

**18th Annual
HIV CONFERENCE**
of the Florida/Caribbean AIDS Education and Training Center

May 1-2, 2009
Orlando, FL

Solid Organ Transplantation In HIV-Infected Persons

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- **Consultant:** Tibotec, BMS, GSK, BIPI, Roche, Virco, Gilead

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ISSUES IN TRANSPLANTATION

- Ethical considerations
- Survival benefits
- NIH Solid Organ Transplantation Study
- Economics

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Need For Liver Transplantation in HIV Infection

- 750,000-1.2 million people infected with HIV with ~55,000 new cases added each year
- AIDS-associated mortality is shrinking
- prevalence of HCV coinfection is high (30%)
- prevalence of HBV coinfection is 10%
- progression to cirrhosis is *rapid* in coinfecting patients
- liver disease has become a major cause of death in people infected with HIV

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Ethical Questions

- **Does transplantation benefit the HIV patient?**
- **Does the graft benefit another patient more?**
 - Based on multiple studies, it appears that transplantation benefits both patient groups equally and this ethical concern should not exist
 - No difference in survival rates has been shown in the HIV patient with either “marginal organs” or using same donor transplants
 - In fact HIV patients if you delay transplantation will die faster

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Immunosuppressants

- **Initially thought to be contraindicated in HIV infected patients**
- **Multiple studies have shown many immunosuppressants have documented antiretroviral properties (CYA, tacrolimus, sirolimus, MMF)**
- **Multiple drug interactions with HAART and immunosuppressants which need to be managed closely**

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Ethical Considerations

- **No prospective studies were performed in patients with diabetes or HCV prior to considering these groups for transplantation, but now it is routine to offer organs to these patients despite evidence of diminished post transplant survival rates**

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Miami Experience

- **Effect of immunosuppression on HIV progression**
 - HIV viral load remained undetectable in all patients maintained on HAART
 - CD4 counts dropped immediately after transplant then rebounded within several weeks
 - Thymoglobulin caused a decrease in CD4 with very slow rebound
 - No AIDS defining opportunistic infections
 - Some severe infections occurred after treatment with thymoglobulin and should be used cautiously

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Miami Experience

1. Neff G.W., **Jayaweera D**, Tzakis A. Liver Transplantation for HIV-infected patients with end stage liver disease. *Current Op in Organ Transplantation* 2002; 7(2):114-123.
2. Guy Neff, Eugene Schiff, John Fung, Margaret Ragni, **Dushyantha Jayaweera**. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. *Liver Transplantation*. March 2003; 9(3):239-47
3. Ian Schreiber, Jeffrey J. Gaynor, **Dushyantha Jayaweera**, et al Outcomes Following Orthotopic Liver Transplantation in Fifteen HIV-Infected Patients. *Transplantation* 2007;84: 697-705

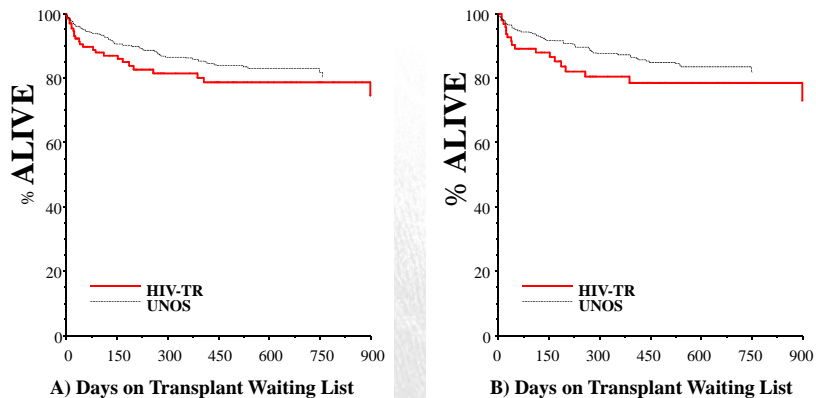
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Survival in Liver Transplants

- **Cumulative survival in HIV patients comparable to HIV (-) at 12, 24 and 36 months**
- **Survival poorer among subjects with post transplant HAART intolerance or Hep C**
- **More rapid demise of the coinfecting HIV transplant candidate observed on waiting lists as the MELD score did not accurately predict outcome in the HIV patient subset**
Ragni – Liver Transplant 2005

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Pre Transplant Mortality over Time



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Should HIV Patients be Transplanted?

- HIV+s have previously been excluded from transplantation due to:
 - Death rates too high to justify organ use
 - Concern that immunosuppression might accelerate HIV disease
- However, OIs, morbidity, mortality have been significantly reduced with HAART
- Immunosuppressives themselves may have anti- HIV effects; cyclosporine, MMF, rapamycin

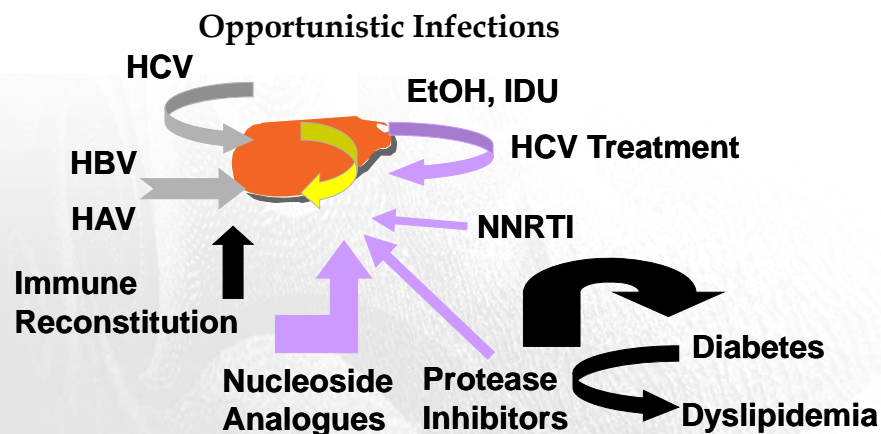
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Survival Benefits of HIV Therapy

- **Greatly exceeds that achieved by many other chronic diseases**
 - Non- small cell lung cancer – 7 months
 - Adjuvant chemo for breast cancer – 29 months
 - Post MI care – 50 months
 - BMT for Hodgkins disease 92 months
 - HAART \geq 4 years

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Factors Affecting the Liver in HIV

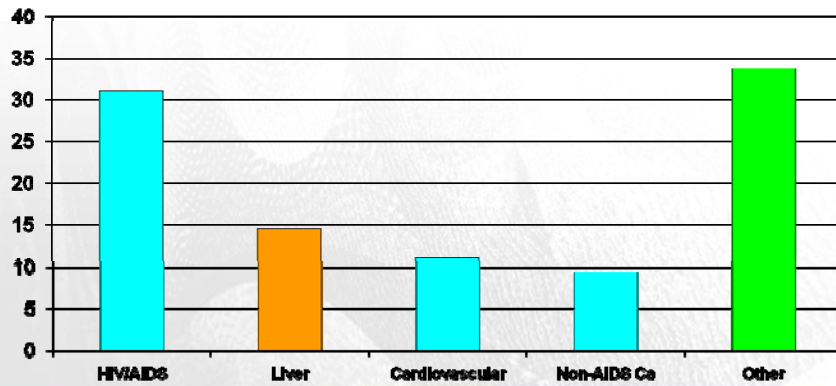


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Recent Causes of Mortality in HIV+

D:A:D Study. *Arch Int Med.* 2006; 166: 1632-1641

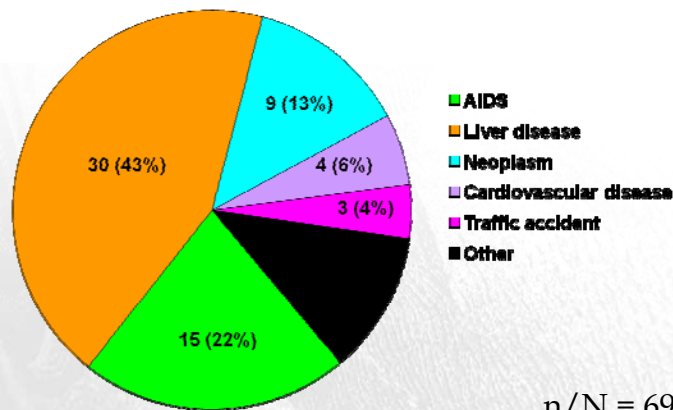
1246 deaths in 23,441 HIV+ pts followed for 3.5 yrs; 22% HCV, 8% HBV



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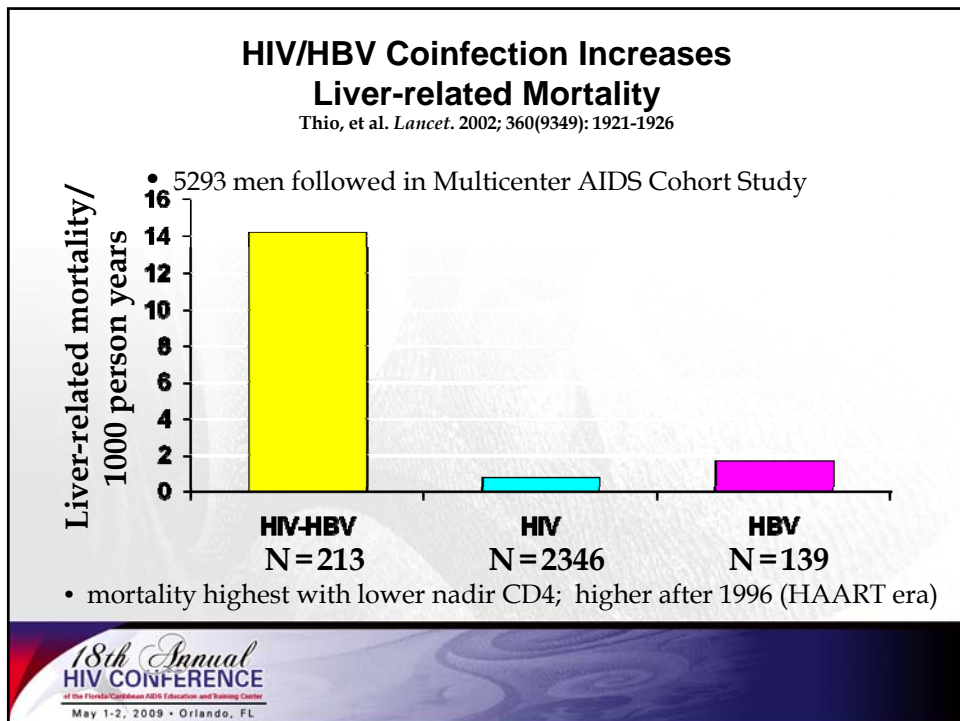
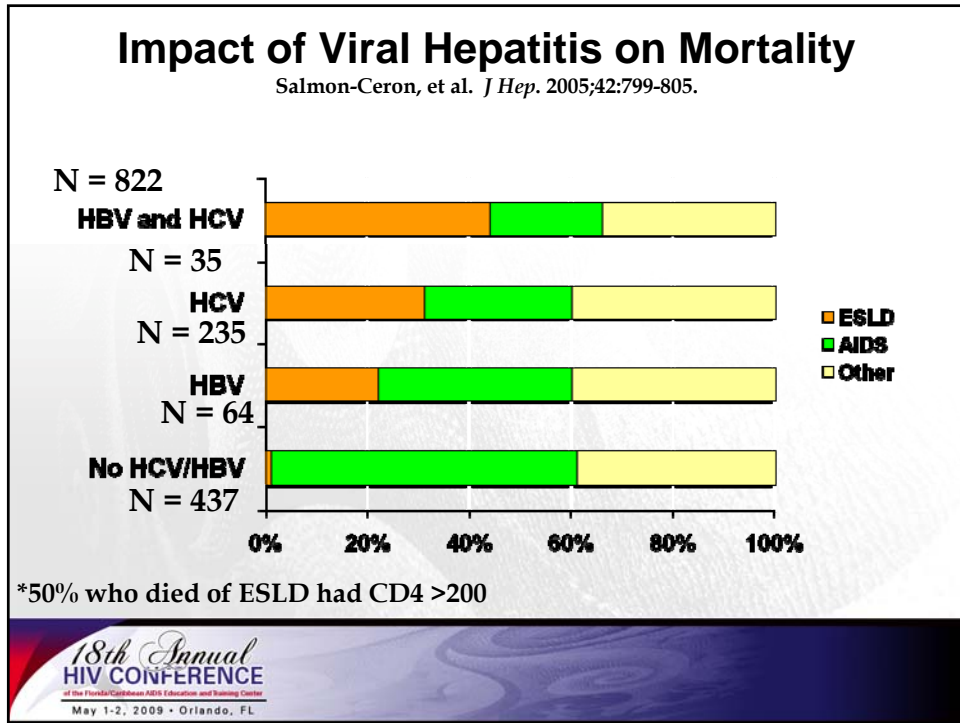
Causes of Death in HIV/HCV Coinfected Population

Pineda JA, et al. *Hepatology.* 2007;46:622-630



n/N = 69/1011

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Screening for End-Stage Liver Disease

Gastrointestinal bleeding	– guaiac, MCV, Fe, INR, EGD
Ascites	– exam, U/S, CT scan
Hepatic encephalopathy	– HX/PE, mental status, NH3, sleep
Subacute bacterial peritonitis	– if fever, tap & culture
Non-obstructive jaundice	– bili, alk phosphatase
Cirrhosis	– biomarkers, CT scan, BX
Hepatocellular carcinoma	– AFP, CT scan
Renal function	– creatinine

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Screening for End-Stage Liver Disease

MELD: *Model for End-stage Liver Disease*

$$= [0.96 \log e (\text{creatinine mg/dL}) + 0.38 \log e (\text{bilirubin mg/dL}) + 1.12 \log e (\text{INR}) + 0.643] \times 10$$

- validated as a predictor of mortality in liver transplant candidates...
- ...but use of MELD as predictor may depend on stage at presentation and may not predict mortality in HIV+s
- scores range from 6 (least ill) to 40 (most ill), and change with pt's health status
- many sites have automatic calculators (www.unos.org)

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Caveats in Predictors of HCV Progression

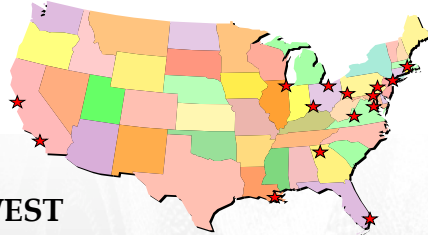
ESLD DX too late	infectious complications, mortality may be inevitable as ESLD alters coags and inflammatory & endothelial function
CD4	may also reflect splenic sequestration
MELD	may predict progressive ESLD better in HIV- than HIV+
ALT	may also reflect adverse drug rx, mitochondrial tox
HIV VL	may also indicate resistance or intolerance
IFN, RBV	may further reduce CD4, affect decision re OLTX

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Solid Organ Transplantation in HIV: Multi-Site Study

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



WEST

San Francisco

UCSF (K, L, Peds K, L)

Los Angeles

Cedars-Sinai (L)

MID-WEST

Chicago

University of Chicago (K, L, Peds K, L)

Rush University (K, L)

Cincinnati

University of Cincinnati (K, L)

Cleveland

Cleveland Clinic (K, L)

SOUTHEAST

Atlanta

Emory University (K)

Charlottesville

University of Virginia (K,L)

Miami

University of Miami (K)

New Orleans

Tulane (K, L, Peds K, L)

NORTHEAST

Baltimore

Johns Hopkins (K,L)

University of Maryland (K)

Boston

Beth Israel Deaconess Medical Center
(K, L)

New York

Mt. Sinai School of Medicine (K, L,
Peds K)

Columbia University (L, Peds L)

Philadelphia

Drexel University (K, L)

University of Pennsylvania (K, L)

Pittsburgh

University of Pittsburgh (K, L)

Washington, D.C.

Washington Hospital Center (K)

Georgetown Medical Center (K, L)

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Overview of Study Design

- Prospective, multicenter cohort study of 275 HIV+ transplant recipients who are followed for 2-5 years
- 150 kidney and 125 liver recipients
- Central hypothesis: HIV+ liver and kidney transplant recipients will have patient and graft survival rates *comparable* to other patient groups without HIV infection that are currently considered acceptable transplant candidates

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Antiretrovirals and OI Prophylaxis

- **All ARVs allowed**
 - AZT and D4T use minimized due to in vitro data showing antiretroviral antagonism with MMF (CellCept)
- **Standard OI prophylaxis for HIV & solid organ transplants employed for PCP, CMV, MAC and Candida**

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Immunosuppression and Rejection Management

- Initial immunosuppression includes cyclosporine or tacrolimus +/- mycophenolate mofetil (MMF), in combination with steroids per local transplant center standards
 - daclizumab use was allowed
- Rejection managed with a steroid pulse, changing calcineurin inhibitors or doses, and/or adding sirolimus and/or thymoglobulin

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Donor Eligibility

- **“High risk” donors are currently being considered at many transplant centers**
- **Because 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, donors must be HIV negative**

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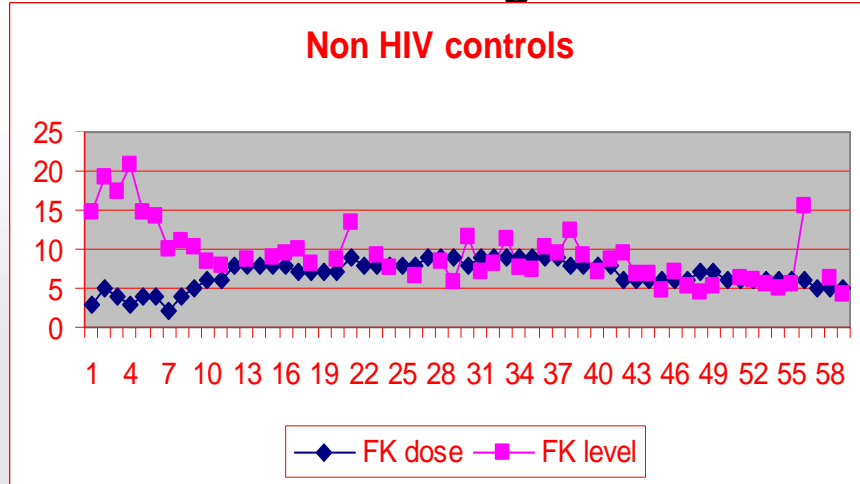
Key Management Issues

The need for a multi-disciplinary health care team to participate actively in patient monitoring and management, with excellent and rapid communication among team members

- all medication changes (drug interactions, viral resistance)
- evaluation of symptoms and lab abnormalities (adequate differential diagnosis and plan)

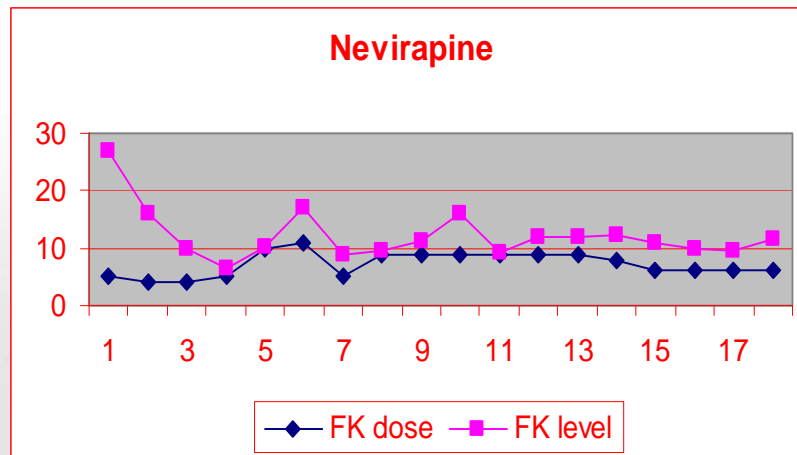
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PK Interactions between HIV and non HIV with Prograft levels



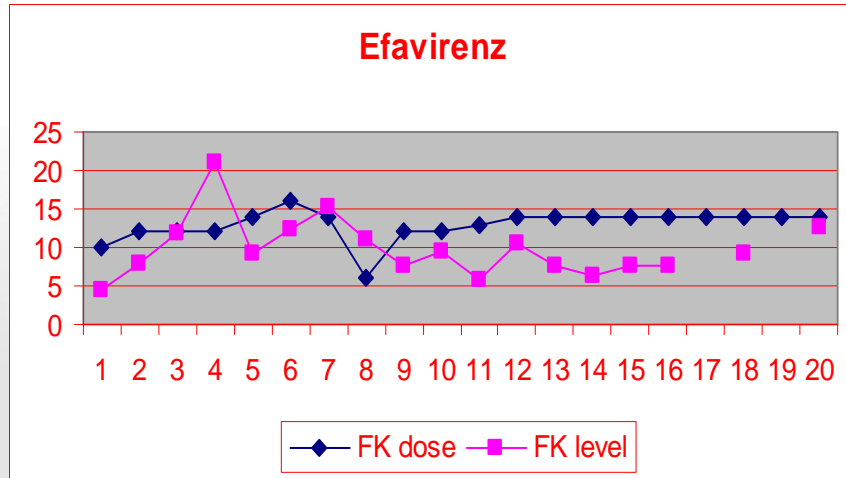
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PK Interactions of Nevirapine on FK



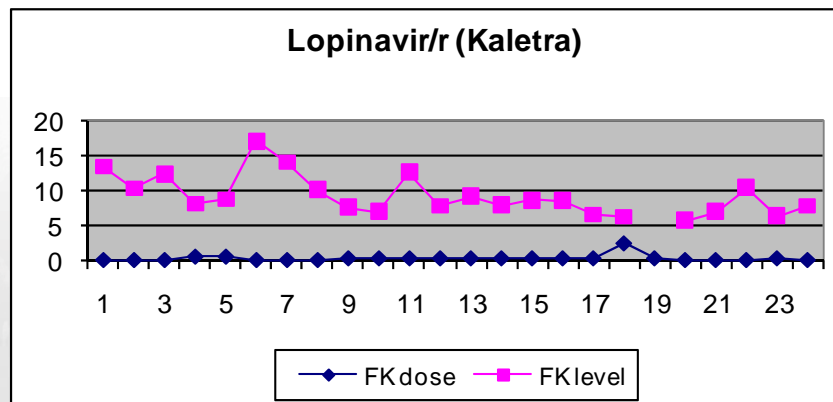
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PK Interactions of Efavirenz on FK



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PK Interactions of Kaletra on FK



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Solid Organ Transplant Study Accrual

- **188 transplants (275 projected), as of 9/08**
 - 80 liver
 - 7 liver-kidney
 - 101 kidney
- **average f/u time: 1.6 years (max = 4.2)**
- **173 pre-transplant phase**
- **270 screening phase**

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Liver Recipient Demographics (n=21)

Age (range)	39.5 yrs (15-64)
Gender (%)	20 M (100%)
Ethnicity	13 Caucasian 2 African-Am. 3 Asian 3 Hispanic
Cause of ESLD	11 - Hepatitis C 9 - Hepatitis B 1 - fulminant Hepatitis A
Donor type	4 living related 17 deceased donor (includes 2 non-heart beating)

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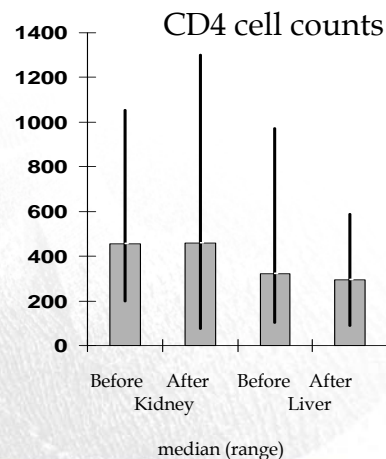
Baseline Data

- **41 “eligible” subjects**
 - 22 Kidney and 19 Liver
- **8 “ineligible” subjects**
 - undiagnosed HIV, HIV RNA > 50 (K), low CD4, altered MS, history of OI/ON
- **CD4+ T Cell Counts**
 - Kidney: 455 (200 - 1054)
 - Liver: 321 (103 - 973)
- **HIV-1 RNA**
 - Liver: <50 (<50 - 115,776)

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Stable Immune & Viral Load Status after Solid Organ Transplantation

- 22 kidney transplant recipients
- 19 liver transplant recipients
- median f/u 279 days
- median CD4+ cell counts
 - kidney 460 (76 - 1300)
 - liver 296 (89 - 590)
- median HIV RNA at f/u < 50 copies/mL in both groups
 - kidney < 50 (< 50 - 11,343)
 - liver < 50 (< 50 - 80)
- re-transplantation: 1 liver
- transplant graft loss: 1 kidney
- rejection
 - kidney 36%
 - liver 11%



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HIV Viral Load and CD4 Counts

- HIV RNA levels currently undetectable in all liver recipients, although 4/21 required changes in HAART therapy for detectable virus
- CD4 counts stable or increased in patients who did not receive therapy for rejection

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Deaths and OIs are Uncommon

Median follow-up	279 days (3 - 1567)
Deaths	1 kidney, 3 liver <ul style="list-style-type: none"> - recurrent hepatitis C - rejection after PI stopped - post-op complications x 2
Opportunistic complications	1 kidney, 1 liver <ul style="list-style-type: none"> - CMV esophagitis - Candida esophagitis

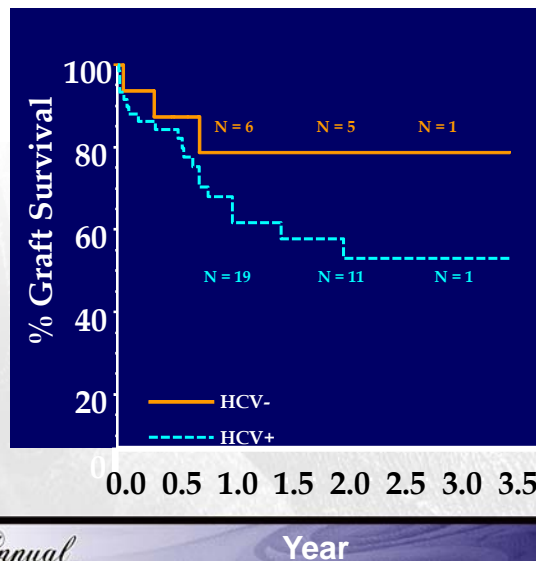
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Complications in 11 HCV/HIV Recipients

- Aggressive recurrent HCV immediately post-OLT_X, pt expired 14 months post-transplant
- Sepsis, MSOF, death 6 months post-OLT_X in recipient of domino (sequential) transplant
- Sepsis, failure to thrive, death 1 year post-OLT_X with normal liver function
- Sepsis and death one week following transplant (pt treated with thymoglobulin post-OLT_X secondary to renal failure)
- Recurrent HCC and death 1.5 years secondary to metastatic disease

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Liver Transplant Graft Survival by HCV Status



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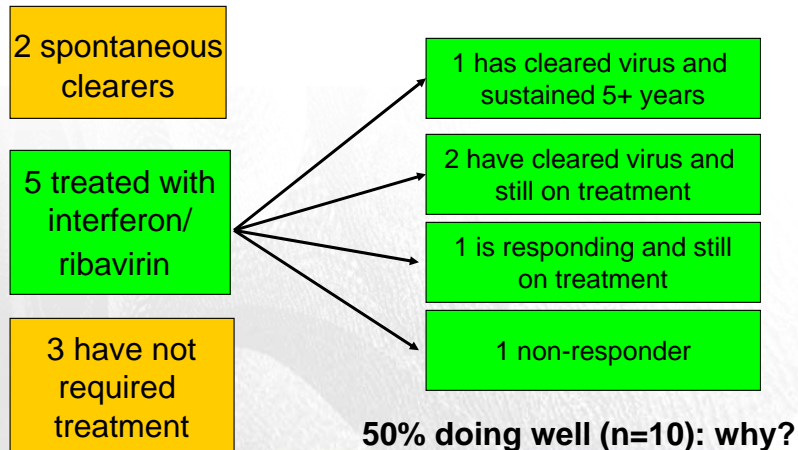
Year

Treatment of HCV+ Liver Recipients: When?

- Interferon/ribavirin poorly tolerated pre-OLT
- HCV treatment is *not* initiated preemptively post-transplant
 - No data to show that HCV clearance rates are higher
 - Minimize drug interactions and toxicity in the early post-transplant period
- HCV treatment is initiated if biopsy shows severe or progressive recurrent HCV disease; the decision to treat will ultimately be determined by the treating physician

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HCV/HIV Liver Transplantation: Clearance of HCV



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Potential factors contributing to poor outcomes in HCV+ liver recipients

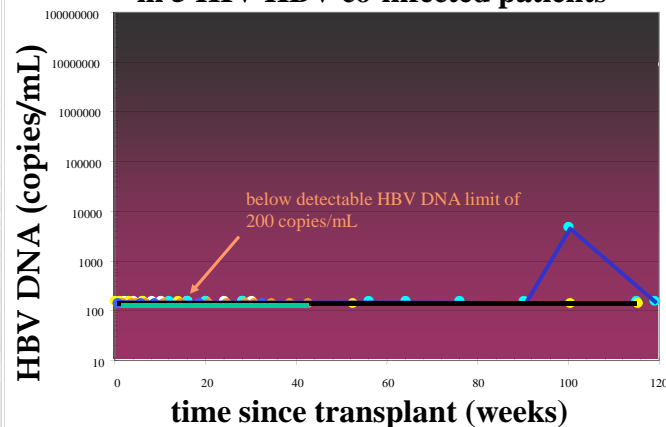
- Donor HCV+ ($p=.02$)
- MELD ($p=.01$)
- BMI <21 at enrollment ($p=.0001$)
- Dual organ ($p=.01$)
- Detectable HIV RNA at enrollment ($p=.005$)
- Initial tacrolimus immunosuppression (vs CsA) ($p=.04$)

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HBV Outcomes

Hepatitis B DNA trends after liver transplant in 5 HIV-HBV co-infected patients

- 8/9 pt and graft survival (mean follow-up 24 months)
- all pts have remained HBV negative post-transplant--success of liver transplantation for HBV is critically dependent on effective viral suppression



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What We Don't Know about Predicting HCV Disease Progression in HIV

- Are HIV+s with ESLD evaluated early enough for OLTX?
- Are HIV+s with ESLD transplanted early enough?
- Is MELD sufficiently sensitive to HIV effects?
- Is there a better marker of disease progression?
 - CD4-MELD
 - duration of CD4 <200-MELD?
 - HIV (and/or HCV) duration-MELD?
 - immune marker-MELD?
 - duration of MELD ≥ 25 ?

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Summary-1

- Overall *and* graft survival comparable to HIV- UNOS transplant recipients
- No significant HIV clinical, virologic or immunologic disease progression in these HIV+s given immunosuppression for graft survival
- No evidence of impaired graft function due to HIV
- Rejection rates unexpectedly high in renal transplant recipients (60%)
- Treatment with anti-T-cell depleting agents results in prolonged depletion of CD4 positive cells

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Summary-2

- Recurrent hepatitis B controlled with antiviral therapy (3TC/FTC and/or adefovir/tenofovir, etc) and monthly HBIg
- Recurrent HCV may be a significant problem, with an increased risk of morbidity and mortality
- HPV – anal CA, HHV8 – KS: problematic ?
- HAART regimens including PIs require major adjustments in calcineurin inhibitor dosing

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How Can I Use this Information in your Practice?

- ▶ **Preliminary results of solid organ transplants in HIV+ patients are encouraging**
- ▶ **Transplant protocol is open at 20 centers in U.S. for livers and/or kidneys**
- ▶ **Liver and kidney transplants may be an option to consider for your patients**
- ▶ **For further information and to schedule a patient for a pre-transplant consultation with U of M 305 243 1000 and for transplantation team**

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Economics

- Reimbursement by third-party payers for experimental procedures is not assured
- No Medicare rules preclude transplantation in the HIV population
- Study investigators believe that private and public insurance will cover the costs of the transplant

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POSITION STATEMENT

- ***“Transplantation in HIV patients should be analogous to transplantation in patients with other chronic illnesses”***

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Thank you

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