

## **Meeting Summary:**

### **Solid Organ Transplantation in HIV Positive Patients** *Multi-Site Trial Planning Meeting*

Hotel Sofitel, 1914 Connecticut Avenue NW  
Washington, D.C.  
August 12-14, 2000

**This document is a companion piece to the Briefing Book**  
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# Protocol Overview Presentation

Presented by M. Roland

## **SPECIFIC AIMS**

- *To evaluate the impact of kidney and liver transplantation, and post-transplant immunosuppression, on HIV disease progression and markers of immune function and activity.*
- *To evaluate the impact of HIV infection on graft function and survival.*
- *To describe the pharmacokinetic interactions between immunosuppressive agents and the hepatically metabolized antiretroviral (ARV) agents.*

### Review of Current Protocols for Kidney and Liver

- Common inclusion/exclusion criteria
- Kidney vs. liver: differences in eligibility
  - CD4, viral load, antiretroviral use
- Medication regimens
  - antiretrovirals, immunosuppressives, prophylaxis (transplant and HIV)
- Clinical and laboratory follow-up
- Special studies and donor issues

### Common Eligibility Criteria

- No history of opportunistic infection or neoplasm
  - except fluconazole sensitive candida esophagitis
- No h/o aspergillus, TB, cocci, resistant fungal infections, specific neoplasia, recent flu or RSV
- No age limitations (peds ok)
- Monitoring (including biopsies) and treatment of HCV co-infection

### Eligibility Criteria Differences

- | <u>Kidney</u>        | <u>Liver</u>   |
|----------------------|--|
| • CD4 $\geq$ 200     | • CD4 $\geq$ 100   |
| • VL < 50            | • VL < 50 on stable ARV regimen <i>or</i>  |
| • Stable ARV regimen | • Detectable viral load off ARVs but ability to predict full suppression post-tx |

### Medication Regimens

- **Immunosuppressive Protocols**
  - Cyclosporine-based therapy
  - Prednisone
  - Anti-metabolites: MMF or imuran
  - Standard rejection therapy
- **Antiviral therapy**
  - Optimize suppression of HIV-1 RNA
  - Minimize development of resistance
  - Avoid AZT, D4T (MMF interactions)
- **Prophylaxis**
  - pneumocystis, cytomegalovirus, fungal infections
  - MAC, TB
  - HCV: interferon and ribavirin
  - HBV: HBIG and lamivudine

### Clinical Follow-Up Schedule

- 5 year follow-up
- Min. 6 GCRC visits (12-24-hour) at Week 1, 4, 6 months, and 1, 2 and 5 years + + +
- --> weekly (x 4)
- --> every other week (x 4)
- --> monthly (x 2)
- --> every 8 weeks (x 4)
- --> every 12 weeks for the next two years
- --> every 6 months for the final two years

### Current Sub-Study Elements

- Immunology Studies
  - HIV
  - Transplant
- Virology Studies
  - HIV
  - HCV, HBV
  - HPV
  - HHV8
- Pharmacology Studies

## Immunology Studies: HIV

- **Immunophenotyping**
  - (T and B cells, naïve vs memory, activation state)
- **LPA**
  - (PTH and recall antigens)
- **Cytokine flow cytometry (CFC)**
  - (to CMV and staph enterotoxin B)
- **NK cell function**
- **Soluble activation markers**
  - neopterin, beta-2-microglobulin
- **CAF** (CD8 mediated antiviral response)
- **CMV, EBV and HHV6 ELISAs**
- **Thymus CT**

## Immunology Studies: Transplant

- LPA against alloantigen (donor)
- Donor reactivity
  - (MLC, CML and CFC)
- Chimerism studies

## Virology Studies HIV, HCV, HBV

- Plasma and tissue HIV-1 RNA quant (bDNA)
- Plasma and tissue HCV RNA quant. (bDNA)
- HCV genotype and quasispecies
- Plasma and tissue HBV DNA quantification (bDNA and PCR)

## Virology Studies: HHV8 and HPV

- HHV8: Ab, cell associated and plasma viral load, cellular immunology, saliva
- HPV: cytology and biopsy with colposcopy

## Pharmacology Studies

- Trough CSA and prograph levels
- ? MMF levels
- Full pK of protease inhibitor and NNRTI
  - HPLC assays
- Urine tox for illegal and prescription drugs

## Donors

- Living related
- Cadaveric
- High Risk

Consensus Document  
Protocol Eligibility Criteria and Modifications

Presented by T. Summers and C. Collins

**ELIGIBILITY: No Changes From Proposed Protocol**

1. *Protocol vs. Registry*

Goal is to design a study protocol that can establish safety and appropriateness of procedure.

2. *CD4 Count*

Kidney: minimum 200 for previous 3 months  
Liver: minimum 100 for previous 3 months

3. *HIV viral load*

Kidney: < 50 for previous 3 months  
Liver: retain flexibility on VL criteria. Likelihood of post transplant viral suppression based on previous ARV history +/- resistance tests, to be decided by a three-person committee on a case-by-case basis.  
Add: undetectable VL without any ARV therapy ok

4. *Opportunistic infections/neoplasms*

No history of OI. Evaluate this criterion as study progresses, particularly with respect to history of PCP for sulpha-tolerant patients.

**HEPATITIS C: Consensus Document in Process (see Appendix C, page 32)**

- Not an absolute exclusion.
- Algorithm for disease staging, pre-transplant treatment options, and post-transplant monitoring and management to be distributed among consultants, with final review by all meeting attendees by Sept. 15<sup>th</sup>. (David Oldach, lead)

## MEDICATION REGIMENS

### 1. Immunosuppressives: Kidney

Regimen:	Prednisone, mycophenlyate plus calcineurin inhibitor of choice (cyclospine or tacrolimus). +/- anti-CD 25
Rejection:	No absolute recommendations or prohibitions. Sirolimus in steroid resistant or refractory rejection. Avoid OKT3.
Delayed Graft Function:	Consider treatment with sirolimus until a calcineurin inhibitor can be initiated. Other considerations for management of ATN include anti-CD25 antibodies.

### 2. Immunosuppressives: Liver

Regimen:	Calcineurin inhibitor of choice Rapid steroid taper Low threshold for mycophenolate use Avoid IL-2 receptor inhibitors
Rejection:	No absolute recommendations or prohibitions. Sirolimus in steroid resistant or refractory rejection. Avoid OKT3

### 3. Antiretrovirals – MMF interactions

- No mandated exclusion of AZT and D4T in those on MMF, but ensure patients and providers are aware of potential antagonism and encourage alternatives when appropriate.
- Consider merits of NNRTI vs. PI based regimen on case by case basis.
- M. Roland to prepare a briefing packet for referring HIV providers

### 4. Prophylaxis – HIV and Transplant

- see consensus document prepared by Marla Keller on page 8

### 5. PEP in the OR

- Plan appropriate PEP drugs before surgery

**LAB/STUDIES- see Appendix B, page 29**

- 1. Clinical:** Accept page 28 in briefing book. All core studies for all sites. See protocol details regarding monitoring frequency in those patients with and without evidence of past disease or pathogen exposure. HIV RNA will be local.
  
- 2. Immunology:** Accept page 30 in briefing book. Some transplant-specific immunology labs need to be local, but the chimerism and alloreactivity labs will be centralized in the Stock lab. There should be further discussion at each site with report back on intentions regarding optional labs. TRECS available at Mt. Sinai; funding will be provided for this assay by B. Murphy.
  
- 3. Virology:** Accept pages 29 in briefing book. Add EBV PCR. Add Kidney tissue for Mt. Sinai studies. Add Hep B DNA for HepBSAg pos.
  
- 4. Funding:** Funding for optional studies and specimen storage is being identified and pursued. Sites will be queried in the coming weeks regarding needs for storage and shipping, as well as special studies planned at individual sites.

## Consensus Document-Opportunistic Infection Prophylaxis

Prepared by Marla Keller

Pneumocystis carinii pneumonia (indicated for all patients for life)

Preferred: Bactrim 1 double strength tablet (160 mg trimethoprim, 800 mg sulfamethoxazole) daily or Bactrim 1 single strength tablet (80 trimethoprim/400 sulfamethoxazole) daily

Alternatives: Bactrim DS 1 tab tiw or Dapsone 50 mg bid or Dapsone 100 mg qd (Dapsone contraindicated if G6PD deficient)

If Bactrim & Dapsone allergic, consider Atovaquone 1500 mg daily or Aerosolized Pentamidine 300 mg via Respigard II nebulizer monthly

Strategies for managing mild reactions include discontinuation of the drug and resuming it at a lower dose or rechallenging with gradual dose escalation:  
Bactrim suspension for dose escalation (8 mg trimethoprim/40 mg sulfamethoxazole) 1 cc qd x 3d, 2 cc qd x 3d, 5 cc qd x 3d, 1 single strength qd

Toxoplasmosis (indicated for Toxo IgG + and CD4 count <100)

Preferred: Bactrim DS 1 tab qd or Bactrim SS 1 tab qd

Alternatives: Dapsone 50 mg daily + pyrimethamine 50 mg weekly + leucovorin 25 mg weekly, Atovaquone 1500 mg qd with or without pyrimethamine 25 mg qd + leucovorin 10 mg qd

Mycobacterium avium complex (indicated for CD4 count <50)

Azithromycin 1200 mg weekly is preferred. If unable to tolerate, consider Clarithromycin 500 mg bid, although must consider drug interactions with immunosuppressive agents. If unable to tolerate a macrolide, consider Rifabutin 300 mg qd.

Cytomegalovirus, Herpes simplex virus and Epstein Barr virus

CMV negative recipient/negative donor: Acyclovir 400 mg bid x 1 year

CMV negative or positive recipient/positive donor: Gancyclovir 5 mg/kg IV qd while hospitalized the 1 gram PO tid x 3 months

If CD4 >100, change to Acyclovir 400 mg bid x 9 months

If CD4 <100, continue Gancyclovir 1 gram PO tid

CMV positive recipient/negative donor: Gancyclo vir 5 mg/kg IV qd while hospitalized then change to Acyclovir 400 mg bid x 9 months

If CD4 <100, change to Gancyclovir 1 gram PO tid

Alternative option is no treatment while hospitalized and Acyclovir 400 mg bid x 1 year with close monitoring for CMV with PCR or antigenemia testing (per standard transplant protocol)

EBV negative recipient/positive donor: Gancyclovir 5 mg/kg IV qd while hospitalized then change to Gancyclovir 1 gram PO tid x 1 year

Reduce the dose of Gancyclovir for prophylaxis and treatment for undialyzed patients with renal dysfunction (Transplantation 2000 Feb 15;69(3):389-94)

Candidiasis: Mycelex troches for 3 months

+PPD (indicated for TST reaction  $\geq 5$  mm or previous +TST reaction without treatment or contact with a person with active tuberculosis)

Preferred: INH 300 mg qd + pyridoxine 50 mg qd x 9 months or  
INH 900 mg + pyridoxine 100 mg biw x 9 months or  
Rifampin 600 mg + pyrazinamide 20 mg/kg qd x 2 mo

Alternatives: Rifabutin 300 mg qd + pyrazinamide 20 mg/kg qd x 2 mo or  
Rifampin 600 mg qd x 4 months

Rifampin should not be administered with protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Rifabutin can be administered at one-half the usual daily dosing (i.e., reduce from 300 mg to 150 mg qd) with nelfinavir, indinavir and amprenavir. Rifabutin should not be used with the protease inhibitor hard-gel saquinavir or the nonnucleoside reverse transcriptase inhibitor delavirdine. Information is lacking regarding coadministration of rifabutin with soft-gel saquinavir or nevirapine.

Consider dose adjustment of all medications based on creatinine clearance and risk of hepatotoxicity.

# Statistical Issues in Data Management

Presented by: Donald Stablein PhD and Matthew McIntosh PhD



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## Projects

- 85% Government
- NIH Institutes
  - NCI
  - NEI
  - NHLBI
  - NIAID
  - NICHD
  - NIDDK
  - NIDCD
  - NIDA

## Projects (Continued)

- Disease Areas
  - Oncology
  - Infectious Disease
  - Vaccine Development
  - Transplantation
  - Autoimmune Disease
  - Ophthalmology

## Services

- Protocol Development
- Data Collection Activities
- Data Systems Design
- Data Quality Control
- Administrative Support
- Analysis and Reporting

## Kidney Transplants in HIV Infected Patients

- Randomization not practical
- Questions

Does renal transplantation benefit recipients?- Time varying covariate

When transplanted, do recipients have adequate function to justify the procedure?- Single arm trial versus external standard

## Design Assumptions

- 5 Year Study
- 3 Year Accrual Period
- 75 patients ie 2/month

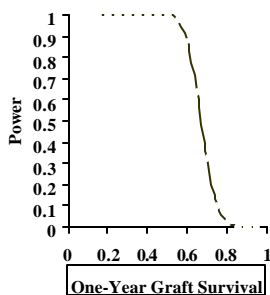
## Monitoring Plan

- Truncated Sequential Probability Ratio Test SPRT (Wald 1954)
- 1-Year Graft Survival
- $H_0$ : 75% versus  $H_a$ : <75%
  - $H_0$ : 75% versus  $H_a$ : 60%
- Test Statistic
  - Total Time on Study and # of Graft Failures

## Monitoring Plan (Cont)

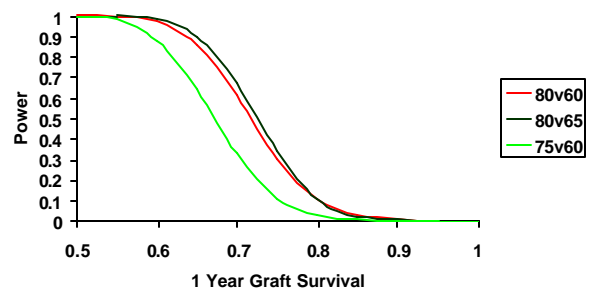
- Assume exponential failure times
- Uniform patient entry
- Observe graft failures through the one year time point
- Construct truncated bounds, if trial does not terminate, choose the null

## Operating Characteristics



- 75% 1-year Graft Surv
  - Size=.10
- 60% 1-year Graft Surv
  - Power=0.88
  - 43 patients
  - 22 Months

## SPRT Designs



- Donald Stablein, Principal Investigator
- Matthew McIntosh, Statistician
- Ilene Blechman-Krom, Protocol Monitor
- Ann Limberger, Protocol Monitor

Antiretroviral Drug Interactions:  
Nucleoside Analogues and Mycophenolate  
 Presented by David Oldach, MD, University of Maryland

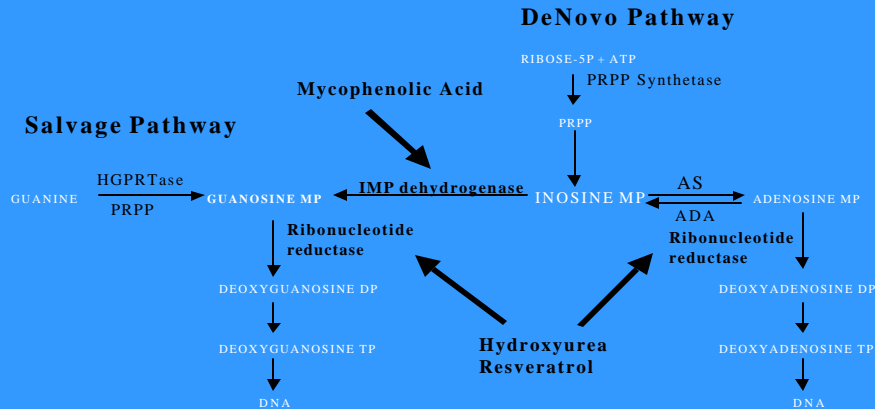
**HIV & Transplantation:**

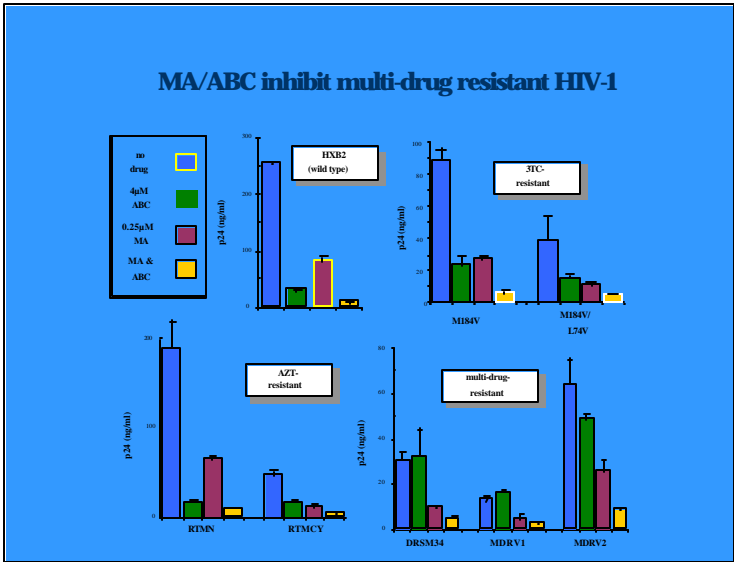
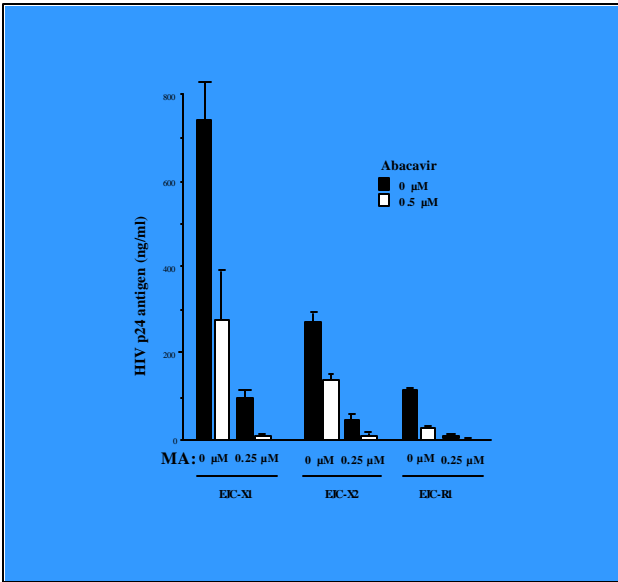
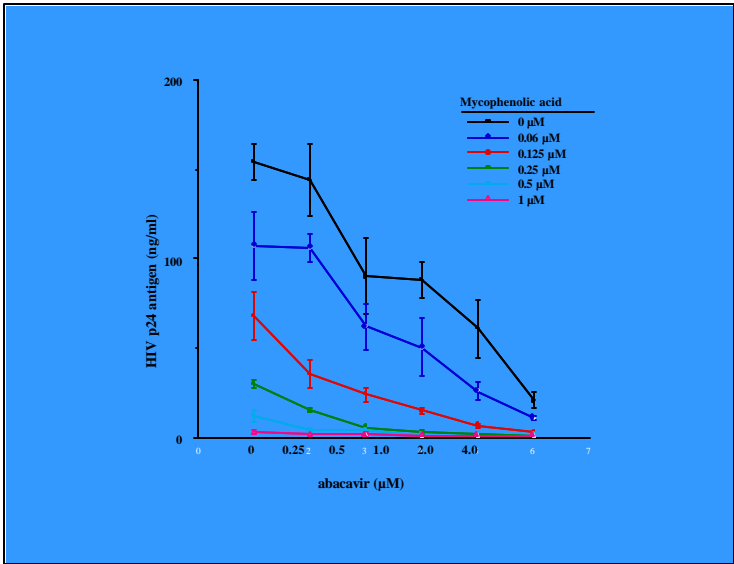
- Will immunosuppression to prevent organ rejection in the HIV + patient result in:
  - Synergistic Immunosuppression . . .
- Or can we exploit antiretroviral activities of immunosuppressive medications to achieve
  - Synergistic Antiretroviral Activity?

**Mycophenolate & Antiretroviral Nucleoside Analogues (NRTIs)**

- Mycophenolate mofetil, an inhibitor of inosine monophosphate dehydrogenase, reduces intracellular GTP pools in cells lacking the purine salvage pathway. . .
- Mycophenolate has intrinsic antiretroviral activity in-vitro, through its inhibition of T-cell activation...

**Mycophenolate & Anti-Retroviral Agents:  
Purine Biosynthesis**



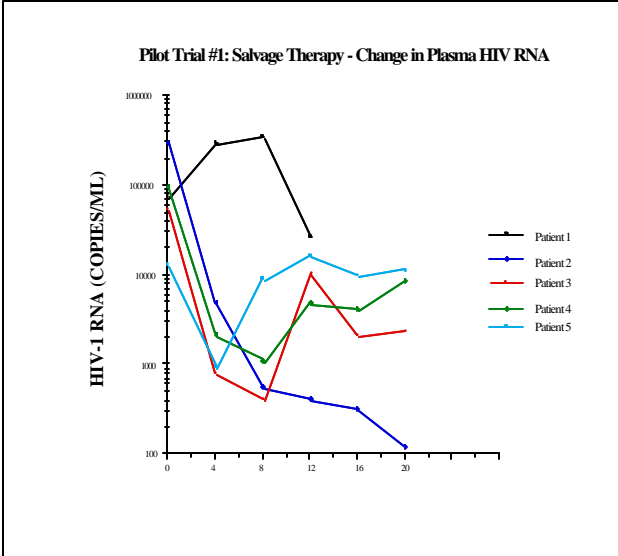


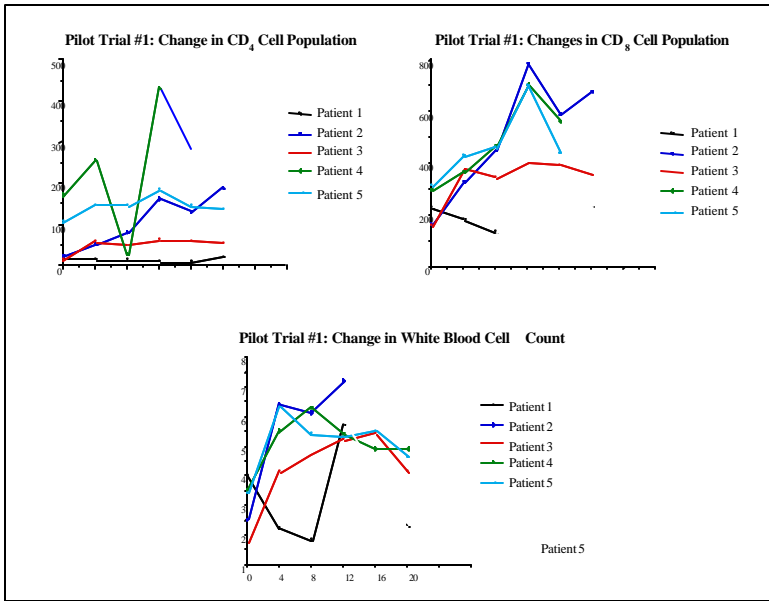
### MM / ABC Salvage Trial

- Phase I, 20 week trial
- ABC 300 mg BID + MM 250 mg BID + at least two other antiretroviral agents
- Inclusion Criteria:
  - HAART & salvage rx failure.
  - Genotype: 3 or more RT mut (ABAC) or multidrug resistance mut and NNRTI or PI resistance

### Baseline Parameters and Therapy, ABC/MM Salvage RX Pilot Study

Pt #	Salvage Regimen	Baseline CD4	Baseline Viral Load	Comments
1	DDI/Amprenavir/ABC/MM	19	75,070	discontinued trial hospitalized weel for pyleonephritis
2	Indinavir/Ritonavir/ABC/MM	23	296,129	
3	DDI/Amprenavir/ABC/MM	13	52,206	
4	DDI/3TC/Amprenavir/ABC/MM	170	93,449	
5	DDI/3TC/Amprenavir/ABC/MM	106	12,401	



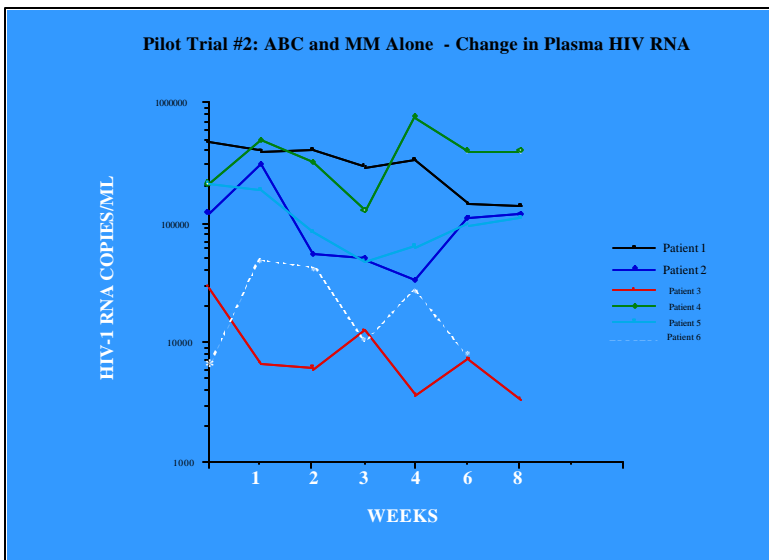
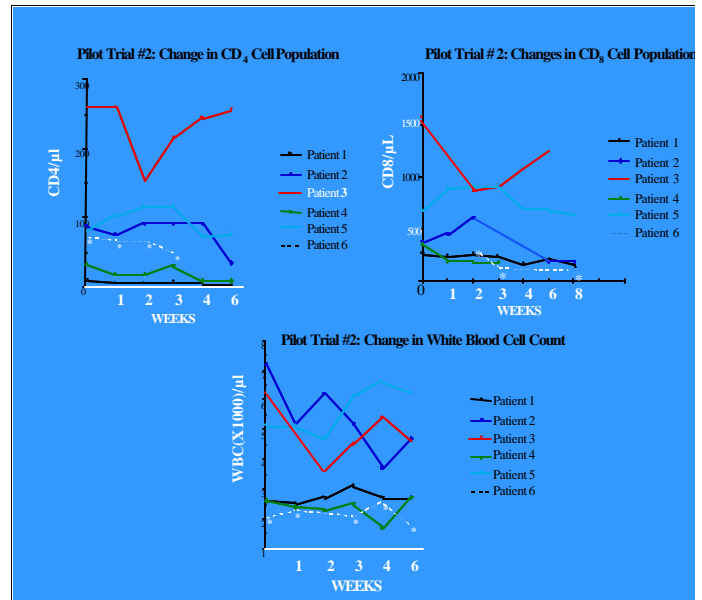


## MM / ABC Dual Therapy

- Open, dose escalation (MM) feasibility study of MM/ABC combination therapy in setting of established ABC resistance
- ABC (300 mg b.i.d) + MM: 250- 500- 750- 1000 mg b.i.d. (dose escalation q week)
- Volunteers, off HIV rx > 2 weeks, HIV RNA >3,000 CPM, HIV genotype: 184 mutation plus 2 additional ABC mutations.

## ABC/MM RX: Volunteers

Pt:	Age:	CD4:	Drugs failed:	Years ART:
• 1	41	10	14	6
• 2	47	88	11	5
• 3	48	259	5	6
• 4	39	32	8	8
• 5	64	80	3	4
• 6	42	78	13	5



## Conclusion

Mycophenolate Mofetil at daily doses between 500 mg and 1500 mg was well tolerated and without evidence of significant toxicity. Two volunteers developed significant adverse events (CMV retinitis and HSV esophagitis) at a daily dosage of 2000 mg. Causal association with high dose MM cannot be excluded.

The use of MM and ABC in combination with additional anti-retroviral agents was associated with a temporal decrease in plasma HIV RNA levels in heavily experienced anti-retroviral-treated patients.

The use of MM and ABC alone failed to demonstrate significant *in vivo* anti-viral activity in patients with multi-RT resistant virus. Although *in vitro* data demonstrated the ability of the addition of Mycophenolic acid to Abacavir to "restore" susceptibility of abacavir-resistant mutant viruses, this observation failed to translate clinically when tested directly *in vivo*.

Whether or not MM will impact the durability of abacavir-induced viral control in volunteers prior to the development of abacavir resistance remains to be determined.

Antiretroviral Drug Interactions:

PI/NNRTI and Immunosuppressives

*Initial UCSF Study Patient Experience*

Presented by Laviero Mancinelli, PharmD., University of California, San Francisco

A. Sub.	Date	Week #	Drug	Dose	C <sub>max</sub>	C <sub>min</sub>	AUC	Notes	IC <sub>95</sub>
003	05/15/2000	1 (Tx. #2)	Neoral	175 mg bid	1559.9	331.3	12726.1	ng/ml	
003	05/15/2000	1 (Tx. #2)	MPA	750 mg q 12h	3.01	0.15	10.5	ug/ml	
003	06/21/2000	6 (Tx. #2)	Neoral	175 mg bid	890.1	296.9	9481.6	ng/ml	
003	06/21/2000	6 (Tx. #2)	MPA	750 mg q 12h	5.7	0.1	20.2	ug/ml	
001	03/28/2000	Pretransplant	Nelfinavir	1250 mg bid	2795.7	1524.0	42210.8	ng/ml	4.6-86.0
003	05/15/2000	1 (Tx. #2)	Nelfinavir	1250 mg bid	4684.0	1047.0	44482.8	ng/ml	4.6-86.0
003	06/21/2000	6 (Tx. #2)	Nelfinavir	1250 mg bid	7063.6	1822.3	56018.4	ng/ml	4.6-86.0
002	04/13/2000	1	Neoral	75 mg bid	223.1	74.5	1587.2	ng/ml	
002	04/13/2000	1	MPA	1000 mg bid	6.3	4.0	93.0	ug/ml	
002	05/04/2000	4	Neoral	75 mg bid	1360.1	231.2	5234.1	ng/ml	
002	05/04/2000	4	MPA	1000 mg bid	5.6	1.2	52.1	ug/ml	
002	05/23/2000	8	Neoral	125 mg bid	2198.6	804.0	44908.3	ng/ml	
002	05/23/2000	8	MPA	1000 mg bid	1.9	0.4	13.0	ug/ml	
002	04/06/2000	Pretransplant	Indinavir	800 mg tid	1754.0	141.8	2991.1	ng/ml	15.3-61.4
002	04/13/2000	1	Indinavir	800 mg tid	2125.9	64.3	3677.9	ng/ml	15.3-61.4
002	05/04/2000	4	Indinavir	800 mg tid	458.5	102.6	1089.5	ng/ml	15.3-61.4
002	05/23/2000	8	Nelfinavir	1250 mg bid	4433.5	1694.1	29391.2	ng/ml	4.6-86.0
005	07/05/2000	1	Neoral	100 mg bid	510.1	1.5	2717.0	ng/ml	
005	08/02/2000	4	Neoral	50 mg A/25 mg P	215.0	107.0	2940.8	ng/ml	
005	07/05/2000	1	MPA	1000mg bid	6.2	0.6	31.3	ug/ml	
005	08/02/2000	4	MPA	1000mg bid	3.2	0.6	40.4	ug/ml	
005	06/28/2000	Pretransplant	Nelfinavir	1250 mg bid	2390.2	552.4	23700.1	ng/ml	
005	07/05/2000	1	Nelfinavir	1250 mg bid	685.3	82.2	3803.2	ng/ml	
005	08/02/2000	4	Nelfinavir	1250 mg bid	4536.0	735.0	33625.8	ng/ml	
006	07/06/2000	1	Neoral	200 mg bid	838.1	68.0	3053.3	ng/ml	
006	08/03/2000	4	Neoral	200 mg bid	948.0	99.0	3476.6	ng/ml	
006	07/06/2000	1	MPA	1000 mg bid	7.3	0.7	60.2	ug/ml	
006	08/03/2000	4	MPA	1000 mg bid	3.2	0.14	29.6	ug/ml	
006	06/28/2000	Pretransplant	Nevirapine	200 mg bid	29.3	24.0	108.2	ng/ml	2.6-26.6
006	07/06/2000	1	Nevirapine	200 mg bid	21.8	15.1	567.5	ng/ml	2.6-26.6
006	08/03/2000	4	Nevirapine	200 mg bid					2.6-26.6

<b>Subject</b>	<b>Medication</b>	<b>Dose</b>	<b>Notes</b>
001/003	Nelfinavir	1250 mg bid	
	ddI	50 mg qhs	
	Epivir	150 mg bid	
	Ribavirin	200 mg qd	
	Acyclovir	800 mg bid	
	Alpha Interferon	1.5 MU qd	
	Neoral	175 mg bid	
	Cellcept (MMF)	750 mg bid	
	Prilosec	20 mg qd	
	Dapsone	100 mg qd	
	Amlodipine	10 mg qd	
	Fluconazole	100 mg q Thursday	
002	Indinavir	800 mg tid	D/C after 05/04/00
	Abacavir	300 mg bid	
	Nelfinavir	1250 mg bid	
	Epivir	150 mg bid	
	ddI	400 mg q A	D/C after 05/04/00
	Cytovene (DHPG)	500 mg tid	
	Neoral	125 mg bid	
	Cellcept (MMF)	1000 mg bid	
	Prednisone	30 mg qd	
	Fluconazole	100 mg q Thursday	
	Cardura	0.2 mg qd	
	Prilosec	20 mg qd	
	Septra DS	1 qd	
<b>Subject</b>	<b>Medication</b>	<b>Dose</b>	<b>Notes</b>
005	Nelfinavir	1250 mg bid	
	Abacavir	300 mg bid	
	Epivir	150 mg bid	
	Neoral	50 mg q A/25 mg q P	
	Cellcept (MMF)	1000 mg bid	
	Prilosec	20 mg qd	
	Prednisone	20 mg qd	
	Metoprolol	150 mg bid	
	Septra DS	1 q MWF	
	Regular Insulin	SS	
006	Nevirapine	200 mg bid	
	Abacavir	300 mg bid	
	Epivir	150 mg bid	
	Cytovene (DHPG)	1000 mg tid	
	Neoral	200 mg bid	
	Cellcept (MMF)	1000 mg bid	
	Prednisone	25 mg qd	
	Norvasc	5 mg qd	
	Acidphex	20 mg qd	
	Septra DS	1 q MWF	

# **NEXT STEPS**

Prepared by Tom Coates

## **1. Protocol Development:**

- Revised protocol and informed consents will be distributed to all sites for review and IRB submission by Sept. 15<sup>th</sup>

## **2. Liver Study:**

- UCSF ARI currently fundraising for data management add-on for Emmes. Sites should plan on enrolling at same time as kidney.

## **3. Optimal lab studies and storage:**

- Funding sources to be explored. Sites will be queried regarding local lab resources and monetary needs for shipping and storage.

## **4. National DSMB:**

- We will use the DSBM for kidney trials—CCTAT

## **5. Site Coordinators/Data Managers:**

- Lawrence Kerr will review funding requests ASAP. Funding decisions will be made in conjunction with Emmes.

## **6. Educational Programs/Best Practices:**

- Will coordinate web-based educational resources and consider further educational meeting.
- Sites are encouraged to share key clinical experiences for inclusion in a developing *Clinical Guidelines in the Management of the HIV Positive Transplant Recipient Manual* (send them to M. Roland and L. Carlson)

## **7. Facilitating ongoing dialogue:**

- Consider list-serve
- Protocol and site information on website
- Conference calls to include: Surgeons, HIV Clinicians, Hepatologists, Nephrologists, Pharmacologists, Clinical Coordinators, Data Managers

## **8. Referrals between sites:**

- Facilitate via contact information on website

**9. Ethical and Policy Issues:**

- UCSF will host a policy forum and write up the results

**10. R01/P01 preparation:**

- The subject of a future meeting—possible writing retreat
- February 2001?
- UCSF ARI to coordinate

\*\*\*\*\*

***Timeline to begin implementation  
of the common protocol:***

- Emmes—data collection tools (CRFs) to be ready at earliest by end of September
- Revised protocol and consent forms—distributed by Sept 15
- Start-up—Nov 15

# Appendix A-1: Background and Patient Data Slides

Presented by Peter Stock

## WHY NOW?

- Epidemiological data show **decreased** incidence of opportunistic infections and hospitalizations with use of HAART.
- HAART in immunosuppressed HIV positive transplant recipients will further improve allograft and patient survival.
- Immunosuppressive agents commonly used in transplant have anti-HIV effects.

## NEED FOR ORGAN TRANSPLANTATION IN HIV + POPULATION

- 750,000-1.5 million people infected with HIV, with 40,000 new cases added each year.
  - Renal failure  
HIV associated nephropathy (HIVAN)
  - Liver failure
    - Hepatitis B
    - Hepatitis C
- Risk factors:  
transfusion, IVDA,  
multiple sexual  
partners

## HIV AND END STAGE RENAL DISEASE

HIV-associated nephropathy (HIVAN) — most common cause of ESRD in seropositive patients

Characteristic lesion:

glomerular — focal sclerosis (FSGS)  
prominent retraction of the glomerular tuft  
visceral epithelial cell hypertrophy

tubulointerstitial — infiltrating mononuclear cells  
interstitial edema  
fibrosis  
microcystic tubule dilatation

## RENAL COMPLICATIONS IN HIV + POPULATION

- HIV-associated nephropathy (HIVAN)- **ESGS**  
Rapid progression to ESRD (weeks to months)  
[predilection in Blacks: genetically determined response to glomerular injury versus genetically determined susceptibility to viral infection]
- Membranoproliferative glomerulonephritis
- Rapidly progressive glomerulonephritis
- IgA nephropathy
- Amyloid

## HIV AND HIV-ASSOCIATED NEPHROPATHY

- Incidence of HIV nephropathy has increased by 30% each year since 1991
- In 1995, HIV nephropathy became the third leading cause of ESRD in Blacks
  - ∞  $\uparrow$  HIV incidence in White men whose risk factor was sex with other men (MSM)
  - ∞  $\downarrow$  HIV incidence in Blacks and women
  - ∞  $\uparrow$  in AIDS-related deaths in men and women of all racial/ethnic groups
- Number of patients at risk for the development of HIVAN increasing at a dramatic rate

## POTENTIAL HIV + CANDIDATES FOR RENAL TRANSPLANTATION

- Dependent on the stage of HIV infection when HIVAN occurs
- Several series show HIVAN occurs in otherwise asymptomatic individuals before the development of opportunistic infections
- Two series demonstrated rapid progression to the development of AIDS defining condition within 1 year of the diagnosis of HIVAN (< average time between seroconversion and AIDS-defining condition 8-10 years)

## HIV POSITIVITY AND END-STAGE LIVER DISEASE

Similar risk factors: IVDA, transfusion, sexual

### Hepatitis C infection:

- Incidence in U.S.: 18% (3.9 million)
- Most common indication for OLT (~25%)
- 90% of HIV infected hemophiliacs and people with IVDA are co-infected
- HIV infection accelerates HCV progression (higher proportion of ESLD in HCV infected hemophiliacs with HIV than without)
- HCV viral RNA levels correlate with decreasing CD4 counts.

### Hepatitis B infection:

- Estimated incidence of 140,000-320,000 infections per year (about 50% symptomatic)
- Depending on geographic location, up to 20% co-infected with HBV

## HIV AND MORTALITY FROM ESLD

- ↑ in AIDS-related deaths from infection and malignancy
- ↓ in mortality from ESLD
- Study from Tufts University: 50% of deaths in HIV + people in 1998, 1999 attributed to ESLD
- Study from Case Western University: Hepatic failure-related death:
 

0-2%	1995
20%	1997
- Study at MCP Hahnemann found that HCV was among three most common causes of death for people with HIV

## SHOULD ALL HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENTS WITH END-STAGE RENAL DISEASE BE EXCLUDED FROM TRANSPLANTATION?

TRANSPLANTATION, MAY 15, 1998  
VIEWS OF U.S. TRANSPLANT CENTER

- Transplant Center Response Rate: 149/248 (60%)
- Is HIV testing required for prospective recipients? YES 100%
- Would a patient who refuses HIV testing be considered for transplantation? YES 12% NO 84% UNSURE 4%
- Would an HIV-infected ESRD be considered for cadaveric transplantation? YES 9% NO 91% UNSURE 3%
- Would an HIV-infected ESRD be considered for living donor transplantation? YES 5% NO 91% UNSURE 4%

## HISTORICAL DATA IN TRANSPLANT

- Difficulties in data
- Outcomes poorly defined [e.g. CD4 time of transplant, opportunistic
- Small, anecdotal
- Do not take into consideration the therapies for prophylaxis against infection, improved antiviral therapies, and diagnostic

## RETROSPECTIVE DATA IN HIV + RECIPIENTS

- Several initial reports demonstrating worse outcomes following solid organ transplant seropositive patients.
  - Drummer et al. Transplantation 1989
  - Poliet al. Transplantation 1989
  - Ragni et al. NEJM 1990
  - Tcakis et al. Transplantation 1990
- Several reports suggesting no adverse effects of HIV infection > 8 yrs, HIV undetectable, no OIs.
  - Jackson et al. Lancet 1991

## HUMAN IMMUNODEFICIENCY INFECTION PATIENTS WITH ORGAN TRANSPLANTS: REPORT OF CASE AND REVIEW

ENRICE ET AL. REVIEWS OF INFECTIOUS DISEASES 1991;13:537

### RENAL

- 6/11 functioning at a mean follow-up time of 31
- 27% with progression to

### LIVER

- 5/7 patients died within 18
- 3/5 deaths were AIDS
- Poor liver results related
  - ↓ morbidity of liver transplant in
  - Severe co-morbidity of viral

## LIVER TRANSPLANTATION IN HIV PATIENTS

PARCHALIAS ET AL. — ILTS CONGRESS 1999  
KING'S COLLEGE HOSPITAL, LONDON, UK

- 4/561 liver transplant recipients from 1995-1998 were HIV +
- Immunosuppression was tacrolimus-based
- All received antifungal, PCP, and CMV prophylaxis
- Utilized antiretrovirals—both NNRTI and PI-based HAART

## RESULTS FROM KING'S COLLEGE HOSPITAL (cont.)

- No opportunistic infections
- 3 patients with HCV
  - All with rejection
  - All with severe recurrence and died with cholestatic hepatitis at 6, 15 and 25 months
  - CD4 counts pre-op >500, 280, 160
  - CD4 counts prior to death 87, 5, 10

## LIVER TRANSPLANTATION IN HIV-POSITIVE PATIENT—POSSIBLE INTERACTION BETWEEN TACROLIMUS AND NELFINAVIR

Söderdahl et al. —Huddinge Hospital, Sweden

- Patient transplanted for HCV on PI-HAART with negative HIV (risk factor: multiple transfusions for hemophilia A)
- Tacrolimus-based immunosuppression — no rejection
- Tacrolimus dose — 0.5 mg/week
- Recurrent HCV — 4.1 million copies/ml 8 weeks following transplantation
- No detectable HIV—survival to 1 year at time of presentation. Patient cured from hemophilia A.

## AN OBSERVATIONAL STUDY OF FRENCH LIVER RECIPIENTS INFECTED WITH

BOUSCARAT ET AL. CLINICAL INF.

1994-19

- 11 patients underwent OLT between 1985-1987 found to be infected with HIV-1
- CSA-based immunosuppression
- 8/11 patients had acute rejection
  - 5/8 required anti-T cell preparations
  - 3/5 had rapid progression to AIDS and death
- 7-year survival rate: HIV + 36%  
HIV - 70%

## JK-39 Y/O Female 8 Years S/P OLT For Fulminant Hepatic Failure (HEP B)

- OLT July 1992 (31 y/o)
- Jan. 1994 ® HEP C +, HIV +
- Immunosuppression ~ 2° HIV +
  - FK, prednisone
  - ∞ ~ FK triggered rejection episode
- Rejection tx with steroid bolus, ↓ FK
- 1996 - initiated on anti-viral therapy EPIVIR, ZERIT (3TC, d4T)
  - no protease inhibitors
- 1996-2000
  - No detectable HIV viral load
  - Negative Hep B staining on liver biopsy
  - No detectable HCV by PCR
  - No opportunistic infections
  - Normal LFT's

## SL-51 Y/O MALE - OLT FOR HEP B

- 9/97 ® ascites, LFT's ↑  
liver biopsy ® CAH, cirrhosis  
serologies ® Hep B Ag +  
HIV +
- 1/98 ® TIPS for ascites  
worsening encephalopathy S/P
- TIPS
- 2/98 ® SBP
- 4/98 ® severe encephalopathy  
hepatorenal syndrome (BUN 105)
- 4/29/98 ® CVVH initiated  
® HIV regimen nelfinavir, d4T,  
lamivudine  
® encephalopathy improved with

## SL (cont) ®

### COURSE

- Extubate on POD#4® continued intermittent confusion. performed 2° to altered mental status (no significant)
- Required CVVH X 2 days, then HD. HD required until
- Immunosuppressi with . Given a single dose Zenapa (IL-2R inhibitor) 2° to renal
- On POD#4 (5/6), a sputum culture from 4/26/98 grew culture® started on a 4 drug anti-TB regimen. subsequently identified as
- Discharged on 6/27 wks post-
  - Norma LFT's
  - No HepB
  - No HepC

## SL (cont) ® POSTOPERATIVE COURSE

- 7/29 - readmitted c/o dizziness and
- MRI showed multiple lesions in cerebral the gray-white matter
- Progressivē in mental status, with lesions in brain MRI c/w JC
- PCR of CSF positive for JC
- 9/1 (3 months post-op) respiratory support and the patient

## PM - 15 Y/O Male with ESLD 2° tHep C/HIV. Both viruses acquired during transfusion (Age 2) fortx ALL.

- Massive ascites, fatigue
- Proteinuria, GFR 80 ml/minute renal biopsy: membranoproliferative GN
- No detectable viral load on HAART
- HCV viral load 9 million copies/ml

## PM- (cont.)

Due to waiting list issues, underwent a living donor (L) lobe liver transplant (donor-mother)

### Post-op Course:

- Severe preservation injury ® C/W small-for-size graft
- Progressive renal insufficiency - inability to administer CSA
- Immunosuppressive therapy - Rapamycin, CellCept, prednisone
- ∞ ↓ in Hep C viral load to 120 million copies/ml
  - Inability to administer Ribavirin 2° renal insufficiency and major hemolysis
  - ? ability to administer to interferon (effects on regeneration)
- Inability to administer anti-virals 2° to poor hepatic function
- Liver biopsy ® continued P.I. No periportal infiltrates
- ∞ ↑ in renal function massive ascites
  - ↓ bilibubin to >30
- ~ 1 month post-op ® re-transplant liver and kidney

## PM-POST COURSE

- Immediate resolution asciteswith normalization of renal function and function.
- Resolution 30.0® 2.0 over 2
- Discharge from hospital
- Tolerates virals(2 NRTI, 1 PI) ~ in HIV viral load to
- Tolerates interferon , with ~ in HCV viral load from 120 million ® 30 million copies over 4

## CW-Living Related Transplant

- Received kidney from nephew (issues informed)
- ESRD 2° to
- No h/o OI, CD4 >200, tolerating
- Pre-tx screening-non-therapeutic anti-dosing
- Uncomplicated post-op DC'edPOD#4
- No , continued undetectable tolerating HAART, normal renal

## WHAT IMMUNOSUPPRESSION?

The Effect of Cyclosporin on the Progression  
Human Immunodeficiency Virus<sup>1/4</sup>  
Schwartz et al. Transplantation

Retrospective review of 53 patients with  
infection 2° to infected peri  
blood

Progression to AIDS at 5

90% (n=13) - no

31% (n=40) - Regimens with

## CLINICAL TRIALS CYCLOSPORINE IN HIV SUBJECT

Hypothesis(1) HIV pathogenesis is in  
mediated by up regulation  
over-activation of the  
system.

(2) Cyclosporin will decrease  
activation and lead to  
markers of HIV disease  
(CD4 T-cell counts and

RNA) and clinical

## PRELIMINARY FROM CLINICAL UTILIZING CSA FOR THERAPY

Levy et Adv Exp Med Biol 1995;

- Significant preservation of CD4 + cell  
HIV-infected persons treated with  
mg/kg/day of
- No effect on total lymphocyte count or  
antigenemi, indicating no effect on  
replication

## A CONTROLLED TRIAL OF CSA IN HIV INFECTION

CALABRESE ET AL. [ACTG334 TEAM]  
Abstract 373:146, 7th Conference on Retrovirus and  
Opportunistic Infection, Jan. 2000

Short-term preliminary results:

Prospective randomized control trial ®  
low dose CSA (4 mg/kg/day).

Safe, but only a modest decrease in immune  
activation.

## POLYMERASE SUBSTRATE DEPLETION: A NOVEL STRATEGY FOR INHIBITING THE REPLICATION OF THE HUMAN IMMUNODEFICIENCY VIRUS

IchimurH and Levy. Virology 1995.

- Mycophenolic acid (CellCept) ® nonnucleoside  
inhibitor of inosine monophosphate dehydrogenase
- Limits the rate of de novo synthesis of guanosine  
nucleotides ® in turn blocking the activity of reverse  
transcriptase
- Shows strong anti-HIV activity in vitro in both human  
peripheral CD4 + lymphocytes and macrophages.

## MYCOPHENOLATE MOFETIL - (MMF)

- Inhibitor of inosine monophosphate dehydrogenase,  
therefore limiting de novo synthesis of guanine  
nucleotides.
- Guanine nucleotides required for the proliferation of  
lymphocytes and monocytes ® potent  
immunosuppression.
- ∞ - guanosine nucleotides ® blocking activity of reverse  
transcriptase
- Strong anti-HIV activity in vitro in CD4 + cells
- Combination of MMF and the nucleoside analog  
reverse transcriptase inhibitor abacazir has synergistic  
anti HIV-1 activity in vitro

## T-CELL ACTIVATION IS FOR HIV-1 ENTRY IN LYMPHOCYTE

Ganda et al. Journal of Immunology 1989;142, 773

- Unstimulate freshly isolated CD4+ lymphocytes not synthesize detectable HIV duplex
- Activation of T-cells with either PHA or OKT3 CD3 mAb before viral exposure resulted in generation of HIV DNA after 6 h and integrate genomic after 24
- Evidence that HIV entry requires T-cell

## POTENTIAL BENEFICIAL ROLE OF STEROIDS IN IMMUNOSUPPRESSIVE REGIMENS IN HIV +

- ∞ HIV expression via ability to decrease activation
- Steroids can rescue CD4+ lymphocytes activation triggered by
- Human trials have demonstrated that can decrease serum p24 antigen levels as increase CD4 cell counts in HIV-1 persons

## DIRECT INHIBITION OF HIV ASSEMBLY BY CSA

Streblow et al. Virology 1998; 245:197

- CSA inhibits HIV-1 Gag processing.
- Inhibition results from binding of CSA to cyclophilin A.
- Cyclophilin A may be required for Gag conformational changes subsequent to assembly.

## PROPHYLAXIS FOR OPPORTUNISTIC INFECTIONS

### Potential Drug Interactions

- Cytovene (oral Ganciclovir) ® ↓ serum levels of Zidovudine and Didanosine
- Ganciclovir (IV), Cytovene (PO) ® bone marrow toxicity [compounding toxicity B.M. toxicity associated with cleoside analog antiviral agents]
- Azole antifungal agents ® potent inhibitors of cytochrome P450
- Pneumocystis/toxoplasma
- Trimethoprim/sulfamethoxazole ® bone marrow toxicity and ↓ renal clearance of Lamivudine

## PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS

- Pneumocystis carinii pneumonia P indicated regardless of CD4 count
  - Toxoplasmosis P indicated for toxo IgG+
  - If Toxo IgG+ - Bactrim DS qd
  - If Toxo IgG- - Bactrim DS 3X/wk
- Alternatives if Bactrim allergic (or neutropenic)
- ⊢ Dapsone (contraindicated if G6PD deficient)
  - ⊢ Aerosolized pentamidine
  - ⊢ Atovaquone

## PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS

- Mycobacterium avium complex (indicated for CD4 count <50)
- ⊢ Azithromycin 1200 mg weekly preferred
- ⊢ Alternative Clarithromycin 500 mg BID
- CAUTION: Exacerbate inhibition of cytochrome P450
- Candidiasis: Mycelex troches X 1 year

## PROPHYLAXIS FOR CYTOMEGALOVIRUS

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- Reactivation or development of CMV disease even in non-HIV infected patients
- Replication of CMV can enhance HIV replication
- CMV - recipients: IV Gancyclovir during hospital, followed by Cytovene x 3 months. Then Acyclovir (400 mg BID) X 9 months (unless CD4 > 100 then continue Cytovene)
- CMV + recipients: Acyclovir X 1 year

## IMPORTANCE OF PROPHYLAXIS IN THE RECIPIENT

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- Immunosuppression enhances the of CMV disease even in non-HIV
- CMV rejection be triggered following CMV
- CMV directly enhances HIV

## Appendix A-2: Background and Patient Data Slides

Presented by John Fung

### SOLID ORGAN FOR HIV+ CANDIDATES

The University of Pittsburgh

JOHN J. FUNG, MD, PhD  
August 13, 2000

### Documented Liver Transplantation in HIV+ Patients

Center	Year Reported	Number
Pittsburgh	1990	6
Minnesota	1991	3
King's College	1996	1
Royal Free	1998	6
Milan	1998	1
King's College	1999	4
Philadelphia	1999	1
Pittsburgh	2000	5 (+2)
San Francisco	2000	2
Miami	2000	3
Bonn	2000	1

### Tzakis et al: Transplantation in HIV+ patients. Transplantation 1990;49:354.

- 15 OLTX recipients from 1981-1988 were HIV positive.
- 6 infected before transplantation, 9 infected perioperatively.
- Cyclosporine based - 68% rejection, 65% given OKT3.
- 2.75 year mean followup, 7/15 patients alive
- 12.75 year mean followup, 2/15 patients alive
  - ◆ 1/6 pre-tx HIV infection
    - ☞ survival: 5,6,9,20,44,>204\* mo.
  - ◆ 1/9 peri-tx HIV infection
    - ☞ survival: 4,5,60,65,70,89,118\*,149,>180\* mo.

\*designates anti-HIV therapy post-OLT

### Additional Pre-HAART OLT

- 2 HIV positive OLTX recipients done under
  - ◆ HIV+ and HBV+ transplanted in
    - ☞ anti-HIV therapy initiated in
    - ☞ survival for 102
    - ☞ death from recurrent
  - ◆ HIV+ and HCV+ transplanted in
    - ☞ no anti-HIV therapy
    - ☞ survival 7
    - ☞ death from recurrent

### Recent University of Pittsburgh Experience

- All patients on antiretroviral therapy pre-transplant
- 5 liver - 2 NRTI and 1 PI
  - ◆ 4 - HCV associated liver disease
  - ◆ 1 - FHF due to nucleoside analog associated toxicity
- Minimum 3 months, maximum 2.50 years
- Tacrolimus dose - 1-2 mg/week on PI-HAART
- Compared to 2 kidney - 2 NRTI and 1 NNRTI
- Tacrolimus dose - .1 mg/kg/d on NNRTI-HAART

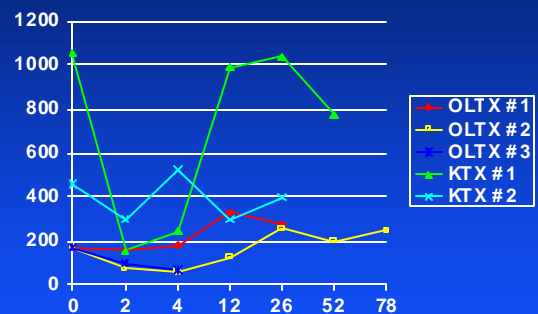
### OLT Experience

- One death - Status 2A, ventilator, renal failure, VREF sepsis
- Four alive, 3, 12, 21, and 30 months
  - ◆ Three with biopsy documented recurrent HCV at 6, 8 and 20 months
  - ◆ Treatment with alpha-IFN and ribavirin
  - ◆ One with clearance of HCV by bDNA
  - ◆ Normalization of ALT and AST
- All patients remain quantitatively HIV negative

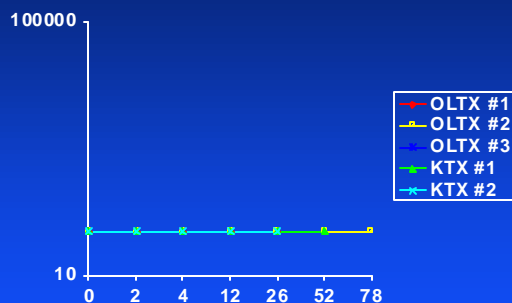
## Complications

- One death - non HIV related
- One episode of CMV reactivation - asymptomatic.
- One case of "fatty liver" with normal LFTs.
- One case of chronic rejection - HIV treating LMD elected to take the patient off of HAART therapy ("drug-free holiday"). The elimination of the PI caused drastic reduction in tacrolimus levels precipitating rejection.
- Two cases of rescinding the original decision to cover OLTX services by the fiscal intermediary.

## CD4 T Cell Counts



## HIV RNA Levels



## Pharmacokinetic Considerations

- Significant interactions between PI and tacrolimus
- Significant interactions between PI and rapamycin
- Potential additive or synergistic effects of nucleoside and nucleotide analogs, e.g. HAART, MMF, ribavirin, anti-CMV, anti-HBV.

## Clinical Benefit in HIV Transplant Recipients under HAART

1. No HIV disease progression, as evidenced by development of opportunistic infection
2. Survival beyond 24 months following transplantation
3. Sustained CD4+ > 200/ul post-transplantation
4. No increase in HIV RNA from baseline, post-transplantation

**Appendix B-1:  
Consensus Document Lab Studies from Briefing Book**

**Routine Safety Labs - Accepted**

<i>Core</i>	<i>Optional</i>	<i>All Local</i>
Cyclosporine Levels	None	Local
Renal/Electrolytes		
LFTs		
Amylase		
Lipase		
CBC-diff		
PT/PTT		
CMV Ab*		
EBV/PCR*		

**HIV Safety Labs - Accepted**

<i>Core</i>	<i>Optional</i>	<i>All Local</i>
CD4+/CD8+ T-cell	None	Local
HIV-1 RNA (bDNA/PCR)		
RPR/VDRL		
Toxoplasmosis Quant.*		
G6PD (once only)		
LDH		
Fasting Lipid Panel		
HepBSAg*		
HepBSAb*		
HepB core Ab*		
HepB DNA*		
MAC-blood*		
MAC-sputum*		
CSF JC virus*		

\* See protocol comments re past infection, indications for monitoring, etc.

**Appendix B-2:  
Consensus Document Lab Studies from Briefing Book**

**Immunology (HIV) Labs - Accepted**

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
	Phenotype	Regional/ ACTG ATL? **
	Cytokine Flow Cytometry	
	Lymphoproliferative Assays	
	Natural Killer Cells	
Soluble Activation Markers (neopterin, B2microglobulin)		Local
	CT Thymus	Local
	HIV specific CTLs	UCSF/Levy Lab
	CAF	
	CMV ELISA	
	EBV ELISA	
	HHV6 ELISA	

**Immunology (Transplant) Labs - Accepted**

<i>Core</i>	<i>Optional</i>	<i>Central</i>
	Chimerism	UCSF/Stock Lab
	Donor alloreactivity	

\*\* Sites to be explored further

**Appendix B-3:  
Consensus Document Lab Studies from Briefing Book**

**HCV Labs - Accepted**

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
HCV Ab*		Local
HCV RNA*		
HCV Genotype*		Central?
	HCV Quasispecies	Central?
Liver Biopsy*		Local

**HHV8 Labs - Accepted**

<i>Core</i>	<i>Optional</i>	<i>Central vs. Local</i>
None	HHV8 Ab	CA State Public Health Lab/J. Martin
	HHV8 Viral Load (cell-associated)	
	HHV8 Viral Load (plasma)	
	HHV8 Cellular Immunology	
	HHV8 Saliva	

**HPV Labs -Not Discussed (sorry, we forgot!)**

<i>Core</i>	<i>Optional</i>	<i>Central</i>
Cytology?		UCSF/Palefsky Lab
	Biopsy?	

**Pharmacology/Pharmacokinetics- Accepted**

<i>Core</i>	<i>Optional</i>	<i>Central</i>
PI/NNRTI pK x12	None	UCSF/BenetLab
CSA pK 1,2,6 hours		

## Appendix C: HCV Diagnostic and Treatment Algorithm

Presented by David Oldach

***NOTE: This document does not reflect a consensus.  
A revised document will be distributed by Sept 15<sup>th</sup>  
with consensus recommendations for feedback from all sites.***

Renal Transplantation for HCV/HIV coinfection. Break-out group discussion. 8/13/00.

- 1) HCV is a more aggressive disease in the setting of HIV/HCV coinfection than in HCV infection alone.
- 2) Patients with HCV infection alone who receive renal transplants have ~ similar (most studies) 5-year graft and patient survival rates (compared with matched renal transplant control patients without HCV). Large cohort 10 year rates are pending. However, even if patient or allograft survival is diminished in the HCV infected cohort (in 10 year or longer follow-up), the appropriate comparison group would be HCV infected patients remaining on dialysis.
- 3) Given these observations (#2), many centers perform renal transplantation for HCV infected patients, using varying HCV-specific qualifying criteria for clinical enrollment. Our task is to establish some agreement on qualifying criteria for renal transplantation in the setting of HIV/HCV coinfection.
- 4) The consensus among the transplant physicians present was that use of IFN to treat HCV infection in a renal transplant recipient was tantamount to “putting a gun to the kidney and pulling the trigger” (thank you, R. Shapiro). Thus, IFN treatment of HCV post-renal transplant is not a viable fall-back option...
- 5) *We do not know* what proportion of HCV infected HIV + renal transplant recipients will have an acceleration of their HCV related disease...but some certainly will.
- 6) Given the problems of #5 and the study’s intention to demonstrate safety and efficacy of renal transplantation, outright exclusion of HCV coinfecting patients from consideration for renal transplantation is an option. However, at some centers, HCV prevalence among HIV infected patients is as high as 60% (or more). Thus the study would not address the important question of clinical outcomes in this patient population.
- 7) We assume that the proportion of HIV/HCV coinfecting renal transplant recipients who will go on to develop severe HCV related liver disease post transplant can be reduced, however, if:
  - a) HCV infection is evaluated, treated, and cleared, pre-transplant (will infection really be cleared? Will relapse occur in the setting of ‘dual’ immunosuppression? Can we realistically expect better than ~25% viral clearance rates with therapy? What about that other 75%? Should we attempt to treat and clear HCV infection, even in patients whose liver biopsies are so benign that, in the absence of proposed renal transplantation, most clinicians would not treat?)
  - b) HCV liver disease is evaluated, and ‘high-risk’ candidates are excluded from consideration (unless successfully treated pre-transplant).

With these considerations in mind, we discussed the following **proposed guidelines**:

- 1) All candidates should have HCV antibody and serum PCR testing.
- 2) All HCV positive patients entering the protocol should be aware of the uncertainties above, and should be informed that they could develop essentially untreatable progressive HCV-related liver disease as a consequence of their renal transplantation. It probably makes sense for this discussion to occur before the risks of liver biopsy are undertaken, unless one is going to offer treatment regardless of transplantation status...
- 3) All HCV EIA (+) patients should have a liver biopsy, regardless of serum/plasma HCV RNA status (this assumes that PCR negative recipients will have had a positive HCV-RIBA assay for confirmation of infection).
- 4) Patients with ‘low risk’ biopsy results may enter the trial without prior treatment.....

HAI score less than/equal to 4  
No fibrosis.

- 5) Patients with 'moderate risk' biopsy results should be offered treatment prior to transplantation....  
HAI score less than or equal to 8,  
Grade 0 or 1 fibrosis (permits limited fibrous expansion of portal tracts)
- 6) Patients with 'high risk' biopsy results may not enter the trial, unless successfully treated....  
Any HAI score >8, with or without fibrosis,  
Any HAI score, with stage 2 fibrosis (fibrous expansion of most portal tracts)
- 7) Patients with 'higher risk' biopsy results are not candidates for renal transplantation alone...  
Any HAI score > 12  
Any HAI score, with stage 3 fibrosis (occasional portal to portal bridging)
- 8) Patients with cirrhosis, or in transition to cirrhosis are not candidates....(rather, these patients should be under evaluation for possible future liver transplantation).

**Plan:** We will consult with a number of hepatology, renal, HIV and transplant colleagues, revise the proposal, and circulate among the group for comment prior to incorporation into revised protocol and consent.

## Appendix D: Educational Resources

### 1. “Quick Reference Guide to Antiretrovirals”

- <http://hiv.medscape.com/Medscape/HIV/TreatmentUpdate/1998/tu01/eng/eng.qckguide0800.PDF>

Note, you need to register for Medscape to access this. It is free and easy to do! This is very nice, brief, concise overview.

### 2. “Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents”

- <http://www.hivatis.org/trtgdlns.html>

### 3. “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection”

- <http://www.hivatis.org/trtgdlns.html>

4. For questions or to find resources related to HIV and AIDS treatment, the HIV/AIDS Treatment Information Service (ATIS) is available Monday through Friday, 9 a.m. to 7 p.m. (ET) at:

800-HIV-0440 (1-800-448-0440)

301-519-6616 Fax

888-480-3739 TTY

[atis@hivatis.org](mailto:atis@hivatis.org) (E-mail)

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HIV Physician	Paul O'Keefe	<a href="mailto:Pokeefe@luc.edu">Pokeefe@luc.edu</a>	(708) 216-3232
Hepatologist	Vanthiel		(708) 216-0364
Nephrologist			
Pharmacologist			
Study/Site Coordinator			

Mayo Clinic, Jacksonville, FL

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Surgeon/Kidney			
HIV Physician			
Hepatologist			
Nephrologist			
Pharmacologist			
Study/Site Coordinator			

Mt. Sinai

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HIV Physician	Marla Keller	<a href="mailto:Marla.keller@mssm.edu">Marla.keller@mssm.edu</a>	(212) 241-5890
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National Institutes of Health

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DIADS	Lawrence Fox	<a href="mailto:Lf6h@nih.gov">Lf6h@nih.gov</a>	(301) 402-0139
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Pharmacology – DIADS	Alice K. Pau	Ap124z@nih.gov	(301) 402-7077
Pharmacology -- DIADS	Stephen Piscitelli	<a href="mailto:Spisc@nih.gov">Spisc@nih.gov</a>	(301) 496-2997
Transplant	Stephen Rose	<a href="mailto:Steve_Rose@nih.gov">Steve_Rose@nih.gov</a>	(301) 496-5598
TX?	Michael Sneller	<a href="mailto:Msneller@niaid.nih.gov">Msneller@niaid.nih.gov</a>	(301) 496-0491
Surgeon/Liver			
Surgeon/Kidney			
Hepatologist			
Nephrologist			
Study/Site Coordinator			

University of Pittsburgh

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Surgeon/Liver	John Fung	Fung@med.pitt.edu	(412) 648-3200
Surgeon/Kidney	Ronald Shapiro	shapiror@msx.upmc.edu	(412) 648-3200
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Hepatologist			
Nephrologist			
Pharmacologist			
Study/Site Coordinator			

University of California, San Francisco

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Surgeon/Kidney	Peter Stock	pgs007@itsa.ucsf.edu	(415) 353-1117
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Nephrologist	Lynda Frassetto/many	Frassetto@gcrc.ucsf.edu	(415) 476-6143
Pharmacologist	Laverio Mancinelli / Les Benet	Laviero@itsa.ucsf.edu Benet@itsa.ucsf.edu	(415) 476-5890 (415) 476-3853
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University of Maryland

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Surgeon/Kidney	Steve Bartlett		
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HIV Physician	David Oldach	<a href="mailto:Oldach@umbi.umd.edu">Oldach@umbi.umd.edu</a>	(410) 706-4609
Hepatologist			
Nephrologist	Ravinder Wali		
Pharmacologist			
Study/Site Coordinator			

University of Miami (not active)

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HIV Physician			
Hepatologist	Guy Neff	Wallyneff@aol.com	
Nephrologist			
Pharmacologist			
Study/Site Coordinator			

University of Minnesota

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Surgeon/Kidney	Arthur Matas	<a href="mailto:Matas001@umn.edu">Matas001@umn.edu</a>	612 625-6460
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Hepatologist			
Nephrologist			
Pharmacologist	Melissa Kamps	Kamps001@umn.edu	
Study/Site Coordinator			

University of Virginia

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