

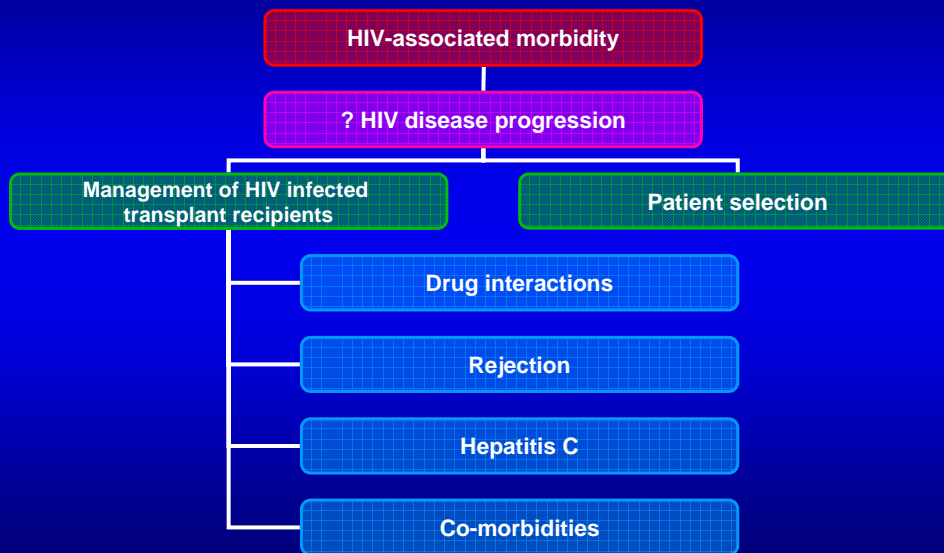
# Solid Organ Transplantation in HIV-Infected Patients *in the HAART-Era*

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## Overview

- 1) What *were* the issues?
- 2) What *are* the issues?
- 3) Outcomes in the HAART era
- 4) Patient management challenges
- 5) Multisite study: when and where to refer

# Evolution of the Issues

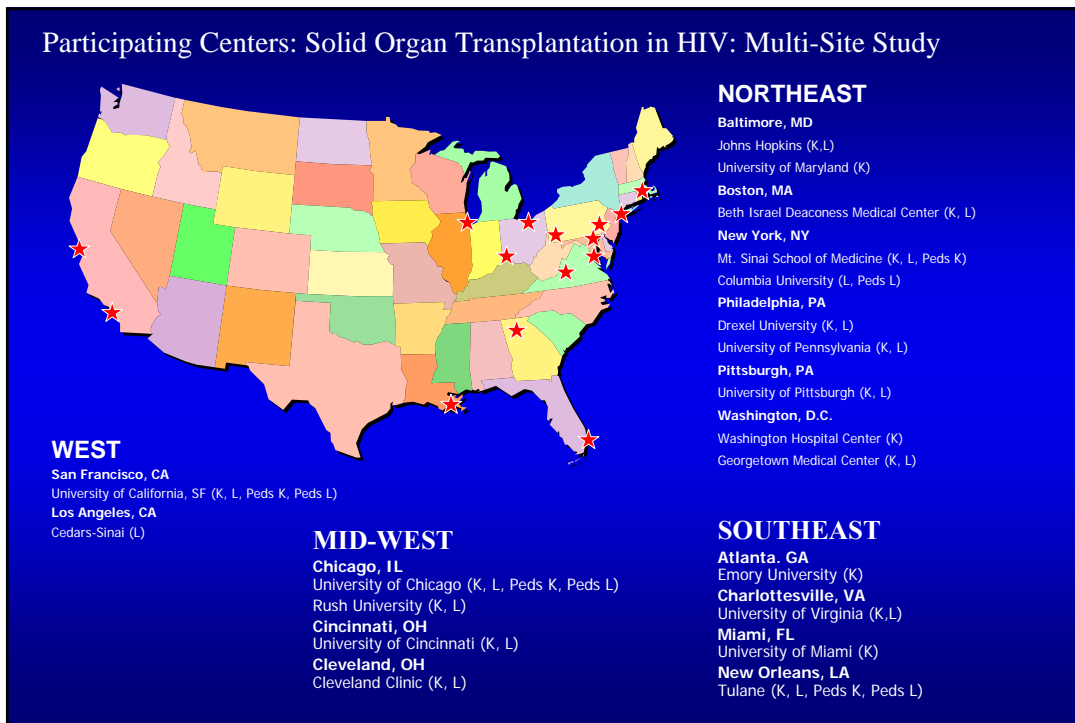


[www.HIVtransplant.com](http://www.HIVtransplant.com)

*A study to evaluate the safety and effectiveness of kidney and liver transplants in a select population of HIV infected individuals is currently in progress at 20 transplant centers across the country.*

- Must meet criteria for transplantation
- Must have a T-cell count >200 (kidney) or > 100 (liver)
- Must meet HIV viral load criteria depending on which organ is needed
- Patients with certain Opportunistic Infections in the past will be considered
- Pediatric patients are being enrolled at several participating centers (see below)

## Participating Centers: Solid Organ Transplantation in HIV: Multi-Site Study



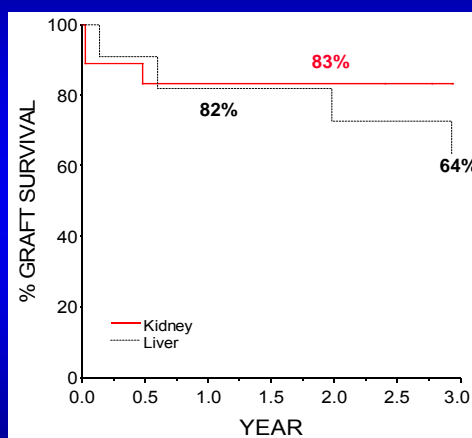
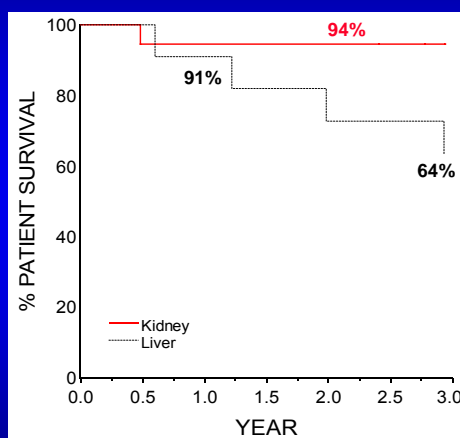
## Pilot multi-site study: kidney & liver

- ◇ 2000 – 2003; follow-up through 11/06
- ◇ Median follow-up 3.4 yrs: 3 yrs liver and 4 yrs kidney
- ◇ CD4+ T-cell count > 200 for K and > 100 for L recipients
- ◇ HIV RNA
  - ❖ undetectable except liver recipients with intolerance and prediction of full post-transplant virologic suppression
- ◇ Opportunistic complication history
  - ❖ all excluded from 3/00 - 4/02, then
  - ❖ continued exclusion of PML, cryptosporidiosis and visceral KS

**Table 1. Baseline Characteristics of HIV-Infected Transplant Recipients**

Characteristic	Liver Recipients (N= 11)	Kidney Recipients (N = 18)
Age – yr ( $\pm$ standard deviation)	46 $\pm$ 12	44 $\pm$ 6
Male sex – no. (%)	11 (100)	17 (94)
Race/Ethnicity - no. (%)		
White	6 (55)	10 (56)
African American	2 (18)	8 (44)
Hispanic	1 (9)	0
Asian	2 (18)	0
Prior Opportunistic Complications - no. (%)	1 (9)	4 (22)
CD4+ T-Cell (cells/mm <sup>3</sup> ) – median (range) <sup>†</sup>	279 (104 - 450)	439 (293-613)
HIV RNA <sup>†</sup>		
Any detectable - no. (%)	2 (18)	0
Copies/mL – median (range)	<50 (<50 – 23,247)	<50 (all <50)
Viral Hepatitis - no. (%)		
Hepatitis C	6 (55)	5 (28)
Hepatitis B Surface Antigen Positive	5 (45)	0
Hepatitis B Core Antibody Positive	2 (18)	2 (11)

## Patient and graft survival



	One Year Patient Survival		Three Year Patient Survival	
	Liver	Kidney	Liver	Kidney
<b>Study subjects</b>	90.9 (73.9, 100)	94.4 (83.9, 100)	<b>63.6</b> <b>(35.2, 92.1)</b>	<b>94.4</b> <b>(83.9, 100)</b>
<b>OPTN (≥65 years)</b>	81.5 (79.4, 83.6)	91.5 (90.7, 92.3)	68.8 (66.2, 71.3)	80.1 (78.9, 81.2)
<b>OPTN (HCV+)</b>	85.8 (84.5, 87.1)	--	75.6 (73.9, 77.3)	--
<b>OPTN (general)</b>	87.7 (87.2, 88.3)	95.9 (95.8, 96.1)	79.9 (79.3, 80.5)	90.8 (90.5, 91.1)

## Minimal HIV disease progression

- ◇ 1 case each of CMV and candida esophagitis
- ◇ CD4+ T-cell counts stable
  - Median (IQR) change compared to baseline
  - ❖ 1 year: -18 (-275, 95; p=0.52)
  - ❖ 2 years: 54 (-129, 177; p=0.55)
  - ❖ 3 years: 109 (-75, 228; p=0.17)
- ◇ HIV RNA generally suppressed

## Cause of death

### Liver

- ◇ 2 recurrent HCV
- ◇ 1 non-opportunistic infection in setting of recurrent HCV
- ◇ Recurrent HCC

### Kidney

- ◇ 1 congestive heart failure
- ◇ Pulmonary fibrosis
- ◇ MI
- ◇ Unknown cause

## Hepatitis B

- ◇ Re-infection rapid and fatal without virologic control
  - ❖ Prior contraindication for liver transplant
- ◇ Standard of care: HBIG and lamivudine
- ◇ Lamivudine resistant HBV common in HIV
- ◇ Adefovir, tenofovir – monitor renal toxicity
- ◇ Entecavir selects M184V
- ◇ \*\*Management to reduce HIV/HBV resistance\*\*

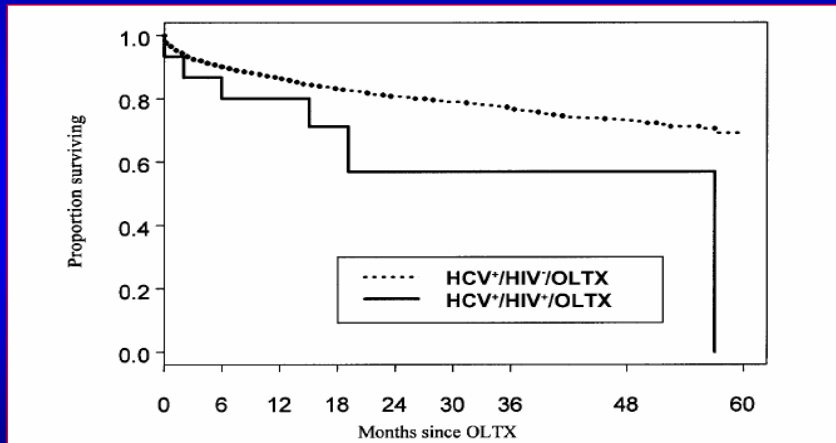
## Hepatitis C

- ◇ Common in liver and kidney candidates
- ◇ Relatively poor outcomes in HIV negative recipients
- ◇ Accelerated natural history in context of HIV
- ◇ Variable post-transplant experience across sites

## 24 liver transplant recipients

- ◇ Prospective cohort at 5 centers
- ◇ 1997 - 2001
- ◇ 15 HCV, 7 HBV, 3 fulminant failure
- ◇ Median follow-up 17 months
- ◇ Survival: 87% 1 year; 73% 2 and 3 years
  - ❖ UNOS: 87% 1 year; 82% 2 year; 78% 3 year
  - ❖ Poorer survival: ARV intolerance, post-transplant CD4 < 200, HIV RNA >400, HCV (50% v 100%; p=.023)

## HCV in HIV+ and Negative Recipients

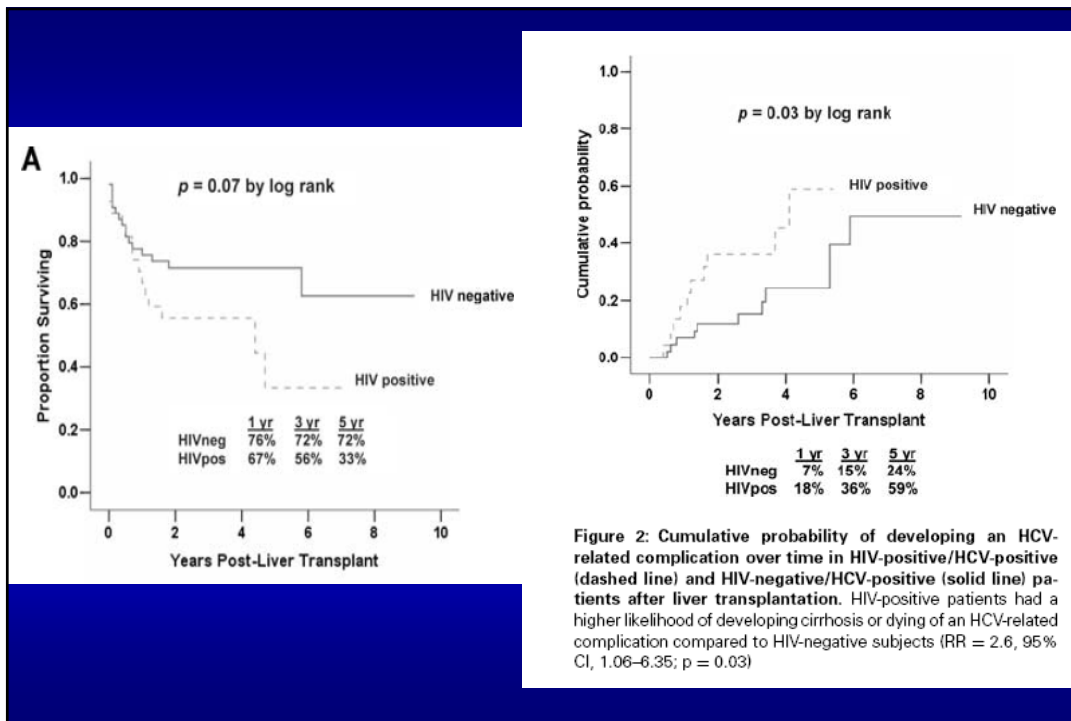


P = 0.058

## 27 HCV+ liver transplant recipients

- ◇ Single center
- ◇ 1997 – 2005
- ◇ 2:1 HIV-uninfected controls
- ◇ Mean follow-up 26.6 months
- ◇ Survival 67%, 56%, 33% at 1, 3 and 5 years
  - ❖ Controls: 76%, 72%, 72% (p=0.07)
  - ❖ Risk factors: AA, MELD >20, HAART intolerance, HCV RNA > 30 million

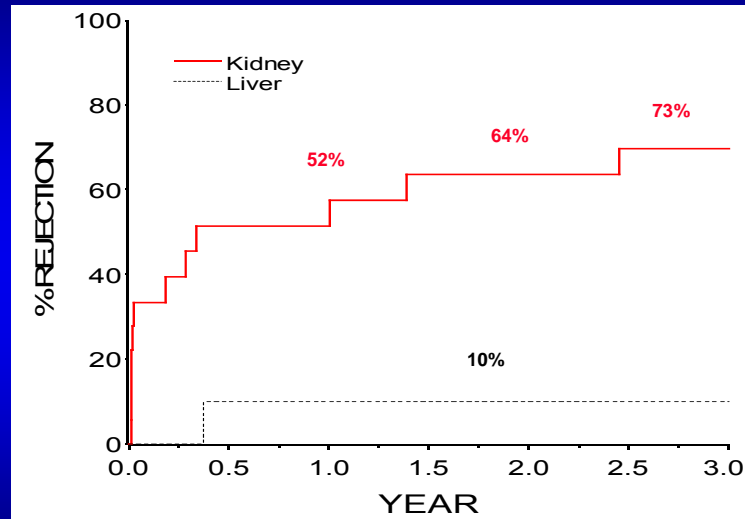
De Vera, et al. AJT 6: 2983-2993



## Treatment of HCV + Liver Recipients: When?

- ◇ Preemptively post-transplant?
  - ❖ No data to suggest superior outcomes
  - ❖ Minimize drug interactions and toxicity in the early post-transplant period
- ◇ Biopsy evidence of severe or progressive recurrent HCV disease

## Allograft Rejection



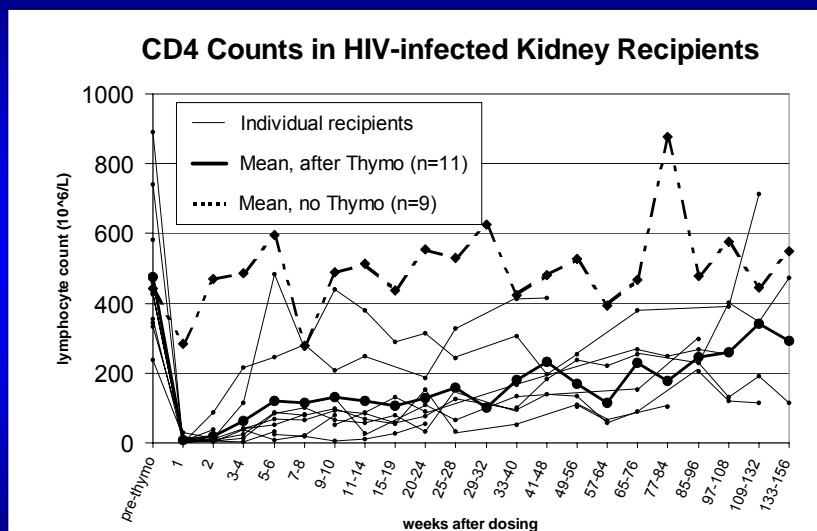
## Rejection

- ◇ Higher than expected rates
- ◇ Suspect liver rates will be higher than in pilot study
  - ◇ Higher in current study
  - ◇ Nearly 50% in Spanish cohort
- ◇ No clear predictors identified
- ◇ Stable creatinine
- ◇ Pilot study: graft losses from acute rejection (1), chronic rejection (2)

## Consequences of Rejection (N=20 kidney)

- ◇ 11 received thymoglobulin
  - ❖ 7 for rejection and 4 for delayed/slow graft function
- ◇ Mean CD4+ T-cell counts
  - ❖ stable in no thymo
  - ❖ thymo:  $475 \pm 192$  to  $9 \pm 10$  cells/ $\mu$ L
- ◇ Recovery time ranged from 3 weeks to 2 years

Carter et al, American Journal of Transplantation 2006



## Infections

- ◇ 1 Candida esophagitis in thymoglobulin user
- ◇ 10 serious infections in 6 thymoglobulin recipients
  - ❖ All bacterial
  - ❖ All but 1 when the CD4+ T-cell count was < 200 cells/ $\mu$ L.
- ◇ 2 serious infections in no thymoglobulin group
  - ❖ 1 bacterial, 1 influenza
  - ❖ 1 occurred when CD4+ T-cell count was 25 cells/ $\mu$ L while the recipient was receiving a high dose of sirolimus

## Drug Interactions

- ◇ Cyclosporine doses:
  - ❖ low with PIs/PI+NNRTI
  - ❖ typical to high with NNRTIs
- ◇ Tacrolimus and sirolimus are similar
- ◇ PI and NNRTI levels affected but have largely remained within adequate treatment ranges

## Cyclosporine Dosing

	<u>Initial dose of CsA</u>	<u>Maintenance dose of CsA</u>	<u>Mean CsA trough (ng/mL) (Range)</u>
<u>PI</u>			
Nelfinavir	50–75 mg bid	25 mg bid	112 (59–174)
Indinavir	75–100 mg bid	75 mg bid	125 (74–175)
<u>NNRTI</u>			
Nevirapine	200–250 mg bid	100–175 mg bid	122 (45–195)
Efavirenz	350–450 mg bid	250–400 mg bid	117 (84–182)
<u>PI and NNRTI</u>			
Nevirapine-nelfinavir	25 mg bid	25 mg bid or qd	169 (152–176)

Frassetto et al. Transplantation 80:13-17; 2005

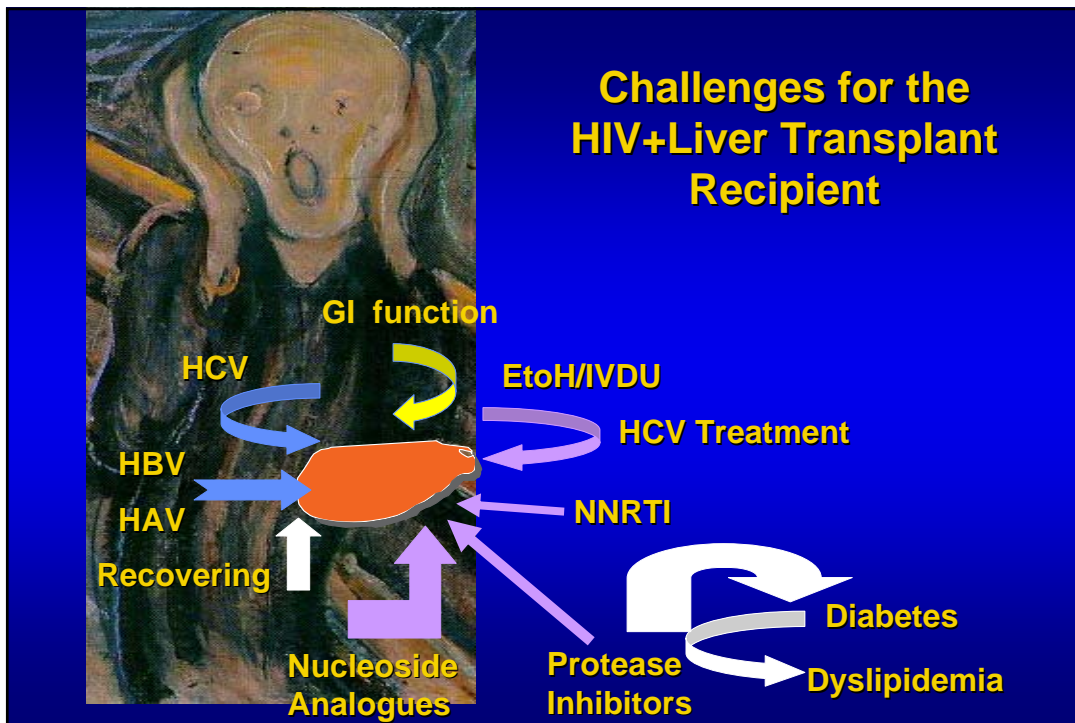
## Drug Interactions and Medical Complexity



Highly Active Antiretroviral  
Therapy

Triple Immunosuppression  
to Prevent Graft Rejection





## Antiretrovirals and OI Prophylaxis

- ◇ Antiretroviral management:
  - ❖ Minimize AZT and D4T - in vitro antiretroviral antagonism with MMF
  - ❖ Atazanavir contraindicated with PPIs
  - ❖ DDI
- ◇ HIV and transplant prophylaxis

## HHV8

- ◇ KS may be reactivated by post-transplant immunosuppression
- ◇ 1 UCSF kidney recipient and 1 heart transplant (NEJM) in recipients with KS history – no recurrence
- ◇ 1 recent de novo KS and 1 reported from Bonn

## HPV

- ◇ HVP-related cervical and anorectal disease, already accelerated in people with HIV infection, may be exacerbated by post-transplant immunosuppression
- ◇ Preliminary experience at UCSF: common, with progression, but not obviously more aggressive than in non-transplant population



## Other Co-Morbidities

1. Cardiovascular disease
2. Bone Diseases
3. Malignancies: skin cancers
4. Diabetes
5. Dyslipidemia
6. Life Adjustment

## Cardiovascular Disease in Transplant

- ◇ Most common cause of morbidity and mortality
- ◇ 75-85% hypertensive post tx
- ◇ 60 % develop hyperlipidemia

## Bone Disorders in Transplant: Osteopenia, Osteoporosis, Osteonecrosis

- ◇ Pre tx renal insufficiency
- ◇ Hyperparathyroidism
- ◇ Smoking
- ◇ Poor dietary calcium intake

## Challenges of Living with...

1. Managing two complex medical
  - ❖ multiple medications and drug interactions
  - ❖ managing and coping with side effects
2. Adjusting pre transplant expectations to post transplant realities
  - ❖ overestimating the benefits
  - ❖ unmet expectations
  - ❖ minimizing the new challenges
3. Emotional adjustment
  - ❖ depression/ post traumatic stress disorder

# When to Refer for Transplant

## LIVER

- ◇ Symptomatic liver disease
  - ❖ hepatic encephalopathy, ascites, variceal bleeding
- ◇ Synthetic dysfunction
- ◇ Child-Pugh score of  $\geq 7$

## KIDNEY

- ◇ On hemodialysis or CAPD
- ◇ Creatinine clearance or GFR  $< 25$ , and not on dialysis

### Pretransplant Survival Is Shorter in HIV-Positive Than HIV-Negative Subjects With End-Stage Liver Disease

*(Liver Transpl 2005;11:1425-1430.)*

In summary, the findings of Ragni et al. confirm the significantly decreased survival of the HIV co-infected patient on the liver transplant waiting list, and emphasize the importance of early referral to permit a complete evaluation and activation for transplantation.<sup>11</sup>

*Liver Transplantation, Vol 11, No 11 (November), 2005: pp 1315-1317*

## Donors

- ◇ “High risk” donors are currently being considered at many transplant centers.
- ◇ The safety of accepting HIV positive donors for HIV positive recipients is unknown, as the question of the prevalence and clinical impact of super-infection remains unknown.

## Multi-Disciplinary Health Care Team

- ◇ To participate actively in patient monitoring and management, with consistent and rapid communication among team members
  - ❖ All medication changes: drug interactions, viral resistance
  - ❖ Evaluation of symptoms and lab abnormalities: adequate differential diagnosis and plan