%)	11.4	11.5
<i>De novo</i> MPGN (%)	45.4	5.8
<i>De novo</i> MGN (%)	18.2	7.7
Recurrent GN (%)	5	15.4

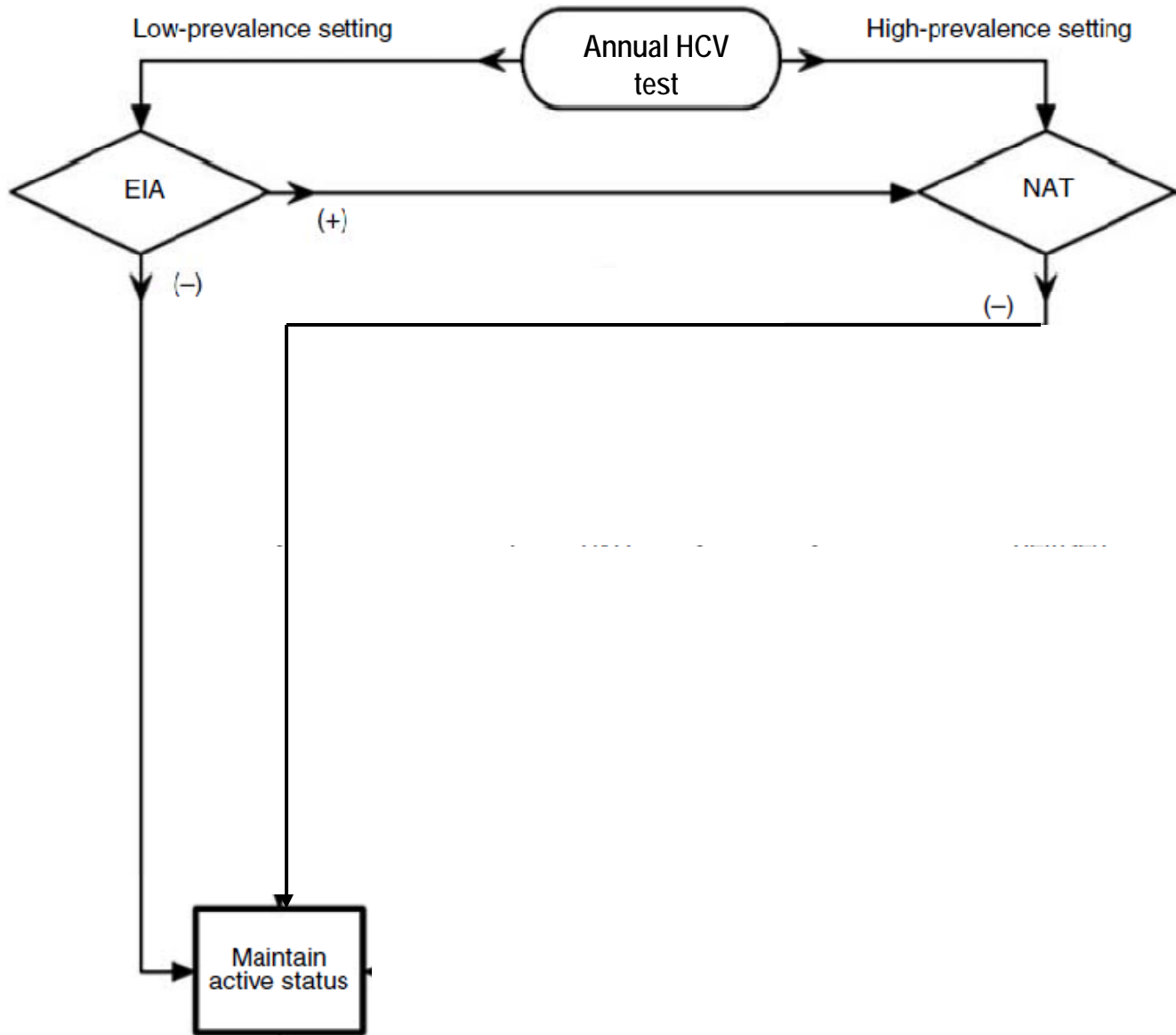
Clearance of HCV-RNA with Pre-Transplant Interferon Reduces Graft Loss



n=78 pts with HCV infection

Cruzado *et al*, Am J. Transplantation 2003





Adapted from KDIGO HCV Guidelines, Kidney Int 2008

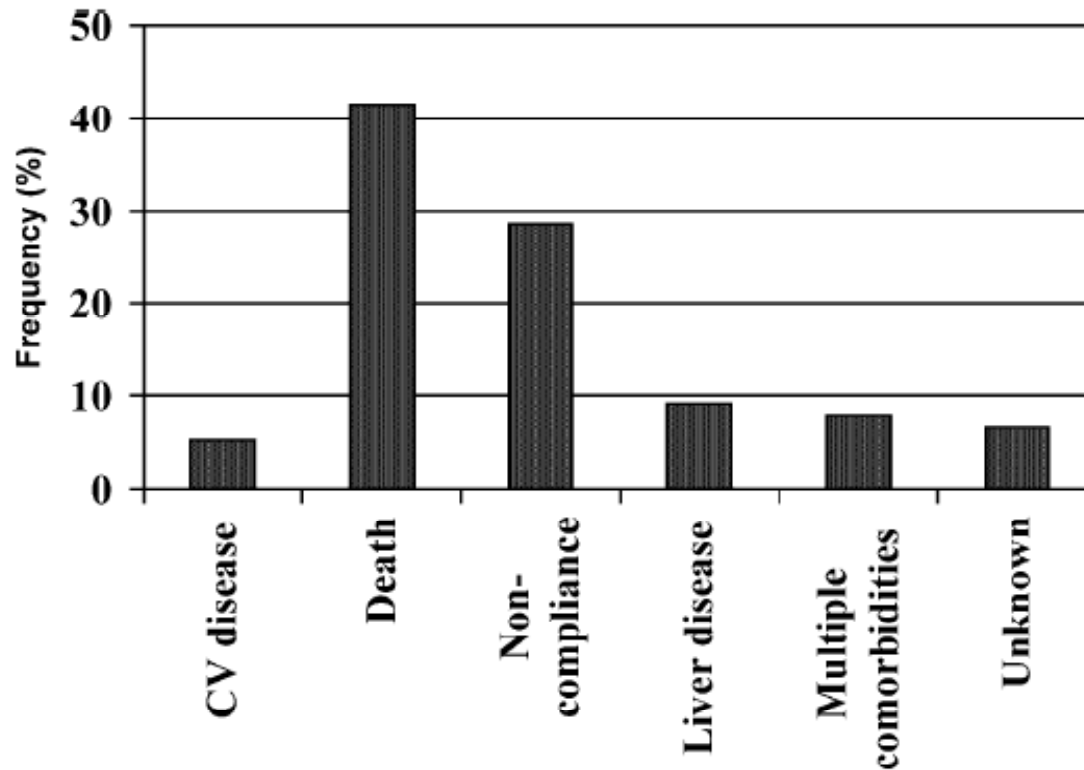
Summary

1. HCV infection is a major cause of post-txp morbidity and mortality
 - Pt survival
 - Graft survival
 - New onset DM
 - Post-txp Glomerulopathy
2. Pre-txp evaluation should include:
 - Viral characterization
 - Liver biopsy
 - Regular re-evaluation

Summary

3. The impact of transplantation on progressive liver damage remains uncertain
4. Most mortality is due to extrahepatic comorbidities
5. Pre-txp IFN is associated with:
 - Durable viral clearance
 - Decreased NODAT
 - Reduced GN and graft loss

Reasons for Removal of HCV-infected Patients from the Waiting List



76/177 waitlisted HCV+ pts de-listed

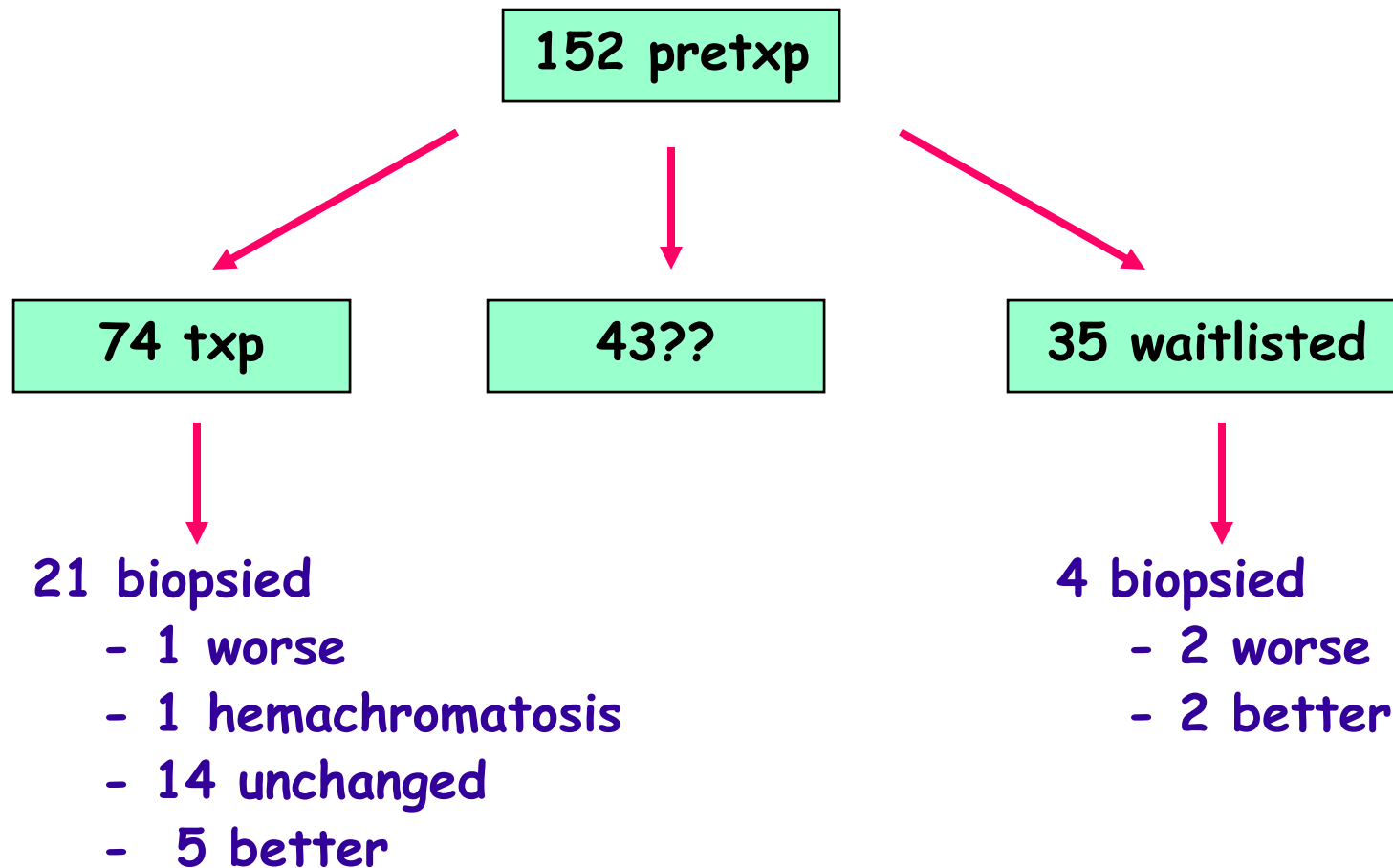
Use of HCV+ Donors in Kidney Transplantation

- Transmission invariable
- Controversial
- Survival advantage vs remaining on list
- Worse outcomes than seen with HCV-neg donors?
 - registry vs single center
- Pulsatile perfusion?

Considerations with HCV+ Donors

- Optimal donor testing
 - EIA vs NAT
 - genotyping
- Genotype superinfection
- Restrict to viremic candidates
- Restrict to genotype 1 patients

Liver Disease After Kidney Transplantation in Hepatitis C Recipients



Characteristics of HCV+ Kidney Candidates

	No/mild fibrosis (n = 90)	Mod/severe fibrosis (n = 18)	p-value
Males (%)	76	83	NS
Black ethnicity (%)	73	58	NS
ESRD duration at Eval (mo)	44 ± 6.7	55.6 ± 10.5	NS
Age (yrs)	47.6	42.7	0.02
Diabetes Mellitus (%)	42	28	NS
IVDA (%)	33	25	NS
H/o alcohol abuse (%)	31	31	NS
Prior transplant (%)	25	35	NS

Association Between Fibrosis Stage and Mortality

Table 3 Association between fibrosis stage and mortality

Patient group	Crude HR (CI), <i>P</i> value	Adjusted HR (CI), <i>P</i> value
All (<i>n</i> = 108)	0.94 (0.63, 1.41), <i>P</i> = 0.78	*1.1 (0.72, 1.7), <i>P</i> = 0.65
Transplanted (<i>n</i> = 58)	0.58 (0.22, 1.51), <i>P</i> = 0.27	**0.64 (0.24, 1.73), <i>P</i> = 0.38

* Adjusted for DM and Txp status

** Adjusted for DM

Mycophenolate Mofetil and Liver Injury in Hepatitis C Infected Recipients

Reference	n	Design	Organ	Outcome
Rostaing, 2000	14	Prosp	Kidney	-
Abbott, 2003	36,956	Retro	Kidney	Better
Jain, 2002	106	Prosp	Liver	N/C
Fisher, 2004	99	Prosp	Liver	N/C
Zekry, 2004	13	Prosp	Liver	N/C
Bahra, 2005	42	Retro	Liver	Better
Kornberg, 2005	21	Prosp	Liver	Better