

# **Renal Transplantation in People Infected with HIV**

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**Do not follow where  
the path may lead. Go  
instead where there is  
no path and leave a  
trail.**

*Ralph Waldo Emerson*

# Questions to be Answered

Is renal transplant in HIV-infected patients safe and effective?

Does HIV disease progress after transplant?

What are the problem areas?

What is the future for transplantation in HIV-infected patients?

# Introduction

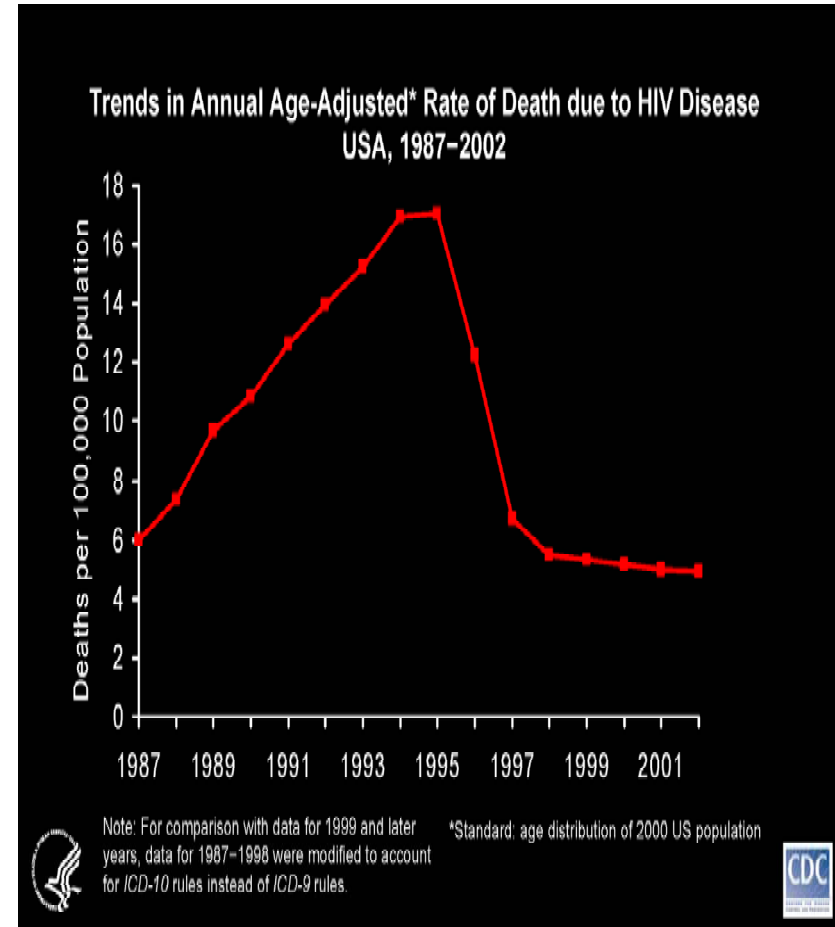
- **1. NIH sponsored study.** 148 patients transplanted, 353 in the referral/ evaluation process
- 2. A New Conversation occurring around transplantation and HIV
- 3. Insurers authorizing Transplants in persons with HIV
- **4. It's a Law:** *California Law Prohibits Insurance Coverage Denials Based Solely on HIV Status*
  - AB 228, authored by Assemblyman Paul Koretz (D-West Hollywood), has been signed by Governor Arnold Schwarzenegger. The bill was passed by the Legislature with bipartisan support and is the first in the nation to prohibit insurers from denying coverage for organ transplants based solely on a patient's HIV status

# HIV and Transplant: The Past

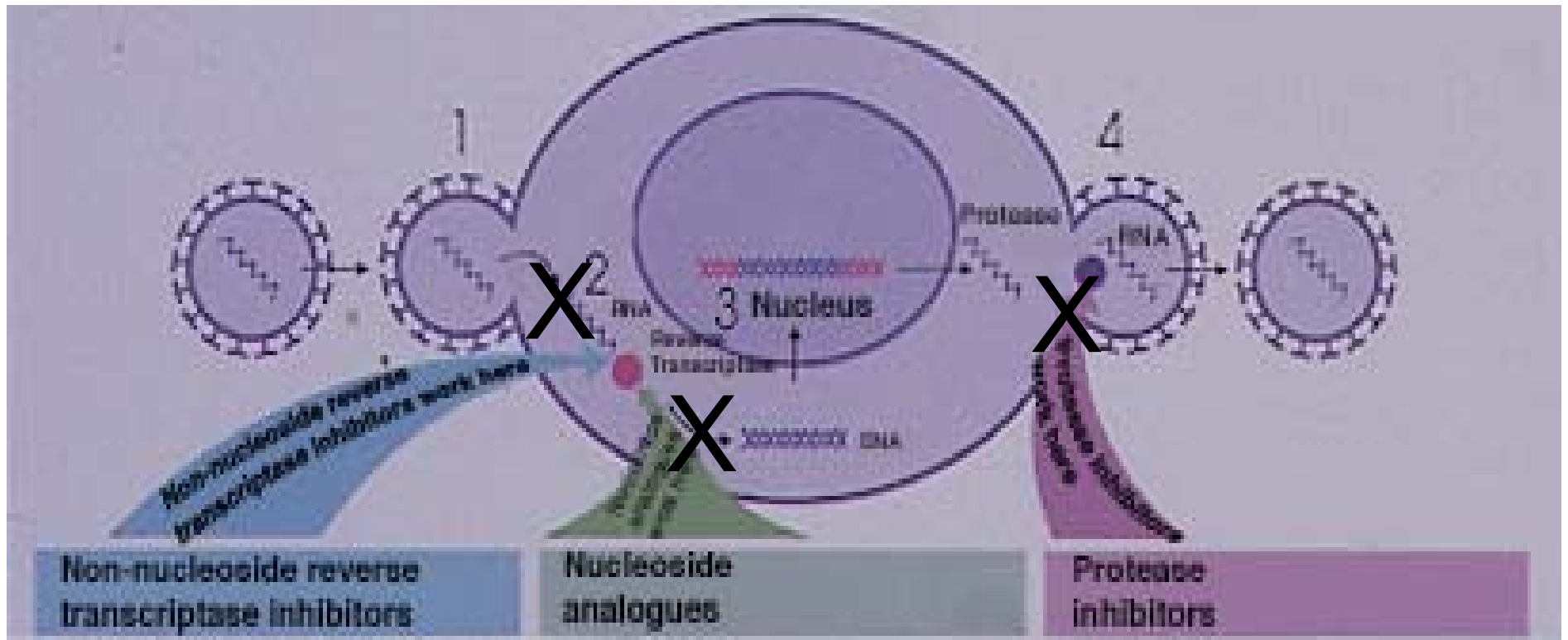
- HIV+ transplants in the 80's had discouraging results
- Factors limiting those initial experiences included:
  - Occurred prior to the advent of HAART therapy and routine prophylaxis against opportunistic infections
  - Limited information on pre transplant HIV status and post transplant management of HIV
  - Predated the newer immunosuppressive medications

# HIV and Transplant: The Present

- **HAART-associated improvements:**
  - decreased mortality
  - decreased incidence of opportunistic infections
  - decreased hospitalization rates



# Immunosuppressive may have anti-HIV effects



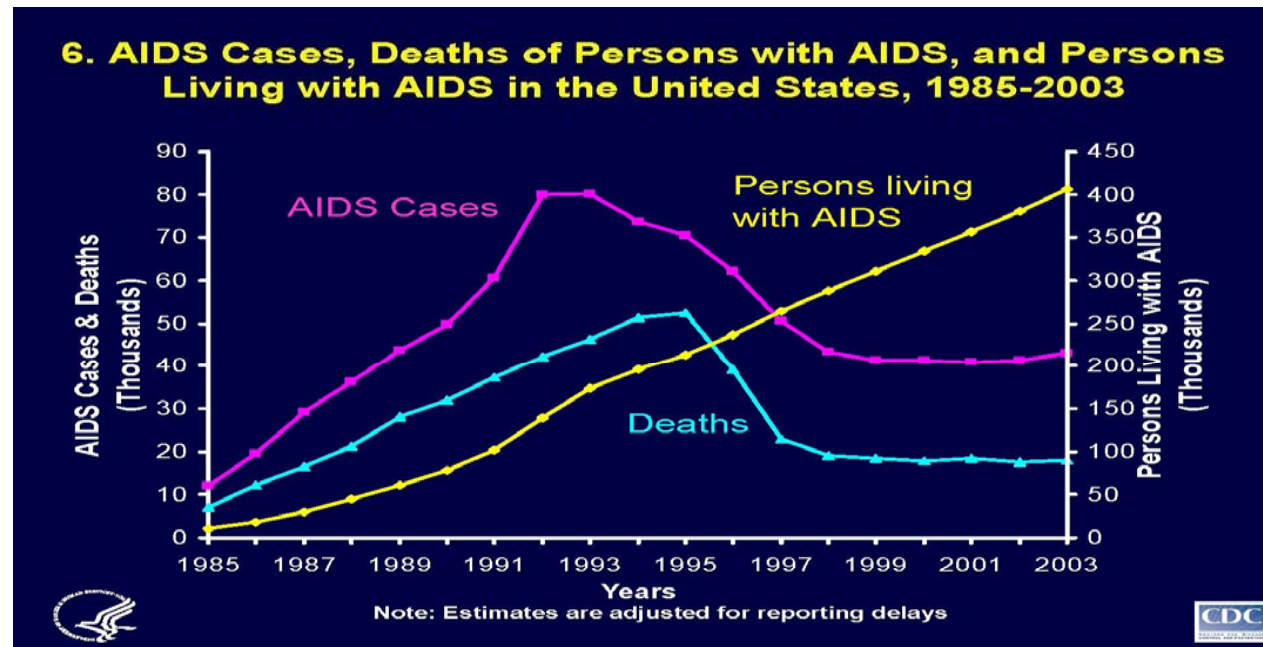
Sirolimus

CellCept

Cyclosporine

# Need for Transplantation

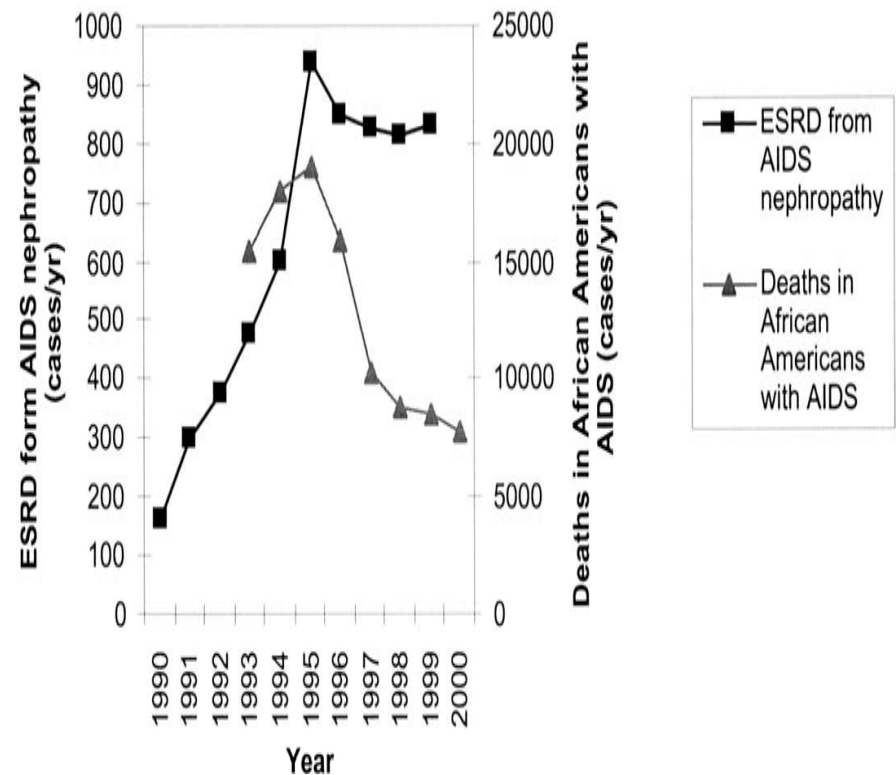
- 750,000-1.5 million people infected with HIV with 40,000 new cases added each year
- Life expectancy is high





# Need for Transplant in HIV + CKD Patients

- Between 1995 –2002 approx 800 new patients a year report HIVAN as the cause of CKD to the USRDS.  
90% of those cases were reported by people of African descent.
- Currently in the US, HIVAN is the most common cause of renal failure among people with HIV and is the 3<sup>rd</sup> most common cause of ESRD in African Americans between the age of 20-60years. (Cosgrove et al, 2000).



# Should All HIV + Patients With ESRD from Be Excluded Transplantation? 1998 and 2004 Survey Results

Transplant Center Response Rate: 149/248 (60%)

Would a patient who refuses HIV testing be considered for transplantation? 1998

Would an HIV-infected ESRD pt be considered for cadaveric transplantation? 1998

Would an HIV-infected ESRD pt be considered for cadaveric transplantation? 2004

Would an HIV-infected ESRD pt be considered for living donor transplantation? 2004

YES	NO	UN SURE
	84%	16%
9%	91%	
29%	68%	3%
5%	91%	4%

# EARLY AND UNEXPECTED RESULTS IN A MULTICENTER STUDY OF KIDNEY TRANSPLANTATION IN HIV- INFECTED RECIPIENTS

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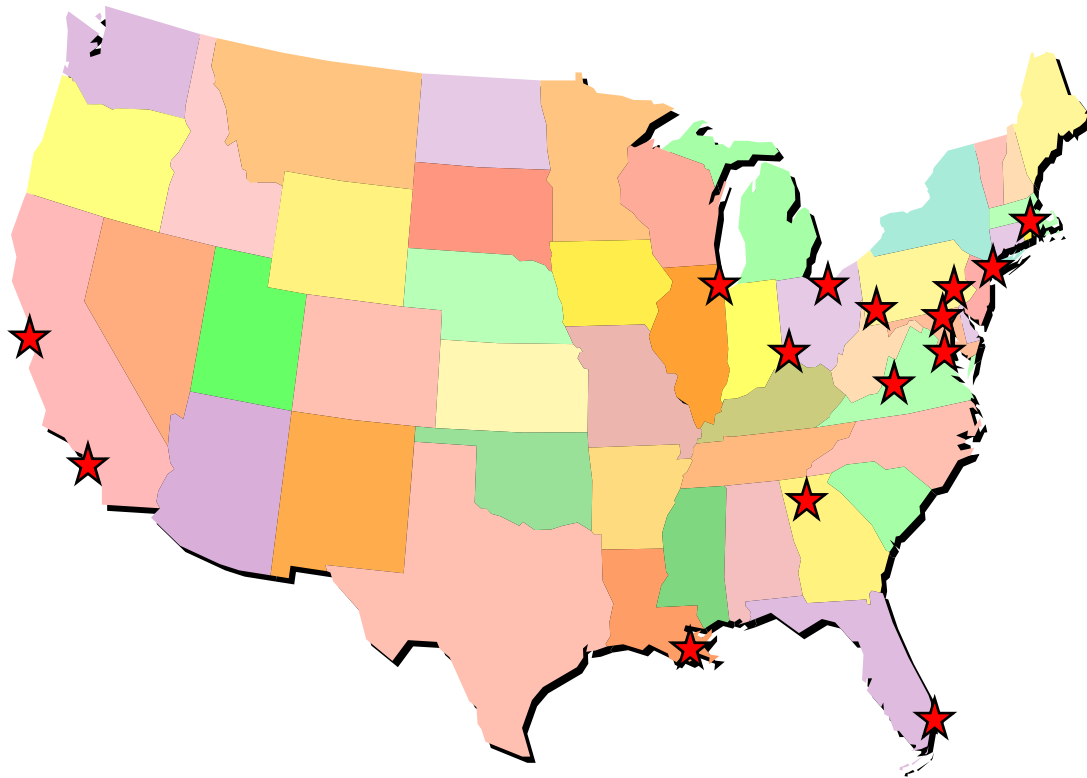
**Barbara Murphy, MD**

Mt. Sinai School of Medicine



***On behalf of HIVTR: Solid Organ Transplantation in HIV Multisite Study: NIH Grant U01  
AI052748***

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



## WEST

*San Francisco, CA*  
**UCSF** (K, L, Peds K, Peds L)  
*Los Angeles, CA*  
**Cedars-Sinai** (L)

## MID-WEST

*Chicago, IL*  
**University of Chicago** (K, L, Peds K, Peds L)  
**Rush University** (K, L)  
**Northwestern** (K,L)  
*Cincinnati, OH*  
**University of Cincinnati** (K, L)  
*Cleveland, OH*  
**Cleveland Clinic** (K, L)

## NORTHEAST

*Baltimore, MD*  
**Johns Hopkins** (K,L)  
**University of Maryland** (K)  
*Boston, MA*  
**Beth Israel Deaconess** (K, L)  
*New York, NY*  
**Mt. Sinai** (K, L, Peds K)  
**Columbia University** (L, Peds L)  
*Philadelphia, PA*  
**Drexel University** (L)  
**University of Pennsylvania** (K, L)  
*Pittsburgh, PA*  
**University of Pittsburgh** (K, L)  
*Washington, D.C.*  
**Washington Hospital Center** (K)  
**Georgetown Medical Center** (K, L)

## SOUTHEAST

*Atlanta, GA*  
**Emory University** (K)  
*Charlottesville, VA*  
**University of Virginia** (K,L)  
*Miami, FL*  
**University of Miami** (K, L)  
*New Orleans, LA*  
**Tulane** (K, L, Peds K, Peds L)

# Specific Aims

- To evaluate the impact of kidney transplantation and post-transplant immunosuppression on HIV disease progression
- To evaluate the impact of HIV disease on kidney function in addition to patient and allograft survival

# Subject Selection Criteria

## HIV+ Kidney Transplant Recipients

- CD4+ T-cell count > 200 for kidney recipients
- HIV RNA undetectable.
- Opportunistic infection history acceptable for most OIs with continued exclusion of PML, chronic cryptosporidiosis and visceral KS.
- Otherwise usual selection criteria for non-HIV-infected transplant candidates

# Immunosuppression and Rejection Management

- Initial immunosuppression included cyclosporine or tacrolimus +/- mycophenolate mofetil (MMF), in combination with steroids.
  - IL2R antagonist use was allowed.
- Rejections managed with a steroid pulse, changing calcineurin inhibitors or doses, and/or thymoglobulin, and/or adding sirolimus

# Study Accrual

(as of May 20, 2009)

148 transplants (150 target)

Average follow-up time: 1.8 years (max = 5.0)

116 eligible candidates in pre-transplant phase

237 active candidates in screening phase



# Demographics

- 20% female
- 28% white, 68% black
- Average age = 46 (range: 9-72)
- 67% Medicare/Medicaid, 30% private insurance

# Indications for Transplant

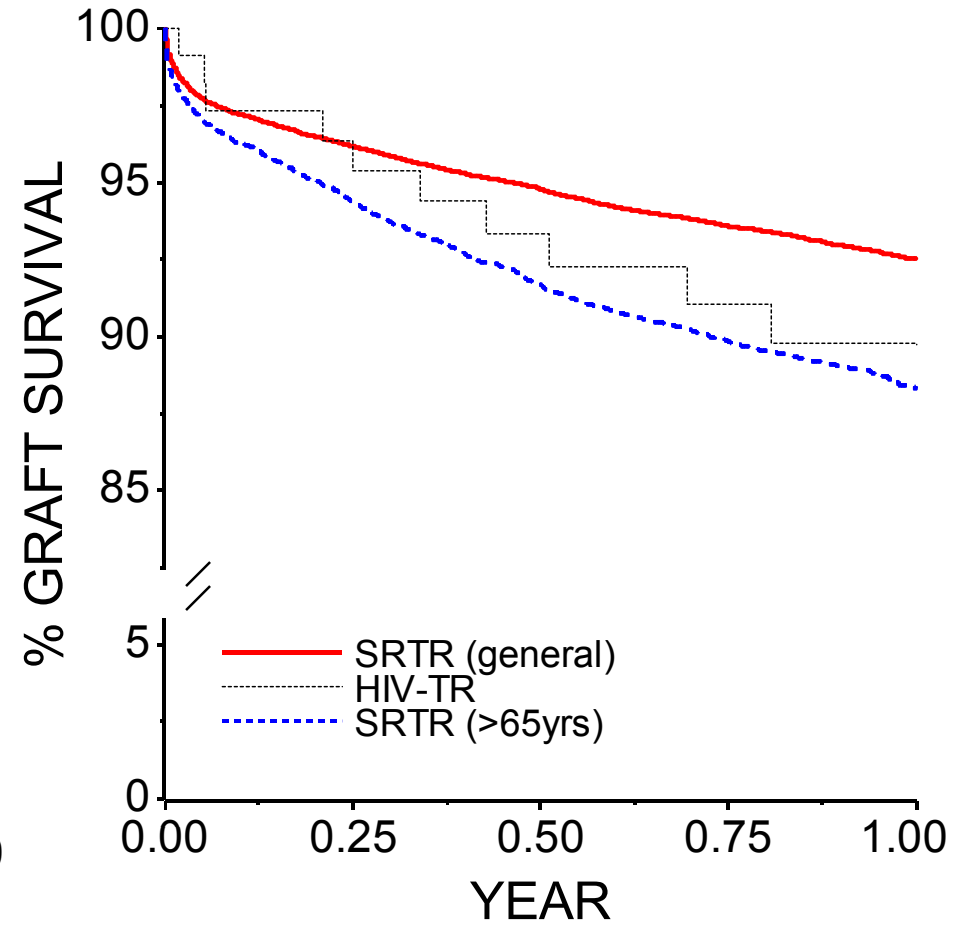
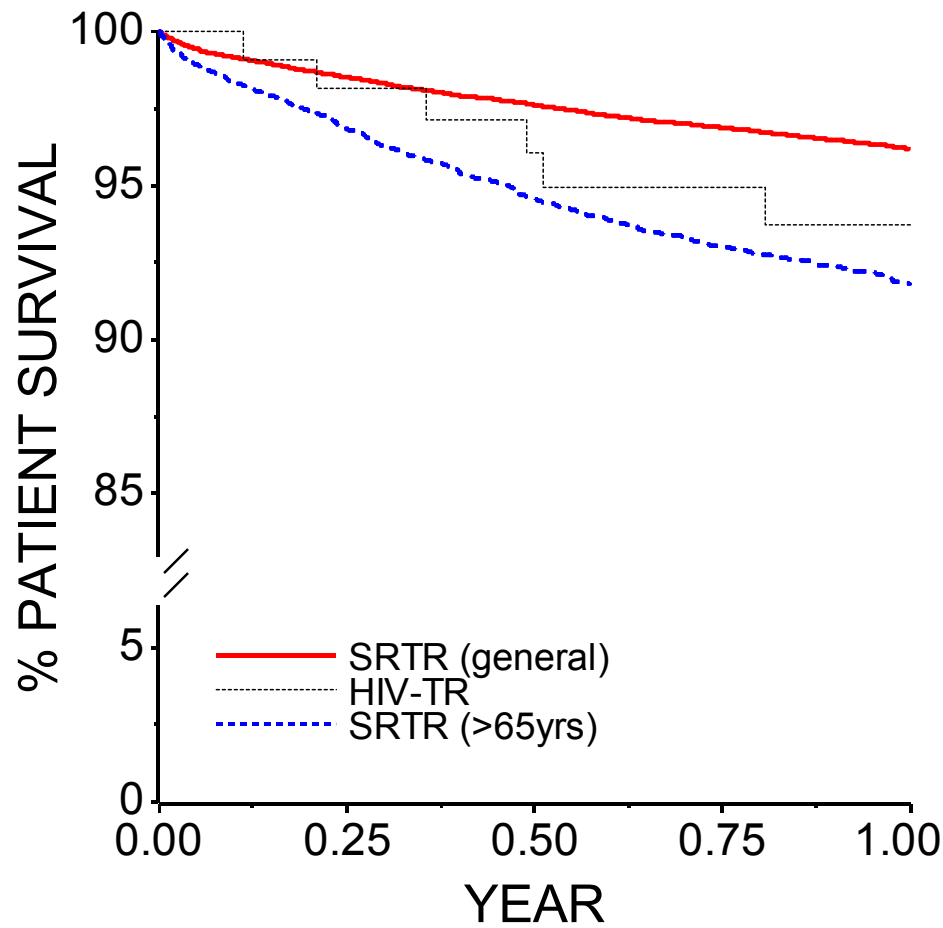
(Not all biopsy confirmed)

- Hypertension/nephrosclerosis (25%)
- HIV nephropathy (23%)
- Diabetic nephropathy/glomerulosclerosis (8%)
- Focal glomerulosclerosis (6%)
- Other (38%)

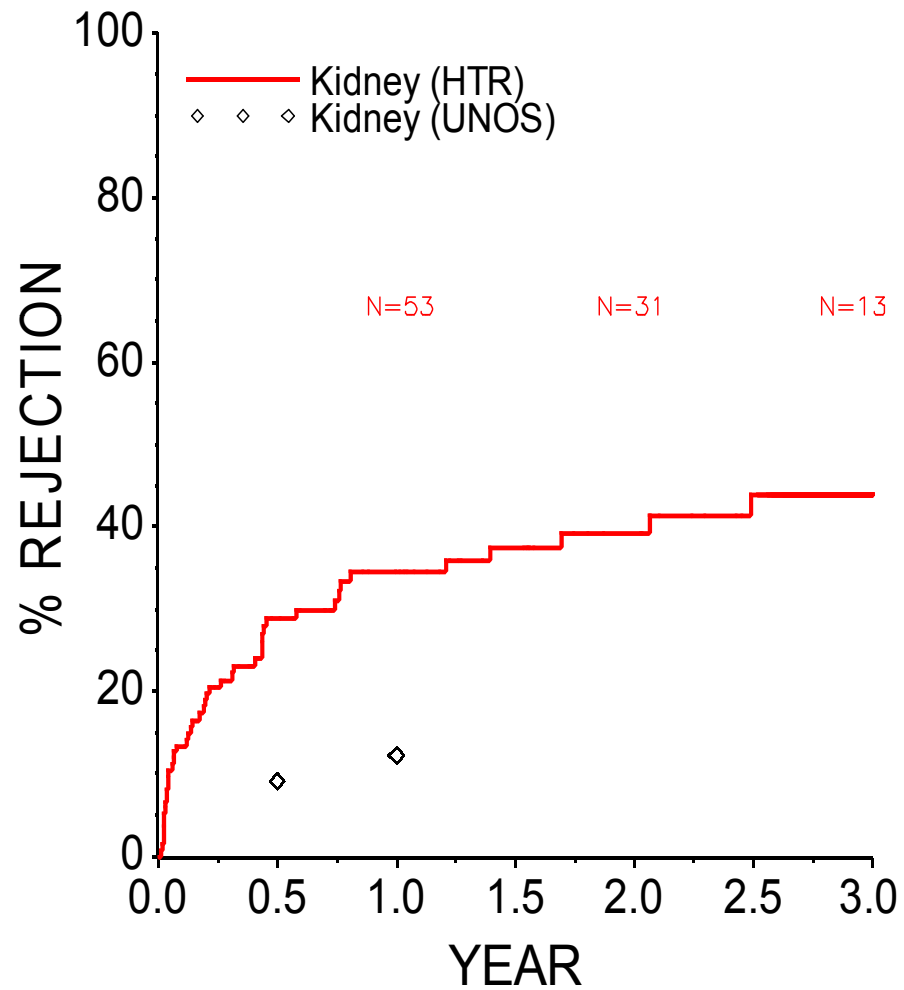
# Donor Characteristics

	<b>%</b>
<b>Live Donor</b>	29
<b>Donor Age &gt; 60 years</b>	5
<b>African-American Donor</b>	20
<b>HBV+ Donor</b>	0
<b>HCV+ Donor</b>	5
<b>Non-heart beating donor</b>	8
<b>High infectious risk donor</b>	19
<b>Extended Criteria Donor (ECD)</b>	18
<b># HLA Mismatch Antigens &gt; 4</b>	41

# 1-Year Patient and Graft Survival



# Time to First Rejection



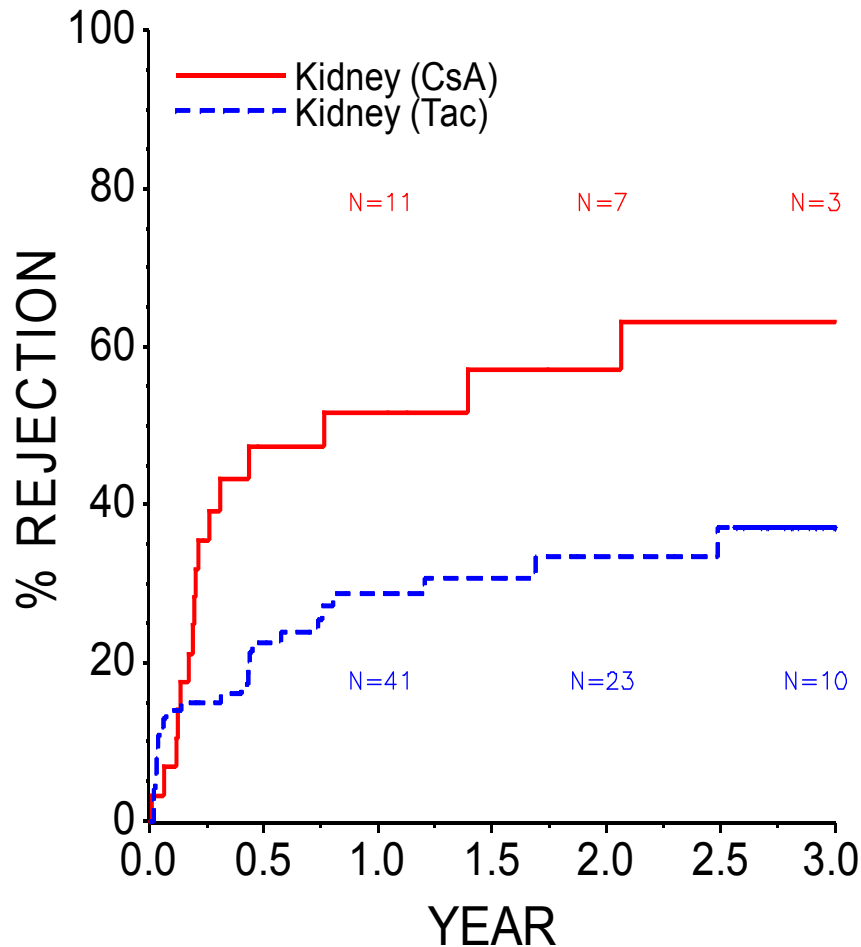
# Risk Factors for First Acute Rejection

## Univariate Models

Baseline Covariates	Hazard Ratio (95% CI)	P Value	Time-Dependent Covariates	Hazard Ratio (95% CI)	P Value
Black Race	0.61 (0.31, 1.20)	0.15	Protease Inhibitor	1.13 (0.64, 1.99)	0.67
Age	0.90 (0.51, 1.58)	0.70	Mycophenolate Mofetil	0.60 (0.33, 1.10)	0.10
Simulect/Daclizumab Induction	1.29 (0.73, 2.28)	0.37	CD4+ Cell Count (Per 50 cells/ml)	0.95 (0.90, 1.00)	0.06
Opportunistic infection history	0.97 (0.51, 1.87)	0.93	Detect. Viral Load	1.49 (0.46, 4.83)	0.50
Hepatitis C infection	1.81 (0.77, 4.26)	0.17	CsA use	2.10 (1.14, 3.89)	0.02
Deceased Donor	2.10 (1.04, 4.21)	0.04	CsA trough level	1.00 (0.99, 1.00)	0.21
# Mismatched Antigens >4	1.68 (0.95, 2.97)	0.07	Tac use	0.61 (0.33, 1.12)	0.61
PRA at tx >0	1.18 (0.60, 2.33)	0.64	Tac trough level	0.89 (0.80, 0.99)	0.03
CD4+ T-cell count (Per 50 cells/ml)	0.99 (0.94, 1.04)	0.64			

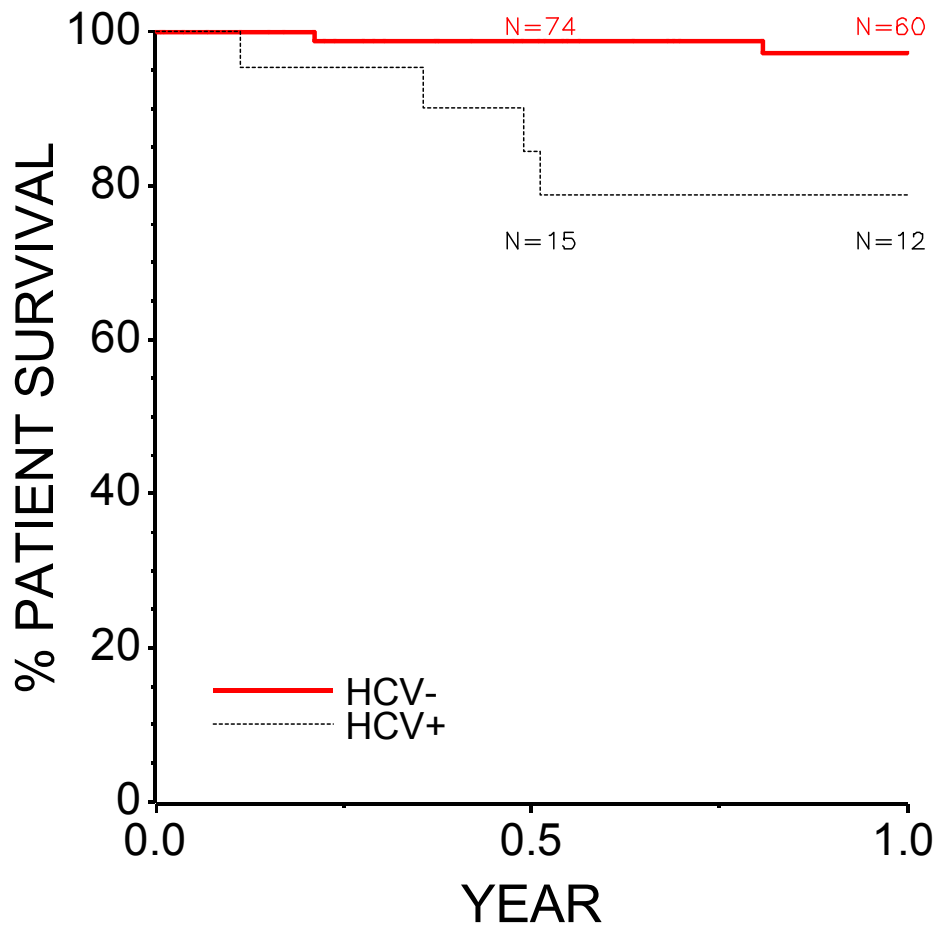
Deceased donor and Tacrolimus trough level remained significant in the multivariate model.

# Time to First Rejection by Initial Immunosuppression



- **Immunosuppression**  
CsA (21%)  
Tac (72%)  
None reported (7%)
- **1-year rejection rates**  
CsA: 52% (CI 35,72)  
Tac: 29% (CI 20,40)  
Log-rank test; p=.02

# 1-Year Patient Survival by HCV Status



❖ 19% of kidney recipients HCV+

❖ 1-year survival rates  
HCV- : 97% (CI 89,99)  
HCV+: 79% (CI 53,92)

Log-rank test; p=.002



# PH Regression Models for Kidney Failure in 1<sup>st</sup> Year

Univariate Predictor	Hazard Ratio (95% CI)	P Value
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## Recipient Characteristics

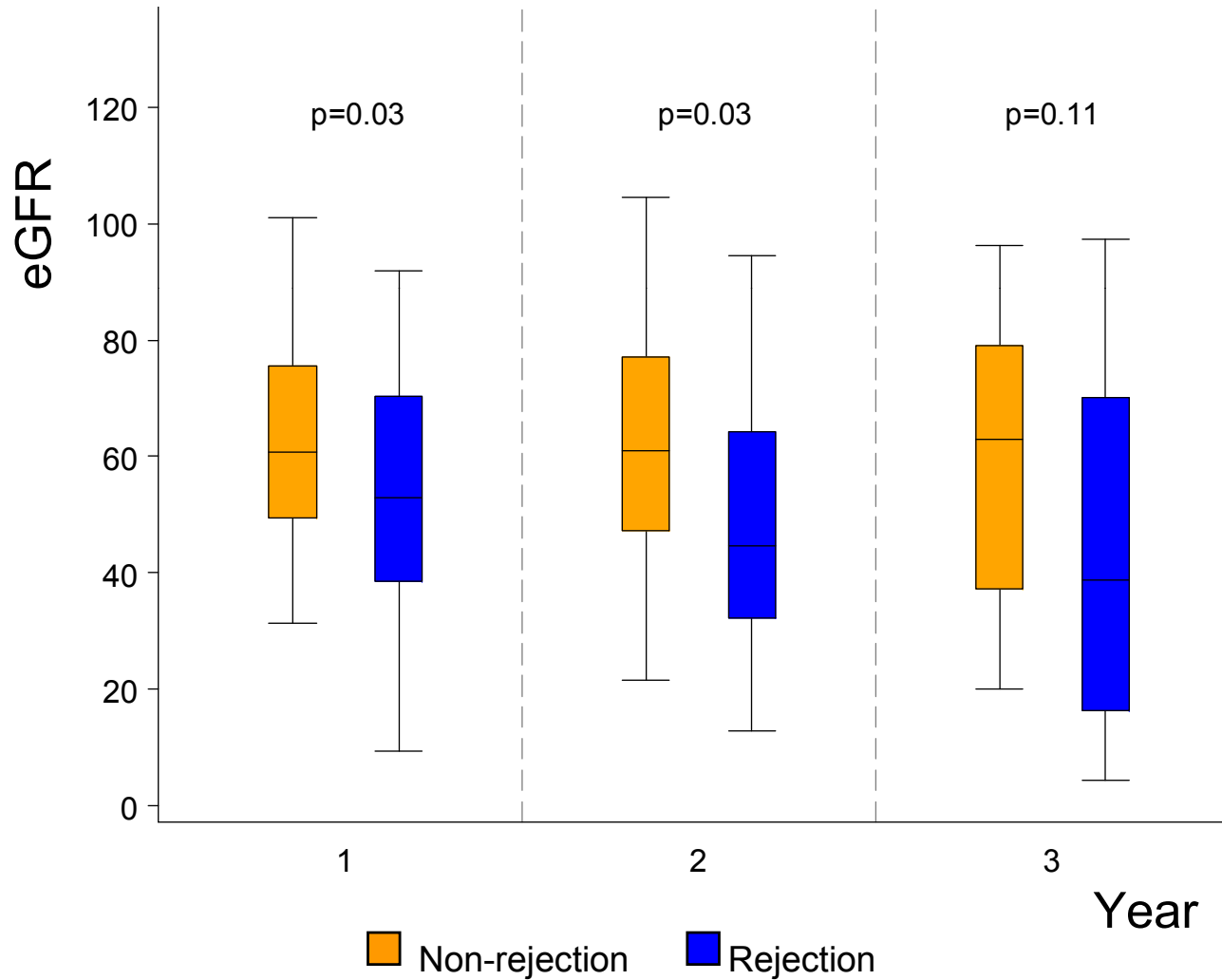
Black Race	1.6 (0.6, 4.5)	0.33
Hepatitis C	1.6 (0.6, 4.5)	0.34
Cyclosporine as Initial IS Med (vs.Tac)	0.6 (0.2, 1.7)	0.36
Delayed Graft Function	2.4 (1.0, 5.7)	0.05
Rejection*	5.9 (2.2, 16.2)	0.001

Multivariate Predictors	Hazard Ratio (95% CI)	P Value
Delayed Graft Function	1.3 (0.5, 3.3)	0.56
Rejection*	5.0 (1.8, 13.9)	0.002
Live Donor	0.4 (0.1, 1.3)	0.12

## Donor Characteristics

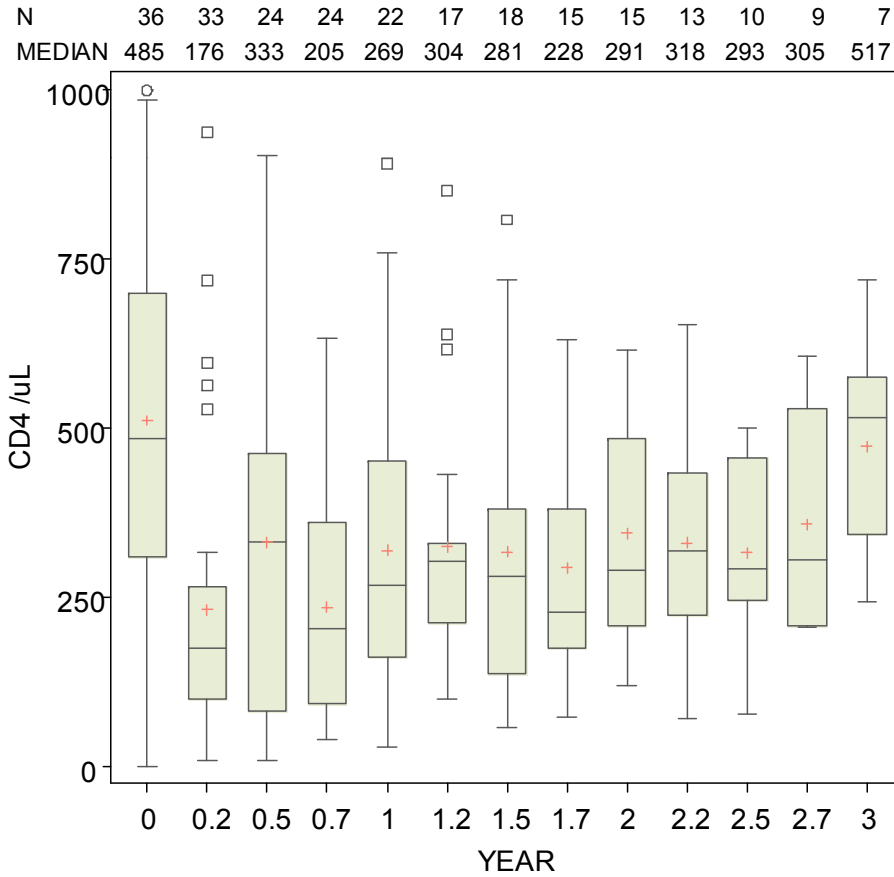
Age ≥ 50	1.3 (0.6, 3.2)	0.53
Live Donor	0.3 (0.1, 0.9)	0.04
>4 Mismatched Donor-Recipient Antigens	1.5 (0.6, 3.5)	0.37
High-infectious Risk Donor	0.8 (0.2, 2.7)	0.71
Extended Criteria Donor	0.8 (0.2, 2.8)	0.73

# eGFR by Rejection Status



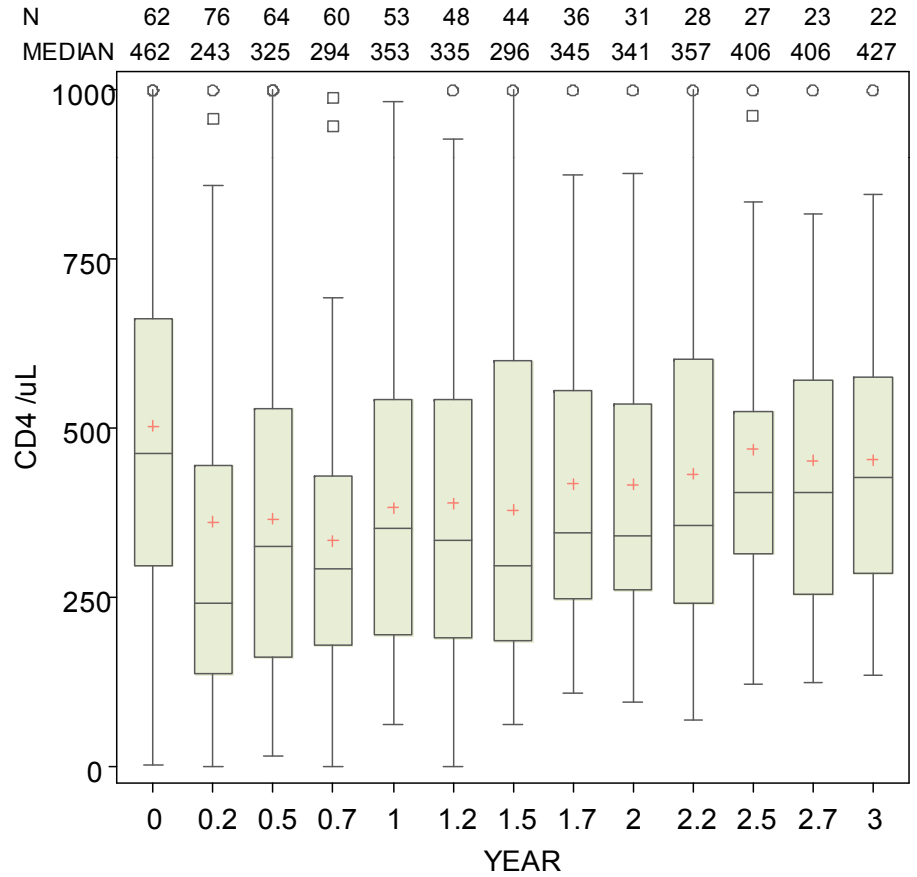
# CD4 Cell Counts

## Thymoglobulin



○ 1 box clipped

## No Thymoglobulin



○ 11 boxes clipped

# BK Polyomavirus Infection

Nephropathy (6), viremia (8)

## Cases of BK Nephropathy

- Onset Day Post-Tx

Median: 100 days (range 61-271days)

- Rejection pre/post BK: 3 cases

- Outcome

1 graft loss due to rejection/compliance

2 resolved; 1 case with significant fibrosis

3 persistent

# Opportunistic Infections and Malignancies

24% with History of AIDS-related OIs pretransplant

2 AIDS-defining OIs post-transplant

1 candida esophagitis, 1 presumptive PCP

No de novo KS

No LPD

HPV mediated dysplasia

6 non-AIDS malignancies

Recurrent metastatic renal cell carcinoma

Metastatic renal cell carcinoma

2 oral squamous cell cancers

1 basal cell skin cancer

Thyroid gland cancer

# Summary

In this study population:

- No significant HIV clinical, virologic nor immunologic disease progression in these immunosuppressed patients.
- No evidence of impaired graft function due to HIV.
- Rejection rates unexpectedly high.
- Treatment with anti-T-cell depleting agents results in prolonged depletion of CD4 positive cells.
- Co-infection with HCV associated with decreased patient and graft survival.

# Conclusions from this Study

- One year graft and patient survival was acceptable with limited HIV/transplant complications
- Unexpectedly high rejection rates suggest the presence of a dysregulated rather than an absent immune system
- Improvements in immunotherapy are needed to decrease rejection and maximize long term graft function

# 2008 UCSF Demographics

		<b>K</b>	<b>K/P</b>	<b>L</b>	<b>L/K</b>
<b>Total Transplants</b>	<b>85</b>	<b>41</b>	<b>2</b>	<b>39</b>	<b>3</b>
<b>Male</b>	<b>78</b>	37	2	36	3
<b>Female</b>	<b>7</b>	4	0	3	0
<b>African American</b>	<b>26</b>	20	0	6	0
<b>Caucasian</b>	<b>47</b>	18	2	27	0
<b>Asian</b>	<b>4</b>	1	0	2	1
<b>Hispanic</b>	<b>6</b>	2	0	3	1
<b>Philipino</b>	<b>2</b>	0	0	1	1
<b>LR Donor</b>	<b>14</b>	11	0	2	1
<b>Deceased Donor</b>	<b>71</b>	30	2	37	2



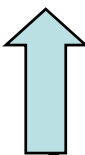
# Challenges in Patient Management

## Short Term Issues

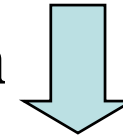
- Drug interactions
- Monitoring of levels and toxicities
- Standard target immunosuppression trough levels result in more toxicity
- Rejection and Infection
- Psychosocial

# Pharmacodynamic Interactions and Medical Complexity



  
**Highly Active  
Antiretroviral Therapy**

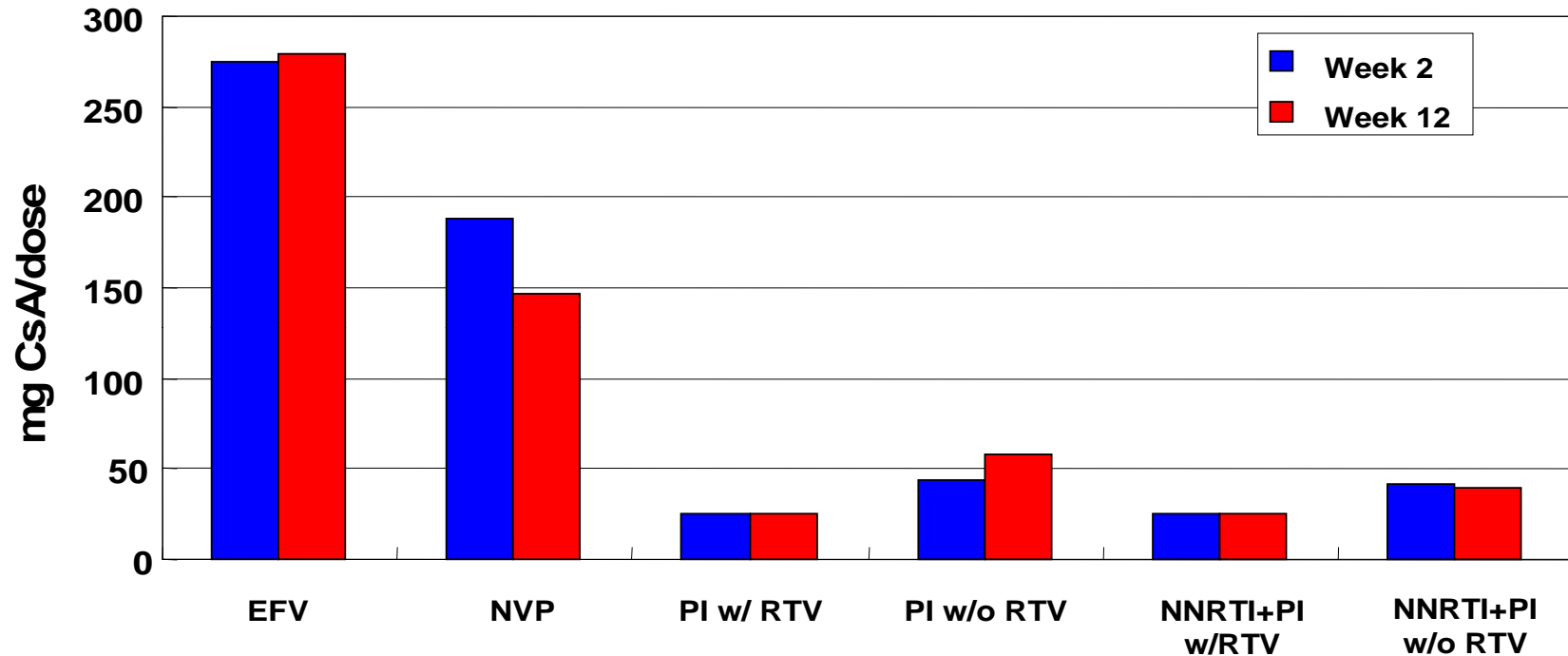
**Triple  
Immunosuppression  
to Prevent Graft  
Rejection**



# 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

# Problems in HIV Transplantation: CNI & ARV interactions



Comedication(s):		EFV	NVP	PI w/ RTV	PI w/o RTV	NNRTI+PI+RTV	NNRTI+PI-RTV
N		20	11	13	7	8	5
CsA dose (mg/dose)	Wk 2	275 ± 129	189 ± 44	25 ± 0	57 ± 31	25 ± 0	42 ± 30
	Wk 12	279 ± 123	147 ± 52	25 ± 0	75 ± 63	25 ± 0	39 ± 28
CsA Cmin (ng/ml)	Wk 2	91 ± 57	130 ± 61	156 ± 67	128 ± 45	168 ± 77	173 ± 25
	Wk 12	84 ± 60	116 ± 57	111 ± 77	185 ± 177	104 ± 61	154 ± 21

# Challenges in Patient Management

## Long Term Issues

- Cardiovascular disease
- Bone Diseases
- Malignancies: skin cancers, anorectal cancers due to HPV disease
- Metabolic syndrome
  - Dyslipidemia
  - PTDM
  - Hypercholesterolemia/ hypertriglyceridemia
- Life Adjustment

# Potential long-term problems

## **Long-term renal function**

- increased nephrotoxicity from CNIs
- increased graft loss from rejection

## **Bone disease**

- HIV-associated low androgen levels in M & F
- ARV- & tx medication- induced low BMD

## **Cardiovascular disease**

- ARV- & tx medication- induced dyslipidemia and insulin resistance

# Cardiovascular Disease

## Transplant

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

## HIV

- Incidence increasing in the past 10 years
- Risk Factors: dyslipidemia, DM, metabolic syndrome, smoking
- 30% with Hypertension

# Bone Disorders: Osteopenia, Osteoporosis, Osteonecrosis

## **Transplant**

- Pre tx renal insufficiency
- Hyperparathyroidism
- Smoking
- Poor dietary calcium intake
- Corticosteroid use

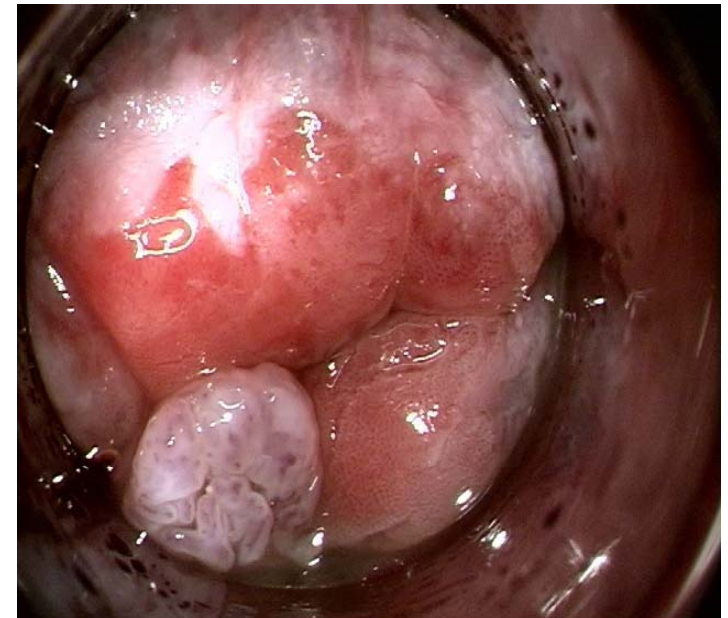
## **HIV**

- Alcohol intake
- Smoking
- Prolonged use of PIs
- Lack of weight bearing exercises
- Body wt <20% or >20% IDW



# HPV Disease

- HPV-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
- First case – anal CA in situ post-transplant



# Challenges of Living with...

## Managing two complex medical problems

- multiple medications and drug interactions
- managing and coping with side effects

## Adjusting pre transplant expectations to post transplant realities

- overestimating the benefits
- unmet expectations
- minimizing the new challenges

## Emotional adjustment

- depression/ post traumatic stress disorder

# Possibilities to Live into....

Living with a chronic illness can transform life in a positive way

- Personal transformation
- Acceptance of death leads to more meaningful living
- Freedom from pre-existing expectations

# Growing experience with renal transplantation in HIV-infected subjects

<b>Country</b>	<b>#</b>
<b>USA</b>	<b>218</b>
<b>France</b>	<b>7</b>
<b>Spain</b>	<b>13</b>
<b>Italy</b>	<b>4</b>
<b>Canada (BC only)</b>	<b>2</b>
<b>Switzerland</b>	<b>1</b>
<b>South Africa</b>	<b>1</b>

# Take home points

Renal transplant in HIV-infected patients appears safe and effective

Progression of HIV disease is not common

Problem areas include:

- drug interactions
- HCV
- rejection
- bone and cardiovascular disease?

Transplant in HIV subjects is increasing worldwide

# A Big Thanks to:

- Laurie Carlson RN
- Peter Stock MD
- Linda Frassetto MD
- Entire NIH Multicenter study sites



# Transplant Study

## *For People with HIV Infection*

Specific Site & Study information  
Study Related Presentations &  
Published Literature  
can be found at:

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