

# RENAL SPARING EFFECTS OF SIROLIMUS IN HIV+ TRANSPLANT RECIPIENTS

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# Background

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- Sirolimus may spare the nephrotoxic effects of calcineurin inhibitors (CNI), but has not been evaluated in the context of HIV
- Sirolimus may increase the risk of hypertriglyceridemia (hTG), especially with protease inhibitors (PI)
- Significant drug interactions exist with the CNIs and sirolimus when used in combination with a PI or efavirenz (EFV) based antiretroviral (ARV) regimen

# Objectives

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- Describe prevalence and indications for use of sirolimus in HIV+ kidney and liver transplant recipients
- Estimate impact of sirolimus on the estimated glomerular filtration rate (eGFR)
- Estimate impact of sirolimus on triglycerides (TG)
  - Describe use of lipid lowering therapy
- Describe sirolimus dosing modifications with ARVs

# Methods

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- Prospective, observational, multi-site study of liver or kidney transplantation in 112 HIV-infected patients
  - Retrospective collection of indications for sirolimus use in 26 (23%) patients
- Immunosuppression, ARV, and lipid lowering therapy individualized
- Univariate and multivariate repeated measures models to identify predictors of eGFR (4 point MDRD) and TG

# eGFR Model Covariates

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- Immunosuppression
  - Sirolimus vs CNI vs Sirolimus + CNI
- Protease inhibitor
- Tenofovir
- Co-trimoxazole
- Transplanted organ
- Gender, Race, Age
- Hepatitis C (HCV) status
- Donor source and age
- Rejection in the previous 3 months
- Time post transplant
- Baseline eGFR

Indications for sirolimus use not yet evaluated in this model

# Baseline Characteristics (N=26)

	Sirolimus use Kidney (n=15)	Sirolimus use Liver (n=11)
Age (mean, years)	45	48
Gender (% male)	80	64
Race (%)		
Caucasian	13	55
Other	87	45
HCV (%)	7	82
Donor source (%)		
Deceased	73	100
Live	27	
Donor age (mean, years)	38	40
Mean time ( $\pm$ SE) from txp to initiation of sirolimus (days)	162 $\pm$ 208	130 $\pm$ 140
Mean duration ( $\pm$ SE) of F/U (days)	323 $\pm$ 303	268 $\pm$ 247

\* - duration of follow-up from time of conversion to sirolimus

# Indications for Sirolimus

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Indication	% patients (n)
<b>Renal dysfunction due to CNI's</b> Tacrolimus (6), Cyclosporine (1)	27% (7)
<b>Neurotoxicity secondary to CNI's</b> Tacrolimus (3), Cyclosporine (2)	22% (5)
<b>Preservation of renal function</b>	15% (4)
<b>Intolerance of anti-metabolite</b>	12% (3)
<b>Cyclosporine/Sirolimus site standard</b>	8% (2)
<b>Malignancy</b>	8% (2)
<b>Rejection</b>	8% (2)
<b>Delayed graft function</b>	4% (1)

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# Results: Predictors of eGFR

## Kidney

Predictor	Estimate	p value
Donor age	- 0.00417	0.0003
Rejection	- 0.1426	<0.0001
Baseline eGFR	0.2428	0.0002
Time post-transplant	- 0.02154	0.0002
Sirolimus + CNI	0.1365	0.0023

## Liver

Predictor	Estimate	p value
Donor age	- 0.00630	0.0207
Rejection	- 0.06217	0.0412
Baseline eGFR	0.1469	0.0158
Gender (male)	0.1708	0.0011

Final multivariate models

# Estimates of eGFR in Kidney Recipients

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- At year 1 post-transplant, assuming a median baseline eGFR (55) and donor age (38) the mean eGFR is estimated to be:
  - CNI: 57 ml/min/1.73m<sup>2</sup>
  - Sirolimus: 63 ml/min/1.73m<sup>2</sup>
  - Sirolimus and CNI: 78 ml/min/1.73m<sup>2</sup>
- The presence of a rejection episode in the past three months results in an additional 28% reduction in eGFR

# Lipid Lowering Therapy

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- Lipid lowering therapy was used in
  - 62% of subjects on sirolimus/PI therapy
  - 31% of subjects on sirolimus without a PI
  - 52% (45/86) of subjects who are not on sirolimus
- Sirolimus use was not associated with triglycerides in the multivariate model

# Sirolimus Dosing

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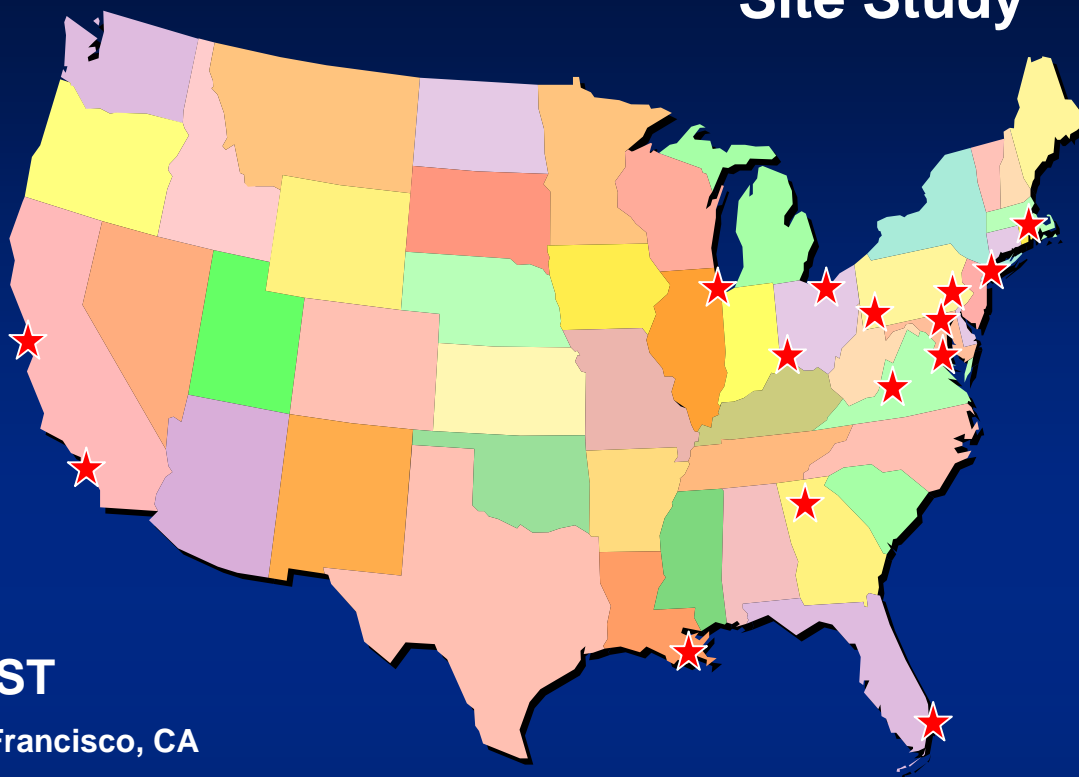
- Protease inhibitor based ARV regimen
  - Un-boosted PI regimen: 2 mg weekly
  - Boosted PI regimen: 0.5-2 mg weekly or 0.05 mg daily
- NNRTI based ARV regimen
  - Efavirenz: 3-6 mg daily
  - Nevirapine: 1-3 mg daily

# Conclusions

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- In this preliminary analysis, use of a CNI free sirolimus based IS regimen in HIV+ transplant recipients was not associated with higher eGFR
  - indications for sirolimus use, which may explain this finding, will be included in future modeling
- Triglyceride levels were also not associated with sirolimus
- Significant alterations in sirolimus dosing is necessary when used in combination with PI or efavirenz containing ARV regimens

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



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